
Prematurity and brain

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Incidence and mortality of the premature infant

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INTRODUCTION — Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. It is associated with approximately one-third of all infant deaths in the United States. Infants born at or before 25 weeks of gestation have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for severe impairment [1].

The incidence and mortality rate of preterm birth will be reviewed here. The risk and pathogenesis of preterm birth and complications of prematurity are discussed separately. (See "Risk factors for preterm labor and delivery" and "Pathogenesis of spontaneous preterm birth" and "Short-term complications of the premature infant".)

DEFINITIONS — Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birthweight (BW).

One classification based upon BW includes the following categories (table 1):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

This classification based upon BW is primarily used in this review.

BW percentiles have been established for the appropriate GA (table 2).

Prematurity is also defined by gestational age (GA) as follows:

- Late preterm infants — GA between 34 weeks and 36 weeks and 6 days
- Very premature infants (VPT) — GA at or below 32 weeks
- Extremely premature infants (EPT) — GA at or below 25 weeks

INCIDENCE — Approximately 550,000 premature infants are born each year in the United States. In 2008, about 12.3 percent of all live births were <37 weeks GA and 2 percent <32 weeks GA (figure 1) [2,3]. Low birth weight (LBW) infants accounted for 8.2 percent of live births in both 2007 and 2008 [2].

In the United States, there has been a 21 percent rise in the overall proportion of preterm births since 1990, which peaked in 2006 with 12.8 percent of all live births born at a GA <37 weeks. This increase over the last two decades is reflected in all stages of prematurity as follows [2]:

- The birth rate of late preterm infants has risen by 25 percent since 1990. The percentage of late term birth peaked at 9.1 percent in 2006, and has slightly declined to 8.8 percent in 2008.
- The percentage of low birth weight (LBW) infants has increased in the United States from 6.7 percent in 1984 to 8.3 percent in 2006, and slightly declined to 8.2 percent in 2007 and 2008.
- The percentage of very low birth weight (VLBW) has increased from 1.2 percent in 1980 to 1.5 percent in 2006, and was unchanged in 2007 and 2008 .

In Norway, a population-based report of all live births in 1999 and 2000 reported an incidence of 0.5 percent of ELBW infants born between 22 and 27 weeks GA [4].

Multiple gestation and ART — In the United States, a major reason for the increased incidence of premature birth is the higher rate of multiple gestations in part due to assisted reproductive technology (ART). Infants of multiple gestation are prone to delivery early; half of all twin births and >90 percent of triplets are born premature. In 2007, 57 percent of twins and nearly all triplets (96 percent) were LBW [2].

- **Twin births** — In the United States, the twin birth rate reached a record high of 32.2 twins per 1000 total births in 2004, which has remained stable from 2004 to 2007. There has been a 70 percent increase in the twin birth rate from 1980 to 2004 [2].
- **Higher-order multiple births** — In contrast, the triplet and higher-order multiple births rate has declined 21 percent from a peak of 193.5 per 100,000 births in 1998 to 148.9 per 100,000 births in 2007 [2]. This is partly due to the American Society of Reproductive Medicine recommendation to limit the number of embryos transferred. (See "Multiple births" and "Strategies to control the rate of high order multiple gestation".)

Ethnicity — The incidence of premature births varies among ethnic groups. In 2007, the percentages of live births in the United States that were preterm by ethnicity were 17.5, 12.1, and 11.1 in non-Hispanic blacks, Hispanics, and non-Hispanic whites, respectively [2]. A higher rate of low birth weight infants in minority populations also occurs in England, with reported percentages of low birth weight live births of 11.5, 9.4, and 5.4 percent in Asian, black, and white mothers [5].

PATHOGENESIS FOR PRETERM BIRTH — Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3).

The four primary causes that lead to preterm labor and delivery are as follow and are discussed in detail separately. (See "Pathogenesis of spontaneous preterm birth".)

- Activation of the maternal or fetal hypothalamic-pituitary-adrenal axis
- Infection
- Decidual hemorrhage
- Pathological uterine distention

Risk factors for preterm birth — Risk factors associated with preterm labor and delivery include the following sociodemographic and obstetric factors, which are reviewed separately (table 4). (See "Risk factors for preterm labor and delivery".)

- Maternal reproductive factors such as history of preterm birth and maternal age. A U-shaped relationship exists between maternal age and the frequency of preterm birth. Women under 16 and those above 35 have a 2 to 4 percent higher rate of preterm birth compared with those between 21 and 24 years of age [6]. Among non-Hispanic black women, the upper age with an increased risk of preterm delivery is lower with preterm birth rates increasing at 27 to 29 years of age compared to 33 to 35 years of age for non-Hispanic white women.
- Maternal disorders such as infection, anemia, hypertension, preeclampsia/eclampsia, cardiovascular and pulmonary disorders, and diabetes.
- Maternal lifestyle issues such as physical activity, history of substance abuse or smoking, diet, weight, and stress.
- Cervical, uterine, and placental factors such as short cervix, cervical surgery, uterine malformations, vaginal bleeding, and placenta previa or abruption.
- Multiple gestation
- Fetal factors such as presence of congenital anomalies, growth restriction, fetal infections, and fetal distress.

MORTALITY — Low birth weight and prematurity are major contributors to infant mortality. In the yearly analysis from the National Center for Health Statistics that links all birth and infant deaths (through the first year of age) in the United States, birth weight less than 2000 g was associated with 61 percent of infant deaths in 2005 [1].

Factors that cause variation in premature mortality rates include:

- Degree of prematurity — Mortality rises with increasing immaturity (ie, decreasing birthweight and gestational age)
- Maternal ethnicity
- Level of neonatal care
- Congenital anomalies

Gestational age and birth weight — Mortality rates amongst premature infants correlate with birthweight and gestational age with decreases in both associated with poorer survival [1,4]. Thus infants born with the lowest gestational age and birthweight have the largest impact on infant mortality because they have the greatest risk of death. As an example, although infants who weigh less than 1000 g account for only 0.8 percent of births in the United States, they accounted for 55 percent of all infants deaths in 2005 [1].

In 2004, infant mortality rates per 1000 live births based upon birth weight were as follows (figure 2) [7]:

- 2500 g — 2.3
- < 2500 g — 56
- < 1500 g — 245
- < 500 g — 850

A similar relationship with increasing mortality rates per 1000 live births and decreasing gestational age (GA) was also noted:

- 37 to 41 weeks GA — 2.43
- 34 to 36 weeks GA — 7.3
- 32 to 33 weeks GA — 17
- Less than 32 weeks — 183

Mortality data for infants born at or below 25 weeks gestation who are at the limit of viability are reviewed separately. (See "Limit of viability".) Overall, more than two-thirds of infant deaths occur during the neonatal period defined as less than 28 days of age. The risk of dying within this neonatal period increases with decreasing gestational age. In addition, lower birth weights due to fetal growth restriction increase mortality at a given gestational age in premature infants born at or below 31 weeks gestation [8]. (See "Small for gestational age infant", section on 'Mortality'.)

Extremely preterm infants — Although infants born at or before 25 weeks of gestation have the highest mortality rate, about 50 percent [9-11], it appears that the survival rate of infants between 24 and 26 weeks gestation has improved with advances in neonatal care [10,11]. (See 'Trends over time' below and "Limit of viability".)

Risk factors for death or severe neurosensory impairment in extremely low birth weight (ELBW) infants (birth weight less than 1000 g) include bronchopulmonary dysplasia, brain injury, severe retinopathy of prematurity, and infection (eg, meningitis, sepsis, and necrotizing enterocolitis) [12]. (See "Short-term complications of the premature infant" and "Long-term neurodevelopmental outcome of premature infants".)

Late preterm infants — Late preterm infants (born between 34 weeks, and 36 weeks and 6 days gestation) are an "at risk population" with a three to five-fold greater risk of mortality than term infants. The mortality of later preterm infants is discussed separately. (See "Late preterm infants", section on 'Mortality'.)

Ethnicity — Mortality rates of premature infants vary among ethnic groups as demonstrated by infant mortality data from the United States in 2004 (figure 3) [7]. The highest mortality rate is in black infants at any given gestational age or birthweight compared to other ethnic groups.

For example, the infant mortality rates per 1000 live births for premature infants with birth weights <1500 g (very low birth weight infants) based upon maternal ethnicity were as follows:

- Overall — 244.5
- White — 231.9
- Black — 274
- Asian or Pacific Islander — 222.7

Similar differences in infant mortality rate based upon gestational age were reported among ethnic groups. The infant mortality rates per 1000 live births for premature infants with gestational age <32 weeks based upon maternal ethnicity were as follows:

- Overall — 182.5
- White — 168.4
- Black — 216.2
- Asian or Pacific Islander — 173.2

Health care disparities may in part explain the higher mortality rate of black infants versus other ethnic groups [13].

Level of neonatal care — Variation in neonatal care impacts on mortality rate and include:

- Changes in care over time with the introduction of new therapeutic interventions and changes in management.
- Delivery of care based upon hospital resources and experiences.

Trends over time — Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality rates of preterm infants, except in those who are at the limit of viability [10,14-17]. (see "Antenatal use of corticosteroids in women at risk for preterm delivery", section on 'Evidence of clinical efficacy' and "Treatment and complications of respiratory distress syndrome in preterm infants" and "Limit of viability")

This was demonstrated by the improved survival rate for VLBW infants (birth weights between 500 and 1500 g) reported by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network over four time periods (74, 80, 84, and 85 percent in 1988, 1990 to 1991, 1995 to 1996, and 1997 to 2002) [14,15]. However, there was little change in the survival rate of infants with birth weights between 501 and 750 g (about 55 percent) from the time periods between 1995 to 1996, and 1997 to 2002 [15].

In a study of extremely premature infants defined as GA at or below 25 weeks born in the Trent region of Great Britain, survival rates were compared from 1994 to 1999 and 2000 to 2005 [10].

- Survival rates increased from 24 to 41 percent in infants with GA of 24 weeks and from 52 to 63 percent in those with GA of 25 weeks.
- There was no change in the survival rate of infants with GA of 23 weeks between the two study periods (18 versus 19 percent).
- None of the 261 infants at or below 22 weeks gestation survived to discharge from the hospital during the entire study period from 1994 to 2005.

A regional population-study of two birth cohorts separated by 20 years (1985 to 1986, and 2005 to 2006) also demonstrated increased survival without severe neurodevelopment impairment [16].

Standard of neonatal care — Survival rates for VLBW infants are higher in centers that deliver a high volume of VLBW infants and provide the highest level of neonatal care (ie, level 3 neonatal intensive care unit [NICU]), as illustrated by the following:

- In a study from California that linked birth and death certificate data from 48,237 VLBW infants born between 1991 and 2000 [18], the highest survival rates for VLBW were in hospitals that had a level 3 NICU and an annual delivery rate of VLBW infants greater than 100 deliveries. In comparison, the lowest survival rate occurred in hospitals with level 1 care (no NICU) and an annual delivery rate of VLBW infants less than 10 (OR 2.72, 95% CI 2.37-3.12).
- A meta-analysis of 41 articles including the above study demonstrated a risk-adjusted increased death rate for VLBW and VPT (gestational age ≤ 32 weeks) infants born at centers without a level 3 NICU compared with those born centers with a level 3 NICU [19]. Calculated risk-adjusted odds ratio based on data from studies determined to be of adequate or high quality demonstrated higher mortality rates for infants born in non-level 3 hospitals for VLBW (adjusted OR, 1.62, 95% CI, 1.44-1.83) and VPT infants (adjusted OR, 1.55; 95% CI, 1.21-1.98). Unadjusted pooled mortality rates comparing infants born at non-level 3 centers to those born at level 3 centers were 38 versus 23 percent in VLBW infants and 15 versus 17 in VPT infants. Subgroup analysis of ELBW infants demonstrated similar results with increased death rates for those born at a non-level 3 center for both unadjusted mortality (59 versus 32 percent) and calculated risk-adjusted odds ratio (adjusted OR 1.8; 95% 1.31-2.46).

These results support perinatal regionalization with maternal transport of women at-risk to deliver a VLBW infant to a center that delivers a high volume of VLBW infants and provides level 3 neonatal care.

In the United States, about three-quarter of VLBW infants are admitted to a NICU based on representative data from 19 states [20]. Data did not distinguish between infants admitted at the facility of birth and those who were transported to a NICU from another facility. Using multivariate analysis, preterm delivery, multiple births, and cesarean delivery were associated with a greater likelihood of NICU admission among VLBW infants.

Substandard neonatal care is associated with increased mortality. A case-control study of the Confidential Inquiry into Maternal and Child Health Program (CEMC) in Great Britain, which matched all neonatal deaths (excluding those due to lethal malformations) in infants born at 27 to 28 weeks gestation in the United Kingdom during a two year period (1998 to 2000) with randomly selected survivors, showed increased infant mortality was associated with substandard neonatal care and early neonatal factors including fetal compromise but not maternal characteristics [21]. Areas where poor neonatal care were associated with an increased risk of dying included:]

- Hypothermia — Infants who died were more likely to be hypothermic (temperature $\leq 36^{\circ}\text{C}$) on admission to the neonatal intensive care unit (NICU) (73 versus 59 percent).
- Substandard ventilatory and cardiovascular management — Infants who died compared to survivors received substandard ventilatory (20 versus 7 percent) and cardiovascular care (15 versus 7 percent). Substandard care was defined as a failure to monitor or properly document blood gases and/or blood pressure, and make therapeutic adjustment to maintain blood gases and/or blood pressure within standard limits.

Congenital anomalies — Premature infants with major congenital anomalies have higher mortality and morbidity rates. In a study from the NICHD Neonatal Research Network, ELBW infants with congenital anomalies (eg, cardiac, renal, central nervous system anomalies, and chromosomal abnormalities) who survived the first 12 hours of life compared to those without any congenital abnormality had a higher mortality rate in the first 18 to 22 months of corrected age [22]. Premature survivors with major congenital anomalies were twice as likely to have neurodevelopmental impairment, have poor growth, and were at three-time greater risk of rehospitalization when compared with ELBW infants without major anomalies.

Time of death — In VLBW infants, about 50 percent of deaths occur in the first three days after delivery. This was illustrated by a study based on information from the National Inpatient Sample Database from 1997 to 2004 that included 115,350 VLBW infants [23]. Patients with congenital anomalies were excluded from the analysis. In this cohort, the distribution of birth weights was 10.6, 18.4, 16.9, and 54.1 percent for infants weighing <500 g, 500 to 749 g, 750 to 999 g, and 1000 to 1499 g, respectively. The following findings were noted:

- The overall survival rate was 77.5 percent. On the first day, 35 percent of the deaths occurred. By the end of the first three days and the 28th day, 58 and 90 percent of the deaths occurred.
- Deaths were more frequent for ELBW infants during the first day of life. Morality increased with decreasing birth weights as follows:
- For infants with birth weights <500 g, only 8 percent survived. Most of the deaths (72 percent) occurred in the first day of life and by the end of the third day 86 percent of deaths had occurred.
- For infants born between 500 and 749 g, the overall mortality rate was 49.2 percent, with 19.6 and 31.4 percent mortality at the end of the first and third day of life.
- For infants born between 750 and 1000 g, the overall mortality was 14.9 percent, with 3.1 and 6.4 percent mortality at the end of the first and third day of life.

In a study from the NICHD of 9575 VLBW infants, the overall mortality rate was 28 percent, and the highest mortality rate occurred in the first 12 hours of life [24].

Long-term mortality — Survivors of prematurity beyond the first year of life still remain at risk for early death compared to those born at term. In a population-based study from Norway of over one million individuals born between 1967 and 1988 and followed through 2002, those born prematurely (5.2 percent of the overall group) had an increased risk of death throughout childhood compared to individuals born full-term [25]. Mortality rates were greater for those born extremely premature (gestational age 22 to 27 weeks) and were generally higher for boys compared to girls at the same gestational age.

SUMMARY AND RECOMMENDATIONS

- Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. Premature infants are classified by birth weight or gestational age (table 1 and table 2). (See 'Definitions' above.)
- In the United States, about 12 to 13 percent of live births are premature and about 2 percent are born at a gestational age less than 32 weeks (figure 1). There has been a 21 percent rise in the overall proportion of preterm births since 1990, which is reflected in all stages of prematurity. Part of this increase in premature births is due to the increase of infants with multiple gestations. (See 'Incidence' above.)
- Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3). The four primary causes that lead to preterm labor and delivery are activation of the maternal or fetal hypothalamic-pituitary-adrenal axis, infection, decidual hemorrhage, and pathological uterine distention. (See "Pathogenesis of spontaneous preterm birth".)
- Risk factors associated with preterm birth include obstetric and sociodemographic factors (table 4). (See "Risk factors for preterm labor and delivery".)
- Low birth weight and prematurity are major contributors to infant mortality. In the United States, prematurity was associated with approximately 37 percent of infant deaths. (See 'Mortality' above.)
- Increased mortality rates in premature infants are associated with the following:
- Increasing immaturity (ie, decreasing birthweight and gestational age) (See 'Gestational age and birth weight' above.)
- Hospitals with lower levels of resource and experience in delivering neonatal intensive care (See 'Standard of neonatal care' above.)
- Congenital anomalies (See 'Congenital anomalies' above.)
- Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality rates of preterm infants, except in those who are at the limit of viability. (See 'Trends over time' above and "Limit of viability".)

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Long-term complications of the premature infant

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INTRODUCTION — Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. It is associated with about one-third of all infant deaths in the United States and accounts for approximately 45 percent of children with cerebral palsy, 35 percent of children with vision impairment, and 25 percent of children with cognitive or hearing impairment.

Complications of prematurity are the underlying reasons for the higher rate of infant mortality and morbidity in preterm infants compared to full-term infants. The risk of complications increases with increasing immaturity. Thus, infants who are extremely premature, born at or before 25 weeks of gestation, have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for long-term morbidity.

In preterm survivors, there is a high rate of long-term neurodevelopment impairment and chronic health problems. These chronic medical and neurodevelopmental complications often require additional health care and educational services, which add to the overall economic cost of caring for the premature infant.

The long-term complications of prematurity and the long-term health care needs of premature survivors will be reviewed here. The short-term complications of the premature infant are discussed separately. (See "Short-term complications of the premature infant".)

DEFINITIONS — Different degrees of prematurity are defined by gestational age (GA) or birthweight.

The classification based upon GA is as follows:

- Late preterm birth — GA between 34 and less than 37 weeks
- Very preterm birth — GA less than 32 weeks
- Extremely preterm birth — GA at or below 25 weeks

Premature infants are also classified by birth weight (BW) (table 1):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

Birth weights by percentile for the appropriate GA have been established (table 2). The above definitions are used throughout this review.

LONG-TERM COMPLICATIONS — In preterm survivors, there is a high rate of long-term neurodevelopment impairment and chronic health problems.

Neurodevelopmental outcome — Premature survivors compared to those born full-term are more likely to have the following neurodevelopment disabilities. The risk of these impairments increases with decreasing gestational age.

- Impaired cognitive skills
- Motor deficits including mild fine or gross motor delay, and cerebral palsy
- Sensory impairment including vision and hearing losses
- Behavioral and psychological problems

The long-term neurodevelopmental outcome in premature infants is discussed in detail separately. (See "Long-term neurodevelopmental outcome of premature infants".)

Chronic health issues — Children who were born preterm are more likely to have recurrent illnesses requiring hospital readmissions compared to those born full-term. Most common causes for rehospitalization include infections, especially respiratory syncytial virus infection, respiratory problems including asthma, feeding problems, and surgical issues. These children are also more likely to have chronic medical problems including bronchopulmonary dysplasia, gastroesophageal reflux, increase risk of sudden infant death syndrome, and vision and hearing impairment. (See "Care of the neonatal intensive care unit graduate", section on 'Hospital readmissions' and "Care of the neonatal intensive care unit graduate", section on 'Common medical problems'.)

Premature children are also more likely to exhibit poor growth compared to those born full-term. Poor growth of ELBW children persists into school age as demonstrated by a follow-up study of 241 ELBW children who were assessed for growth and blood pressure at a median age of six years and four months [1]. Compared to normative growth data from normal children who were born full-term, children who were ELBW infants were lighter, shorter, and had a lower body mass index and smaller head circumference.

Impairment of lung function — Children who were born prematurely are at risk for impaired lung function that may result in reduced exercise capacity or an increase in respiratory symptoms.

- In a cross-sectional study of 126 children (mean age: 10 years), children with a mean gestational age of 27 weeks had one-half the exercise capacity and reduced lung function as measured by spirometry compared to term-born controls [2].
- In a follow-up report of 219 of 307 ELBW survivors from the EPICURE study (a large prospective population-based cohort outcome study of ELBW infants from Great Britain and Ireland), 56 percent of 182 children who had adequate spirometry data at 11 years of age had impaired baseline function [3]. Of note, patients in whom spirometry could not be obtained were more likely to be in a special school setting and were more seriously ill as neonates. In comparison to full-term school classmates, children who were ELBW were more likely to have a diagnosis of asthma (25 versus 13 percent) and had a higher incidence of chest deformities, such as pectus excavatum (17 versus 2 percent).

In particular, survivors of prematurity who had BPD are more likely to have respiratory problems as children and adults. (See "Pulmonary outcomes of bronchopulmonary dysplasia", section on 'Childhood'.)

Effect on adult health — As the survival rate of preterm infants improves, the potential impact of prematurity on adult health has become more apparent.

- **Insulin resistance** — Preterm adults appear to be more likely to have insulin resistance and higher blood pressure compared to adults born full-term [4,5]. In one study, adults (18 to 27 years of age) who were born prematurely (birth weights below 1500 g and a mean GA of 29 weeks) compared to full-term controls had higher blood pressure and impaired glucose regulation when evaluated by a standard 75 g oral glucose tolerance test with higher serum glucose and insulin concentrations two hours after glucose administration [4].
- **Hypertension and vascular changes** — Adults born premature may have higher blood pressure compared to those born full-term [5,6]. It has been proposed that low birth weight may play a role in the development of essential hypertension in adulthood. (See "Possible role of low birth weight in the pathogenesis of essential hypertension".)
- **Reproduction** — Prematurity has been associated with decrease reproduction in adulthood. This was illustrated in a large population-based study from Norway of over 500,000 individuals born between 1967 and 1976 and followed through 2004 that demonstrated preterm adults had a lower reproductive rate compared to individuals born full-term [7]. The reproductive rate was lowest in the adults with the lowest GA; rates were 25 and 68 percent in women born at 22 to 27 weeks and at term, respectively (adjusted RR 0.33, 95% CI 0.26-0.42), and were 14 and 50 percent in men born at 22 to 27 weeks and at term, respectively (adjusted RR 0.24, 95% CI 0.17-0.32). In addition, preterm women but not men were at increased risk of having preterm offspring.

LONG-TERM HEALTH AND EDUCATIONAL NEEDS — As discussed above, premature survivors are at increased risk for chronic medical and neurodevelopmental complications, which often require additional health care and educational services. As the number of survivors of premature birth increase and reach school-age, it is imperative that their health and educational needs are identified and resources are committed to address their needs. This is especially true for the children who were ELBW infants who are at the greatest risk for poor health and neurodevelopmental outcome. (See "Long-term neurodevelopmental outcome of premature infants", section on 'Extremely preterm infant'.)

This was illustrated in a study that demonstrated ELBW school-aged children compared to full-term children were more likely to have chronic medical conditions and disabilities resulting in increased use of health and educational services [8]. In this study, 219 ELBW children born between 1992 and 1995 (92 percent of the survivors) and full-term controls were evaluated at eight years of age for chronic medical conditions and the consequences of chronic medical conditions by parent questionnaire, neurologic assessment (including hearing, vision, and cognitive function testing), measurement of academic achievement, and motor skills. Children who were ELBW were at increased risk for asthma, cerebral palsy, loss of visual acuity, limited academic skills, and poor motor skills and adaptive function. These chronic conditions led to increased functional limitations (ie, limited physical ability, decrease social skills, sensorineural deficits, and growth, development, or mental delay) in the ELBW group compared to controls (64 versus 20 percent).

As a result of the increased risk of chronic medical conditions and functional limitations, the ELBW group had greater compensatory dependence needs (48 versus 23 percent) including medication use, and need for help or equipment for walking, and other daily routine activities (eg, feeding, dressing, and washing). In addition, the ELBW group more frequently utilized services beyond those routinely required by children (65 versus 27 percent). These included acute care visits to health care professionals, and special school arrangements or an individualized education program.

Moderately LBW infants (birth weight between 1500 to 2499 g) are also more likely than normal birth weight infants to have special health care needs (eg, use of medical services and/or medication), chronic conditions (eg, intellectual disability [mental retardation], cerebral palsy, or asthma), learning disabilities, and/or attention-deficit or attention deficit hyperactivity disorders [9].

SOCIETAL COST — If preterm delivery could be avoided, there would be tremendous savings to society worldwide [10-15]. This is demonstrated by the following studies in several different developed countries:

- Sweden — In a Swedish cohort study based upon 2002 data from the National Board of Health and Welfare and Statistics Sweden registers of 522,310 young adults born between 1973 and 1979, decreasing gestational age was associated with a stepwise increase in disability rates in young adulthood, and a stepwise decrease in net salary and the likelihood of completing a university education [11]. Government economic assistance was provided to 13 percent of individuals born at 24 to 28 weeks gestation and 6 percent born at 29 to 32 weeks gestation. If preterm delivery could have been avoided, the 2002 estimated economic cost savings would have amounted to 65 million euros.
- Norway — In a population-based study of all infants who were born alive and without congenital anomalies in Norway between 1967 and 1983, adults born prematurely at a gestational age between 23 and 27 weeks compared to those born fullterm were more likely to have cerebral palsy (9.1 versus 0.1 percent), be mentally retarded (4.4 versus 0.4 percent), and receive a disability pension (10.6 versus 1.7 percent) [12]. Among adults without medical disabilities, the gestational age at birth was associated with the level of educational achievement, income level, receipt of Social Security benefits, and the ability to have a family but did not correlate with rates of unemployment or criminal activity.
- United States — In 2001, the estimated cost of preterm and low birth weight admissions in the United States was 5.8 billion dollars, which represented 47 percent of costs for all infant hospitalizations and 27 percent of all pediatric stays [13]. The annual costs associated with preterm birth in the United States was estimated to be 26 billion dollars [14]. This included the costs of the medical care of the infants, mothers, and expenditures for the long-term care of patients born preterm.
- England and Wales — Based upon 2006 estimates of the number of preterm births and the cost of medical care through the first 18 years of life in England and Wales, the total societal cost was estimated to be almost 3 billion pounds (4.6 billion dollars) at 2006 prices [15]. The mean incremental cost per child was about 23,000 pounds (\$35,500) and the cost increased with decreasing age with

estimated costs for a very preterm child of 62,000 pounds (\$96,000) and for an extremely preterm child 95,000 pounds or (\$147,000).

SUMMARY — Complications of prematurity are the underlying reasons for the higher rate of infant mortality and morbidity in preterm infants compared to full-term infants. The risk of complications increases with increasing immaturity. Thus, infants who are extremely premature, born at or before 25 weeks of gestation, have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for long-term morbidity.

- In preterm survivors, long-term neurodevelopmental disability is the major cause of morbidity. In addition, chronic medical problems including respiratory abnormalities and poor growth are common in preterm children resulting in frequent hospitalizations. (See "Long-term neurodevelopmental outcome of premature infants" and 'Chronic health issues' above and "Care of the neonatal intensive care unit graduate", section on 'Hospital readmissions' and "Care of the neonatal intensive care unit graduate", section on 'Common medical problems'.)
- Prematurity appears to have long-term effects upon adult health. Premature adults compared to those born full-term appear to have increases in insulin resistance and blood pressure, and a decrease in reproductive rate. (See 'Effect on adult health' above.)
- Because premature children have a high rate of chronic medical conditions including neurodevelopmental disabilities that result functional limitations, they commonly require additional health care and educational services beyond those routinely required by children. (See 'Long-term health and educational needs' above.)
- If premature birth could be avoided, there would be tremendous savings to society from reduced expenditures from the initial medical costs for care in the neonatal period and additional health and educational costs in childhood, and increase productivity in adulthood. (See 'Societal cost' above.)

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Perinatal mortality

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INTRODUCTION — Mortality rates in the perinatal period are used to evaluate the outcome of pregnancy and monitor the quality of perinatal (prenatal and neonatal) care. The perinatal mortality rate encompasses late fetal and early neonatal mortality.

TERMINOLOGY — The use of standard terminology facilitates comparisons of mortality rates among states and countries. Standard definitions for reporting reproductive health statistics are published by the National Center for Health Statistics (NCHS) (available at www.cdc.gov/nchs) [1] and in Guidelines for Perinatal Care, a joint publication of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice [2]. The following definitions are recommended and used in this review.

Live birth — The newborn shows signs of life after the delivery (ie, heartbeats, umbilical cord pulsations, breathing, or voluntary muscle movement). Heartbeats should be distinguished from transient cardiac contractions and breathing distinguished from fleeting respiratory efforts or gasps.

In the United States, the 2002 Born-Alive Infants Protection Act defined live birth as "the complete expulsion or extraction from his or her mother of that member, at any stage of development, who after such expulsion or extraction breathes or has a beating heart, pulsation of the umbilical cord, or definite movement of voluntary muscles regardless of whether the umbilical cord has been cut, and regardless of whether the expulsion or extraction occurs as a natural or induced labor, cesarean section, or induced abortion" [3].

Fetal death (stillbirth) — Death of the fetus occurs prior to expulsion or extraction from the mother. Fetal death is determined by no signs of life after delivery. Signs of life include heartbeats, umbilical cord pulsations, breathing, or voluntary muscle movement, as noted above. Heartbeats should be distinguished from transient cardiac contractions, and breathing from fleeting respiratory efforts or gasps. (See "Incidence, etiology, and prevention of stillbirth".)

NCHS reports fetal deaths that occur ≥ 20 weeks gestation. However, because birth weight can be more objectively and accurately measured than estimated gestational age, Guidelines for Perinatal Care and ACOG recommend that requirements for reporting fetal deaths should be based upon birth weight ≥ 500 g. This has not been adopted by all states or the NCHS [1,2,4]. (See 'Fetal death rate' below.)

Fetal death rate — The fetal death rate is the number of fetal deaths ≥ 20 weeks gestation that occur during a year divided by the sum of live births plus fetal deaths during the same year, and expressed per 1000 live births plus fetal deaths. NCHS defines late fetal death rate as the number of fetal deaths ≥ 28 weeks gestation during a year divided by the sum of live births plus late fetal deaths during the same year, expressed per 1000 live births plus late fetal deaths.

Neonatal death — Neonatal death is defined as an infant death occurring through 28 days of age. Early neonatal deaths occur within the first 7 days of birth, and late neonatal deaths occur between 8 and 28 days of age.

Neonatal mortality rate (NMR) — The neonatal mortality rate (NMR) is the number of neonatal deaths during a year, divided by the number of live births during the same year, expressed per 1000 live births.

Perinatal mortality rate (PMR) — The NCHS definition of perinatal mortality rate (PMR) is the sum of late fetal deaths plus early neonatal deaths (ie, deaths within the first seven days of birth) during a year divided by the sum of live births plus late fetal deaths during the same year, expressed per 1000 live births plus late fetal deaths.

Infant mortality rate (IMR) — The infant mortality rate (IMR) is the number of infant deaths less than one year of age (0 to 365 days of life) during a year, divided by the number of live births reported during the same year, expressed per 1000 live births.

COMPARISON OF MORTALITY RATES — Comparison of mortality statistics across states or countries is challenging for the following reasons:

- Differences in the definitions employed — In the United States, the minimum gestational age used to calculate fetal death is 20 weeks, and the postnatal days used to calculate PMR is 7 days [5,6]. In comparison, the minimum gestational age ranges from 16 to 28 weeks among European countries, and the perinatal period used to calculate PMR ranges from 7 to 28 postnatal days [5].
- Birth weight versus gestational age — Use of birth weight rather than gestational age may further limit some comparisons because birth weight data do not identify fetal growth restriction, which frequently compounds prematurity [7].
- Differences in birth and death registration — The process of birth and death registration varies considerably among countries, especially when infants are born very prematurely or die soon after delivery. Perinatal statistics are particularly unreliable in developing countries, and whenever a substantial number of births takes place outside of hospitals or birthing centers unattended by trained individuals. (See 'Prematurity' below.)

Other countries

Developing countries — In 2000, neonatal deaths accounted for 38 percent of all child deaths worldwide [8]. Almost all of the four million neonatal deaths (99 percent) occurred in developing countries. Poverty was strongly associated with NMR. NMR was almost 10 times greater in countries with moderate and low income than in high income countries (33 versus <4 deaths per 1000 live births). The highest NMR occurred in sub-Saharan Africa (over 45 deaths per 1000 live births), but the greatest absolute number of deaths occurred in south-central Asia. The main causes of death were prematurity (28 percent), infection (26 percent), and perinatal hypoxic insult (23 percent).

In a population-based study performed in Bangladesh, maternal complications during labor increased NMR five-fold and accounted for 30 percent of deaths [9]. Complications included prolonged or obstructed labor, abnormal fetal position, and hypertensive disorders of pregnancy.

A systemic review and cost analysis identified 16 cost-effective interventions (eg, maternal folic acid supplementation, detection and treatment of mothers with asymptomatic bacteriuria, and antibiotics for preterm rupture of membranes) that would improve neonatal survival in developing countries [10]. This analysis provided a health system structure to implement these interventions at the family-community and individual patient level (pregnancy, delivery, and birth). With universal application, the study estimated that mortality rates would decrease by 59 percent.

Effect of prenatal diagnosis — Differences in the availability of timely/accurate prenatal diagnosis and pregnancy termination facilities, as well as population acceptance of termination of anomalous pregnancies can greatly influence regional PMR. In developed countries, timely and accurate prenatal diagnosis followed by termination of anomalous pregnancy can decrease PMR up to 50 percent. This was demonstrated by a large screening prenatal ultrasound trial in Finland that reported a 50 percent reduction in PMR for pregnancies in

women who were randomly selected to receive ultrasound screening between 16 and 20 weeks gestation compared to controls who received standard of care (4.6 versus 9 percent) [11,12].

In a birth cohort study of all live births, stillbirths, and infant deaths in Canada for the years 1991 to 1998, IMR decreased about 15 percent from the time period between 1991 to 1995 (range 6.1 to 6.4 percent) and 1996 to 1997 (range 5.4 to 5.5 percent), while fetal deaths caused by pregnancy termination increased [13]. Over this time period, infant deaths from congenital anomalies declined from 1.9 to 1.5 percent.

PERINATAL AND NEONATAL MORTALITY RATES — In the United States, the PMR has declined consistently by 25 percent with reported rates of 9 to 6.7 deaths per 1000 live births in 1990 and 2003, respectively (figure 1 and figure 2). Since 2003, the PMR has not significantly changed and was 6.64 per 1000 live births in 2005 [1,14] despite an evolving obesity epidemic, delayed childbearing with increasing use of assisted reproduction technologies, and higher prevalence of hypertensive and diabetic disorders of pregnancy. Over forty years, the neonatal mortality rate (NMR) has also declined to its current level of 4.4 per 1000 live births.

Major factors that influence mortality rates include ethnicity, gestational age, and multifetal pregnancies.

Ethnicity — The relative disparities in perinatal and neonatal mortality among different racial/ethnic populations have not substantially changed overtime. The PMR for black infants was 2.3 times that of white infants in 2005 (12.2 versus 5.4 percent) [15], and the infant mortality rate (IMR) was similarly higher in 2004 (13.6 versus 5.7 percent) (figure 3) [16]. The PMR in 2005 for Hispanic infants was 5.9 percent, and the IMR in 2004 was 7.8 for Puerto Rican infants and 5.5 for Mexican infants.

The racial disparity is explained largely by the higher incidence of prematurity in blacks. In 2007, the percentages of live births in the United States that were preterm by ethnicity were 18.3, 12.3, and 11.5 in non-Hispanic blacks, Hispanics, and non-Hispanic whites, respectively [14].

Gestational age

Term pregnancies — The NMR varies with estimated gestational age at delivery among term pregnancies. This was illustrated by a review of linked live birth-infant death files compiled by the United States NCHS of singleton term infants [17]. In the main study sample of non-Hispanic white infants born at 37 to 41 weeks gestation between 1995 and 2001, the NMR had a U-shaped relationship with advancing gestational age: NMR decreased with increasing gestational age from 37 to 39 weeks, remained stable from 39 to 40 weeks gestation, and increased ≥ 41 weeks gestation.

In a large Swedish population-based study of 656,134 singleton pregnancies between 1987 and 1997, the time point when the rate of fetal death exceeded the NMR was identified as 40 weeks and 3 days, thus providing a functional definition of prolonged pregnancy [18].

Prematurity — Prematurity is a major contributor to neonatal and infant mortality. PMR and NMR increase with decreasing gestational age in premature infants (gestational age <37 weeks). (See 'Low birth weight' below and "Incidence and mortality of the premature infant", section on 'Mortality'.)

The NMR of extremely low birth weight infants (ELBW) with birth weights <750 g may be underreported. This was illustrated by a report that demonstrated the deaths of 7 percent of ELBW infants that died in Ohio between January and June of 2006 were not registered [19]. The failure to register deaths was attributed to the short lifespan of these infants, resulting in the potential for their deaths to be misclassified as fetal deaths, thereby falsely lowering the early NMR and increasing the late fetal death rate.

Multifetal pregnancies — Multiple births accounted for 33.7 per 1000 live births in the United States in 200. Between 1980 and 2007, the twin birth rate increased by 70 percent (from 18.9 to 32.2 per 1000 live births) [20]. Higher-order multiple gestations quadrupled between 1980 and 1998 (0.37 to 1.8 percent) but decreased by 21 percent from 1998 to 2006 [1].

The increased rate of multiple births is associated with the related trends of delayed childbearing and increased use of ovulation-inducing drugs and assisted reproductive technologies [21,22]. This trend is especially prominent in women ≥ 30 years of age and in non-Hispanic whites [23].

Multiple gestation is a strong risk factor for neonatal mortality. This was illustrated in an analysis of the 1989 to 1991 and 1999 to 2001 United States linked birth/infant death data sets [24]. Although the overall infant mortality rate (IMR) decreased during the two epochs, IMR increased with plurality as follows:

- Singletons (6 to 5 per 1000 live births)
- Twins (29 to 20 per 1000 live births)
- Triplets (69 to 47 per 1000 live births)
- Quadruplets/quintuplets (120 to 94 per 1000 live births)

A high proportion of multiple births (approximately one-half of twins, and the majority of triplets, quadruplets, and quintuplets) are preterm or LBW, which contributes to the higher mortality rate [25]. They also are at higher risk for birth defects [26]. (See "Antepartum issues in management of twin gestations".)

The risk of infant mortality in twin births is increased by young maternal age, in contrast to the U-shaped relationship with age that occurs in singleton births. In a retrospective cohort study in the United States during three epochs (1985 to 1986, 1990 to 1991, and 1995 to 1996), the infant mortality rate for twin births was 7, 2.7, and 2.0 percent for women <20 years, 30 to 34 years, and 40 to 49 years of age, respectively [27]. Neonatal mortality was slightly elevated in the younger mothers. Postneonatal infant mortality (28 to 365 days) was most affected.

CAUSES OF FETAL DEATH (STILLBIRTH) — Approximately one-third of fetal deaths remain unexplained [28]. In the remaining two-thirds of fetal deaths, identifiable causes include:

- Fetal (eg, structural defects, syndromes, and aberrant growth)
- Placental (eg, abruption, large chorioangiomas, hypertensive disorders of pregnancy)
- Maternal (eg, acute chorioamnionitis, diabetes mellitus, rheumatologic disorders)

Maternal factors that increase the risk of fetal death include extremes of maternal age, unmarried status, smoking, prior stillbirth, and prior multiple gestation [29,30]. Black race is a strong confounding factor. In the report noted above of fetal death and linked infant birth-death certificate data for 1995 to 1998, blacks had twice the perinatal mortality rate (PMR) and a higher ratio of late fetal to neonatal deaths compared to whites [31]. This difference persisted even when rates were adjusted for socioeconomic status and medical complications.

From 1980 to 1998, the United States fetal death rate decreased by 26.4 percent (9.1 to 6.7 per 1000 live births plus late fetal deaths) [25]. From 1994 to 2005, the early fetal death rate has remained stable at 3.2 per 1000 live births plus late fetal deaths, while the late fetal death rate has declined from 4.3 to 3.1 per 1000 live births plus late fetal death [1,15,25]. This decline is likely related to the widespread use of prenatal sonography, biophysical profile and umbilical artery velocimetry in high-risk pregnancies, improved management of gestational disorders (eg, diabetes mellitus and hypertension), decreasing TORCH infections and fetal anemia, and the practically universal use of continuous intrapartum fetal heart rate monitoring [29,32].

Causes and management of fetal deaths are discussed in greater detail separately. (See "Incidence, etiology, and prevention of stillbirth".)

CAUSES OF INFANT DEATH — In 2008, the five leading causes of infant death in the United States were as follows [20]:

- Congenital malformations or chromosome abnormalities — 20 percent
- Low birth weight or prematurity — 17 percent
- Sudden infant death syndrome (SIDS) — 8 percent
- Neonatal death due to maternal complications — 6 percent

- Unintentional injuries — 4 percent

Among term infants, the major causes of neonatal death were asphyxia and infection, and in postneonatal infancy, SIDS [17].

Other causes of neonatal death include pregnancy complications (6.1 percent), respiratory distress (3.4 percent), placental complications (3.4 percent), bacterial sepsis (2.7 percent), diseases of the circulation (2.4 percent), and fetal hypoxia and perinatal hypoxic events (2.1 percent). Other causes make up 31.6 percent of deaths.

With improved perinatal care, neonatal deaths caused by fetal hypoxia and perinatal hypoxic events have decreased substantially in the United States (71.5 and 85.2 percent, respectively, from 1979 to 1997) [32,33]. Substantial reduction in the number of deaths caused by prematurity has been associated with increased use of antenatal glucocorticoids and the availability of surfactant treatment of respiratory distress syndrome. (See "Antenatal use of corticosteroids in women at risk for preterm delivery" and "Overview of neonatal respiratory distress: Disorders of transition".)

In China, the neonatal mortality rate has fallen from 34 to 10.2 deaths per 1000 live births, and the postnatal infant (1 to 11 months of age) mortality rate from 53.5 to 14.9 deaths per 1000 live births from 1990 to 2008 [34]. In 2008, the proportional contribution of causes of neonatal deaths included the following:

- Birth asphyxia — 29 percent
- Other (eg, tetanus, intracranial hemorrhage, accidents, scleroderma, accidental asphyxia, and meningitis) — 27 percent
- Prematurity — 26 percent
- Congenital anomalies — 10 percent
- Infections (ie, sepsis, diarrhea, and pneumonia) — 6 percent

The proportional contribution of causes of postnatal infant deaths included the following:

- Pneumonia — 47 percent
- Congenital abnormalities — 16 percent
- Sudden infant death syndrome — 12 percent
- Diarrhea — 9 percent
- Accidents — 7 percent
- Other (birth asphyxia, neonatal sepsis, prematurity) — 9 percent

Low birth weight — Birth weight is a major determinant of neonatal morbidity and mortality (figure 4). Low birth weight includes infants with fetal growth restriction and those born preterm.

The proportion of deaths associated with prematurity likely is greater, as other attributed causes (eg, respiratory distress, hemorrhage, and necrotizing enterocolitis) primarily affect this population. This was illustrated in an analysis of the 2002 United States linked birth/infant death file, which contains information from birth and death certificates for all infants born in 2002 who died during the first year of life [35]. Results from this study demonstrated that 34 percent of the 22,273 infant deaths that occurred in 2002 were attributable to prematurity. Of these 9596 deaths, 95 percent occurred in infants ≤ 32 weeks gestation with birth weights ≤ 1500 g, and two-thirds of the deaths occurred during the first 24 hours of life. (See "Incidence and mortality of the premature infant".)

The mortality rates of preterm infants and limit of viability are discussed in greater detail separately. (See "Incidence and mortality of the premature infant".)

Regional differences — Regional differences exist in the United States in the incidence of perinatal mortality and neonatal deaths [20]. Neonatal mortality also may differ among local institutions, even when adjustments are made for prematurity rates. These differences may be due in part to specific characteristics of newborn care, and

suggest that infants at high risk should be delivered in hospitals with tertiary level neonatal intensive care units (NICU). This was illustrated by two studies [36,37].

- In a report from the Canadian Neonatal Network, risk-adjusted outcomes were compared in infants born ≤ 32 weeks gestation and admitted to 17 NICUs in Canada during 1996 and 1997 [37]. Infants born outside of tertiary care centers who required transfer to a NICU were at greater risk of death (adjusted odds ratio 1.7, 95% CI 1.2-2.5) and other adverse outcomes compared to inborn infants.
- In a report that evaluated outcomes of infants with birth weight < 2000 g born in 1992 and 1993 in California, survival was more likely with birth at a regional center [36]. Risk-adjusted mortality was higher when infants were born in hospitals with no NICU (odds ratio 2.38, 95% CI 1.81-3.13), an intermediate NICU (odds ratio 1.92, 95% CI 1.44-2.54), or a small community NICU with average census < 15 (odds ratio 1.42, 95% CI 1.14-1.76) compared to hospitals with a regional NICU (average census of ≥ 15 patients and availability of tertiary care).

The availability of neonatologists likely affects neonatal mortality. In a study of the relationship of the distribution of neonatologists and neonatal death, the supply of specialized services varied across regions and was not consistently related to improved outcome, even after adjustment for the numbers of extremely low birth weight infants (birth weight < 1000 g) [38]. The risk-adjusted mortality rate was lower in regions with 4.3 compared to 2.7 neonatologists per 10,000 live births (odds ratio 0.93, 95% CI 0.88-0.99); additional increases did not further reduce the risk of death, suggesting that the supply of neonatologists in most regions was adequate or possibly excessive, and inadequate in some. However, the effect of the regional distribution of neonatologists on proliferation of smaller NICUs (associated with higher mortality) or on neonatal morbidity is unknown.

Congenital anomalies — Congenital malformations, including syndromes and chromosomal abnormalities, account for approximately 20 percent of neonatal deaths. These conditions are associated with higher rates of fetal death, preterm birth, and fetal growth restriction. Congenital anomalies occur in 3 percent of live born infants. (See "Genetic and environmental causes of birth defects" and "Cytogenetic abnormalities in the embryo, fetus, and infant".)

Timely and accurate prenatal diagnosis can reduce morbidity and mortality from congenital anomalies by modifying perinatal management. More importantly, timely and accurate prenatal diagnosis of fetal structural defects, followed by termination of anomalous pregnancies, substantially decreases the NMR. (See 'Effect of prenatal diagnosis' above.)

Other factors — Other maternal characteristics are associated with increased neonatal mortality, and are similar to risk factors for fetal death. These include age less than 20 years or more than 40 years, late or no prenatal care, unmarried status, smoking, and lower education level [39].

SUMMARY — Mortality rates in the perinatal period are used to evaluate the outcome of pregnancy and monitor the quality of perinatal (prenatal and neonatal) care.

- The use of standard terminology facilitates comparisons of mortality rates among states and countries. Standard definitions for reporting reproductive health statistics are published by the National Center for Health Statistics (NCHS) (available at www.cdc.gov/nchs). (See 'Terminology' above.)
- Comparison of mortality rates across states or countries is challenging because different definitions are often used, and there are regional differences in the level of perinatal care, the availability of prenatal diagnosis and pregnancy termination facilities, and societal acceptance of termination of anomalous pregnancies. Neonatal mortality rates are almost 10 times greater in countries with moderate and low income than in high-income countries. (See 'Comparison of mortality rates' above and 'Regional differences' above.)
- In the United States, the perinatal mortality rate (PMR) declined to 6.7 per 1000 live births plus late fetal deaths in 2003, and has remained stable through 2005 (figure 1). Neonatal mortality rates are higher in infants who are non-Hispanic black infants, premature, at or greater than 40 weeks 3 days gestation, or a product of a multifetal pregnancy. (See 'Perinatal and neonatal mortality rates' above.)
- The etiology of fetal death can be divided into fetal (eg, structural defects, syndromes, and aberrant growth), placental (eg, abruption, hypertensive disorders of pregnancy), and maternal causes (eg, acute

chorioamnionitis, diabetes mellitus, rheumatologic disorders). However, one-third of fetal deaths remain unexplained. (See 'Causes of fetal death (stillbirth)' above.)

- The majority of infant deaths are attributed to congenital malformations or chromosome abnormalities, low birth weight or prematurity, sudden infant death syndrome, maternal complications, unintentional injuries, and complications of the placenta, cord, or membranes. (See 'Causes of infant death' above.)

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Apparent life-threatening event in infants

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INTRODUCTION — An apparent life-threatening event (ALTE) is not a specific diagnosis but a description of an acute, unexpected change in an infant's breathing behavior that is frightening to the caretaker and that includes some combination of the following features [1]:

- Apnea — usually no respiratory effort (central) or sometimes effort with difficulty (obstructive)
- Color change — usually cyanotic or pallid but occasionally erythematous or plethoric
- Marked change in muscle tone (usually limpness or rarely rigidity)
- Choking or gagging

In some cases, the observer fears that the infant has died. Recovery occurs only after stimulation or resuscitation. However, episodes are often mislabeled as "ALTEs" even when a parent reports that the child resumed normal breathing after simply being picked up and patted.

After early anecdotal reports of deaths from sudden infant death syndrome (SIDS) in infants with recurrent apnea [2], enormous amounts of attention, research, and clinical resources were focused on the problem of ALTE in infants. Although various cardiorespiratory, autonomic, and neurophysiologic differences have been demonstrated in ALTE infants as a group, these findings have NOT distinguished individual ALTE infants from normal controls nor provided premortem markers for the risk of SIDS [3]. ALTE infants represent a heterogeneous group of patients of varying ages with diverse pathophysiology. As a result, appropriate evaluation and management should be individualized. (See "Sudden infant death syndrome".)

DEFINITION AND EPIDEMIOLOGY — It is important to recognize that ALTE is not a specific diagnosis; rather, it describes a "chief complaint" that brings an infant to medical attention. The term ALTE was coined by the 1986 National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring. ALTE replaced misleading terms, such as "near-miss SIDS" or "aborted crib deaths", that implied a direct association between these symptoms and SIDS [1]. The potential for over-diagnosis is substantial, since the case definition depends upon the observations of frightened, medically untrained caretakers [4]. The incidence of ALTEs is estimated to be 0.05 to 1 percent in population-based studies [5-8].

Lack of causal relationship between ALTE and SIDS — An association between SIDS and ALTE had been suggested because of prior ALTE events in 5 percent of SIDS victims [9] and early anecdotal reports of SIDS in infants with recurrent apnea [2]. However, the vast majority of SIDS victims do not experience apnea prior to death. Furthermore, studies over the past two decades have failed to confirm a causal relationship between preexisting apnea and SIDS. Several other factors argue against a relationship between SIDS and ALTE:

- ALTE refers to a heterogeneous group of problems ranging from benign to near-fatal, whereas SIDS denotes a fatal problem.
- The case definition in ALTE depends upon parental observations, which have been shown to be unreliable in several studies [4,10-14].
- Over 80 percent of SIDS deaths occur between midnight and 6 AM [15], whereas 82 percent of ALTE episodes occur between 8 AM and 8 PM [16].
- Interventions to prevent SIDS (eg, supine sleeping) have not resulted in a decreased incidence of ALTE [17]
- The risk factors for SIDS and ALTE differ [18,19]. In one prospective population-based study, prone sleeping, lack of breast feeding, and maternal smoking were risks for SIDS, whereas behavioral characteristics (eg, repeated apnea, pallor, history of cyanosis, and feeding difficulties) were risk factors for ALTE [17].

ETIOLOGY — A specific cause for the ALTE can be identified in over one-half of patients after a careful history, physical examination, and appropriate laboratory evaluation (table 1) [20]. Gastroesophageal reflux, neurologic problems (such as seizures or breath-holding spells), and infection account for the greatest number of ALTE-type episodes [21].

- Gastroesophageal reflux is frequently invoked to describe feeding-associated events, and is diagnosed in approximately 30 percent of infants presenting with an ALTE. However, there is little evidence that this represents pathologic reflux or that the events can be prevented by treatment for reflux, as discussed below. (See 'ALTE and gastroesophageal reflux' below.)
- A central nervous system disorder (most presenting as seizures, but ventricular hemorrhage or hydrocephalus were found in some) was ultimately diagnosed in 15 to 20 percent of infants with an ALTE presentation (data from two case series) [22,23].

- Less frequent causes are cardiac disease, upper airway obstruction, metabolic disorders, anaphylaxis, and other miscellaneous conditions.
- Accidental or intentional poisoning may be responsible for a small number of ALTE in some populations. In one institution, toxicology screens were performed in nearly half of the infants evaluated for ALTE. Of 274 results, 8 percent revealed clinically significant ingestions. Five percent of the infants screened positive for over-the-counter cold medications, although none of the parents admitted to administering these [24]. However, the extent to which the ingestion may have contributed to the ALTE is uncertain.
- The remaining cases are considered idiopathic if no cause can be identified after a thorough assessment.

ALTE and gastroesophageal reflux — Recurrent vomiting or regurgitation occurs commonly in patients with apparent life-threatening events (ALTE), but also in healthy infants. An association between reflux and apnea or bradycardia has not been demonstrated convincingly [25-27]. As a result, the role of reflux in infants with ALTEs is uncertain. Even when an episode of gastroesophageal reflux appears to have immediately preceded the ALTE, the direct cause of the respiratory event is probably laryngospasm. The reflux may have triggered the laryngospasm, but this does not mean that it is pathologic or that treatment of reflux will prevent future ALTEs [28,29]. Laryngospasm also may occur during feeding in the absence of gastroesophageal reflux.

Esophageal pH monitoring may be useful in the evaluation but only if an apparent event occurs while monitoring and can be temporally associated with a preceding episode of reflux by using simultaneous polysomnography or continuous oxygen saturation monitoring. Barium esophagrams are neither sensitive nor specific for detecting pathologic gastroesophageal reflux in infants. (See "Gastroesophageal reflux in infants", section on 'Diagnostic tests'.)

ALTE is more likely to be related to reflux, and the infant is therefore more likely to respond to antireflux therapy when:

- Gross emesis or oral regurgitation occurs at the time of the ALTE.
- Episodes occur while the infant is awake and supine.
- ALTE is characterized by obstructive apnea.

In infants with these characteristics, low-risk medical interventions (eg, thickening of feeds, trial of a milk-free diet, acid suppression, and possibly prokinetic agents) may be used, but these interventions should not replace or delay an evaluation for other causes of ALTE [29]. Because a causal association between reflux and ALTE rarely is established with certainty, and because the overall risk for death in these infants is low, invasive approaches such as antireflux surgery are rarely appropriate for this type of patient. (See "Gastroesophageal reflux in infants", section on 'Treatment options'.)

Feeding difficulties may be associated with ALTE even in the absence of gastroesophageal reflux. In a study of infants evaluated for ALTE in Austria, feeding difficulties were associated with a more than two-fold increase in ALTE events (multivariate relative risk 2.5, 95% CI 1.3-4.6) [17].

ALTE and child abuse — When an infant suffers recurrent, severe ALTE events requiring cardiopulmonary resuscitation (CPR) that occur only in the presence of a single caretaker, and a thorough diagnostic evaluation reveals no reasonable explanation for these dramatic repetitive events, then the diagnosis of intentional suffocation (Munchausen syndrome by proxy, a form of child abuse) must be considered.

In these cases, the deceptive parent (usually the mother) appears to be a dedicated caretaker [30-34]. This parent often has a health care employment background and a personal history of unusual illnesses. Extraordinary illnesses or SIDS may have occurred in previous siblings. A large case series of patients diagnosed with covert video surveillance provides a shocking chronicle of historical markers and clinical observations in infants who suffer life-threatening child abuse from intentional suffocation [34]. (See "Munchausen syndrome by proxy (medical child abuse)".)

Abusive head injury is another form of child abuse that must be considered in infants with ALTE. In a prospective series of 243 infants (<12 months) admitted to a tertiary care medical center for evaluation of ALTE, six (2.5 percent) were diagnosed with abusive head injuries, two of whom died in the hospital [35].

The presence of physical findings such as facial injury or bruising or a bulging anterior fontanel should prompt a thorough evaluation for abusive head injury. In a series of infants evaluated at a single center for ALTE, other factors that suggest abusive head injury include recurrent episodes of ALTE, vomiting or unexplained irritability, and a call by the caretaker to Emergency Medical Services (911) [36]. If abusive head injury is suspected, further investigation should include neuroimaging and dilated fundoscopic examination. (See "Epidemiology, mechanisms, and types of abusive head trauma in infants and children".)

Retinal hemorrhages are associated with ALTE from abusive head trauma, but not other causes of ALTE. For example, an observational study of 108 children two years of age and younger admitted for an ALTE found that none had retinal hemorrhages on indirect ophthalmoscopy performed by an ophthalmologist [37].

DIAGNOSTIC EVALUATION — The diagnostic evaluation of the infant who presents with ALTE includes a thorough history and examination with additional testing directed by the findings of the initial clinical assessment. In a series of infants admitted to a tertiary center with ALTE, the diagnosis was made on the basis of the history and physical examination alone in 21 percent of cases, and confirmed with testing prompted by the history and physical examination in an additional 49 percent [38]. Furthermore, 18 percent of the tests ordered were positive, and only 6 percent contributed to the diagnosis.

If the detailed description of the event suggests that the child was physiologically compromised, then in-hospital observation with cardiorespiratory monitoring is indicated.

History — The most important diagnostic tool is a detailed description of the event and intervention obtained from the caretaker who witnessed the episode and any emergency personnel involved in the case. The key elements in the history are summarized in the table (table 2). With this information, the physician can determine whether the episode was truly life-threatening or merely frightening, a key factor in subsequent management decisions.

In addition, the history should include information about the pregnancy and perinatal period, the infant's usual behavior, sleep and feeding habits, a family history (including a history of siblings with ALTE, early deaths, genetic, metabolic, cardiac, and neurologic problems), a social history (including the presence of smoking, alcohol or substance use in the home, and a list of medications in the home) [14]. The family should be asked specifically about the possibility of accidental or intentional administration of poisons or medications, including over-the-counter cold preparations [24]. Such information may help in defining an etiology for the event (eg, heritable metabolic disease, unintentional or intentional ingestion).

Specific characteristics of the history that might suggest an association with gastroesophageal reflux are discussed separately. (See 'Management' below and 'ALTE and gastroesophageal reflux' above.)

A history of previous episodes of ALTE should particularly prompt consideration of abusive head trauma. (See 'ALTE and child abuse' above.)

Examination — Infants presenting with an ALTE should undergo careful physical examination, with particular attention to abnormalities in the neurologic, respiratory, and cardiac systems [39]. The examination should include:

- Measurement of height, weight, and head circumference and comparison of these values to standards for age and sex
- Measurement of vital signs
- Examination for physical signs of trauma (bruising, bulging anterior fontanel)
- Developmental assessment
- Evaluation for upper airway obstruction, including assessment of facial dysmorphism [40,41]

A dilated funduscopic examination should be considered [35,42], particularly if abusive head trauma is suspected. (See 'ALTE and child abuse' above.)

Initial evaluation — If the history and physical examination suggest that the event was not life-threatening, or if a probable explanation for the event is identified (eg, transient laryngospasm after an episode of gastroesophageal reflux), then no laboratory evaluation may be required. In some cases, a limited evaluation is performed to confirm the suspected diagnosis.

When the event is judged to be truly life-threatening and an explanation for the ALTE is not apparent based on the history and physical examination, the initial laboratory evaluation usually (but not necessarily) includes a complete blood count, urinalysis, plasma concentrations of glucose, electrolytes, blood urea nitrogen (BUN), calcium, magnesium, chest radiograph, and electrocardiogram. In addition, particularly if the infant has a change in sensorium, a toxicology screen to detect accidental or intentional ingestions of poisons or medications, including over-the-counter cold preparations, may be of value [24].

Additional evaluation — Further specific diagnostic studies may be indicated in selected cases (table 3). The additional evaluation depends upon the presenting symptoms and findings in the history, examination, and initial evaluation [39,43,44].

In the consecutive series of 243 infants with ALTE described above [38], among 171 infants in whom a particular diagnosis was suggested by the history and examination, the following tests contributed to establishing the diagnosis:

- Blood counts, chemistries, and cultures
- CSF fluid analysis and cultures
- Metabolic screening
- Screening for respiratory pathogens
- Screening for gastroesophageal reflux
- Chest radiograph
- Brain neuroimaging
- Skeletal survey
- Electroencephalogram
- Echocardiogram
- Polysomnography

Among the 72 infants in whom the history and examination were noncontributory, only the following tests contributed to establishing the diagnosis [38]:

- White blood cell count
- Screening for gastroesophageal reflux
- Urine analysis and culture
- Brain neuroimaging
- Chest radiograph
- Polysomnography

Consultation with a specialist in infant apnea and developmental aspects of respiratory control can be useful. Polysomnography may be helpful in the evaluation of on-going respiratory, cardiac, and neurologic dysfunction during sleep. Some authors believe that it can contribute to the prediction of subsequent ALTE [45,46], but it cannot predict the risk for future ALTE episodes or SIDS [47].

Multi-channel polysomnography typically includes [39]:

- An EEG to evaluate the sleep-wake state of the infant
- Measurement of thoracic and abdominal wall movement to evaluate breathing patterns and apnea characteristics (if present)

- Electrocardiogram sensors to evaluate heart rate
- Oximetry to measure oxygen saturation during sleep and after apnea
- Airflow changes (using thermistors that sense alterations in heat exchange or an end-tidal CO₂ monitor)
- Esophageal pH monitoring can be added when a temporal relationship between gastroesophageal reflux and apnea is strongly suspected

Multichannel polysomnograms are to be distinguished from two-channel "pneumograms", which should not be used in the evaluation of ALTE. "Pneumograms" provide continuous 12 to 24 hour recordings of chest movement and heart rate but provide no data on oxygenation or airway obstruction.

For infants with a history of recurrent difficulties while feeding (eg, observations of choking or repeated ALTEs) a videofluoroscopic swallowing study may be useful to evaluate for swallowing dysfunction.

MANAGEMENT — The history of ALTE must be taken seriously, even if the infant appears entirely well by the time he or she is evaluated. The apparent well-being should not be considered evidence that a potentially life-threatening event with successful resuscitation did not occur if the clinical history indicates otherwise.

In-hospital observation with cardiorespiratory monitoring is indicated for infants whose initial evaluation (whether by history, examination, or other diagnostic studies) suggests physiologic compromise. A brief period of in-hospital observation and monitoring immediately after an ALTE may provide important clinical information:

- Additional episodes may be witnessed by medical personnel. In one case series, the occurrence of documented in-hospital events during the initial investigation period increased the likelihood of additional events at home, especially in the first month after the initial event [14].
- Serious, underlying medical conditions (eg, hypoventilation or hypoxemia) may become apparent [43,44,48]. Documentation of apnea or bradycardia in association with clinical findings of inadequate respiratory effort, color change, or loss of tone will confirm the need for more specialized diagnostic studies (eg, extended Holter monitoring, esophageal pH monitoring, epilepsy monitoring, polysomnography, computed tomography or magnetic resonance imaging of the central nervous system, metabolic studies, or more invasive studies such as bronchoscopy).

Medical or surgical treatment of an underlying disorder is possible in about 50 percent of ALTE cases if additional studies identify a specific cause of the ALTE [16,49]. Management of the remaining 50 percent of cases depends upon the clinical history and the identification of infants at potentially high risk for adverse events.

Risk factors for recurrence — Multiple studies have reported a high frequency of subsequent apnea in infants with idiopathic ALTE episodes. The clinical significance of these subsequent "alarm conditions" is questionable because of the high incidence (>90 percent) of false apnea alarms on home monitors and the unreliability of parental observations [4,10-14]. As an example, 90 percent of parents report repeated alarms, but only 10 percent of children with an ALTE history have additional events that are considered clinically significant [16].

Risk factors for clinically significant recurrences include immaturity, a history of multiple ALTE preceding the hospital admission, and a viral respiratory tract infection, as illustrated by the following studies:

- A study of 59 infants presenting to an emergency department with an ALTE sought to identify characteristics that predicted recurrence and, therefore, required hospital admission [50]. Eight of these infants subsequently had serious events that required inpatient management (including apnea, infection, or seizures). All eight infants were either younger than one month of age or had a history of multiple ALTE during the 24 hours prior to admission. Although this study is small and lacks external validation, it suggests these may be useful characteristics for identifying infants at high risk.
- In another study of 625 infants admitted because of an ALTE, 7.4 percent had recurrence with an extreme event (defined as central apnea lasting more than 30 seconds, or extreme bradycardia or oxygen desaturation <80 percent lasting more than 10 seconds) [51,52]. In most cases, the event occurred within 24 hours of the hospital admission. The main risk factors for recurrence with an

extreme event were viral respiratory tract infection, postconceptional age under 43 weeks, or history of prematurity (even if postconceptional age >43 weeks).

General recommendations — The caregivers of infants who have had an ALTE should receive training in standard cardiopulmonary resuscitation (CPR) for infants [39]. They should also be instructed in safe infant care practices including supine sleep position with face free, safe sleeping environments (avoiding adult or loose bedding, excessive clothing, extreme room temperatures), and elimination of prenatal and postnatal exposure to tobacco smoke [39]

Home monitoring — The diverse characteristics of infants with a history of ALTE preclude universal policies regarding the use of home CR monitoring [53]. The decision should be made on a case-by-case basis after considering with the family the potential benefits, uncertainties, and stresses involved.

Studies of infants with a history of ALTE but who are otherwise asymptomatic have failed to demonstrate a therapeutic benefit of home CR monitoring. However, in selected cases, monitor recordings may provide some diagnostic value, or may provide reassurance that clinically important events are not occurring. Providers and families should recognize that currently available home monitors only detect chest wall movement and heart rate. For some infants, particularly those in whom obstructive apnea is suspected, monitoring oxygen saturation by pulse oximetry may be a more appropriate physiologic signal to monitor. These issues are discussed in more detail in a separate topic review. (See "Use of home cardiorespiratory monitors in infants".)

PROGNOSIS — ALTEs that occur in infants with a history of prematurity usually represent an immaturity of respiratory control and generally resolve with maturation. In a longitudinal cohort study of 1079 infants, cardiorespiratory events recorded on home monitors were compared in healthy term infants, term infants with idiopathic ALTE, preterm infants with idiopathic ALTE, term siblings of SIDS victims, preterm siblings of SIDS victims, symptomatic preterm infants, and asymptomatic preterm infants [52]. Conventional alarm events were common among all groups, but only preterm infants were at increased risk of extreme alarm events, and these events disappeared once those infants reached 43 weeks postconceptional age. (See 'Risk factors for recurrence' above.)

Death — The overall risk of subsequent death in ALTE infants is estimated to be less than 1 percent [3], but the heterogeneity of the underlying conditions that present as apparent life threatening events limits the clinical usefulness of this estimate. Certain patient groups within the ALTE population are believed to have a greater mortality risk. Infants with recurrent ALTE requiring CPR have a very high risk of subsequent SIDS, ranging from 10 to 30 percent [54,55]. Unusual diagnoses, including metabolic diseases, neurodegenerative problems, or intentional suffocation, should be considered.

Long-term follow-up — The overall long-term outcome for "uncomplicated" ALTE infants is excellent. Controlled follow-up studies have reported a slight increase in subtle neurologic abnormalities at one to three years and an increased frequency of breath-holding spells; however, no differences were observed at 10 years [16,56,57].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics: (See "Patient information: Sudden infant death syndrome (SIDS)".)

SUMMARY AND RECOMMENDATIONS

- An apparent life-threatening event (ALTE) is not a specific diagnosis, but a description of abrupt changes in an infant's breathing, color, and state that are frightening to the caregiver. (See 'Definition and epidemiology' above.)
- Medical efforts should be focused on diagnosis of specific medical conditions for which specific treatments can be identified (table 1). Single events may never be adequately categorized. (See 'Etiology' above.)
- When ALTEs are recurrent and not explained by maturational delay (as in persistent apnea of prematurity), then an aggressive diagnostic approach, as outlined above, is required. (See 'Diagnostic evaluation' above.)

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Incidence and mortality of the premature infant

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INTRODUCTION — Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. It is associated with approximately one-third of all infant deaths in the United States. Infants born at or before 25 weeks of gestation have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for severe impairment [1].

The incidence and mortality rate of preterm birth will be reviewed here. The risk and pathogenesis of preterm birth and complications of prematurity are discussed separately. (See "Risk factors for preterm labor and delivery" and "Pathogenesis of spontaneous preterm birth" and "Short-term complications of the premature infant".)

DEFINITIONS — Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birthweight (BW).

One classification based upon BW includes the following categories (table 1):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

This classification based upon BW is primarily used in this review.

BW percentiles have been established for the appropriate GA (table 2).

Prematurity is also defined by gestational age (GA) as follows:

- Late preterm infants — GA between 34 weeks and 36 weeks and 6 days
- Very premature infants (VPT) — GA at or below 32 weeks

- Extremely premature infants (EPT) — GA at or below 25 weeks

INCIDENCE — Approximately 550,000 premature infants are born each year in the United States. In 2008, about 12.3 percent of all live births were <37 weeks GA and 2 percent <32 weeks GA (figure 1) [2,3]. Low birth weight (LBW) infants accounted for 8.2 percent of live births in both 2007 and 2008 [2].

In the United States, there has been a 21 percent rise in the overall proportion of preterm births since 1990, which peaked in 2006 with 12.8 percent of all live births born at a GA <37 weeks. This increase over the last two decades is reflected in all stages of prematurity as follows [2]:

- The birth rate of late preterm infants has risen by 25 percent since 1990. The percentage of late term birth peaked at 9.1 percent in 2006, and has slightly declined to 8.8 percent in 2008.
- The percentage of low birth weight (LBW) infants has increased in the United States from 6.7 percent in 1984 to 8.3 percent in 2006, and slightly declined to 8.2 percent in 2007 and 2008.
- The percentage of very low birth weight (VLBW) has increased from 1.2 percent in 1980 to 1.5 percent in 2006, and was unchanged in 2007 and 2008 .

In Norway, a population-based report of all live births in 1999 and 2000 reported an incidence of 0.5 percent of ELBW infants born between 22 and 27 weeks GA [4].

Multiple gestation and ART — In the United States, a major reason for the increased incidence of premature birth is the higher rate of multiple gestations in part due to assisted reproductive technology (ART). Infants of multiple gestation are prone to delivery early; half of all twin births and >90 percent of triplets are born premature. In 2007, 57 percent of twins and nearly all triplets (96 percent) were LBW [2].

- Twin births — In the United States, the twin birth rate reached a record high of 32.2 twins per 1000 total births in 2004, which has remained stable from 2004 to 2007. There has been a 70 percent increase in the twin birth rate from 1980 to 2004 [2].
- Higher-order multiple births — In contrast, the triplet and higher-order multiple births rate has declined 21 percent from a peak of 193.5 per 100,000 births in 1998 to 148.9 per 100,000 births in 2007 [2]. This is partly due to the American Society of Reproductive Medicine recommendation to limit the number of embryos transferred. (See "Multiple births" and "Strategies to control the rate of high order multiple gestation".)

Ethnicity — The incidence of premature births varies among ethnic groups. In 2007, the percentages of live births in the United States that were preterm by ethnicity were 17.5, 12.1, and 11.1 in non-Hispanic blacks, Hispanics, and non-Hispanic whites, respectively [2]. A higher rate of low birth weight infants in minority populations also occurs in England, with reported percentages of low birth weight live births of 11.5, 9.4, and 5.4 percent in Asian, black, and white mothers [5].

PATHOGENESIS FOR PRETERM BIRTH — Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3).

The four primary causes that lead to preterm labor and delivery are as follow and are discussed in detail separately. (See "Pathogenesis of spontaneous preterm birth".)

- Activation of the maternal or fetal hypothalamic-pituitary-adrenal axis
- Infection
- Decidual hemorrhage
- Pathological uterine distention

Risk factors for preterm birth — Risk factors associated with preterm labor and delivery include the following sociodemographic and obstetric factors, which are reviewed separately (table 4). (See "Risk factors for preterm labor and delivery".)

- Maternal reproductive factors such as history of preterm birth and maternal age. A U-shaped relationship exists between maternal age and the frequency of preterm birth. Women under 16 and those above 35 have a 2 to 4 percent higher rate of preterm birth compared with those between 21 and 24 years of age [6]. Among non-Hispanic black women, the upper age with an increased risk of preterm delivery is lower with preterm birth rates increasing at 27 to 29 years of age compared to 33 to 35 years of age for non-Hispanic white women.
- Maternal disorders such as infection, anemia, hypertension, preeclampsia/eclampsia, cardiovascular and pulmonary disorders, and diabetes.
- Maternal lifestyle issues such as physical activity, history of substance abuse or smoking, diet, weight, and stress.
- Cervical, uterine, and placental factors such as short cervix, cervical surgery, uterine malformations, vaginal bleeding, and placenta previa or abruption.
- Multiple gestation
- Fetal factors such as presence of congenital anomalies, growth restriction, fetal infections, and fetal distress.

MORTALITY — Low birth weight and prematurity are major contributors to infant mortality. In the yearly analysis from the National Center for Health Statistics that links all birth and infant deaths (through the first year of age) in the United States, birth weight less than 2000 g was associated with 61 percent of infant deaths in 2005 [1].

Factors that cause variation in premature mortality rates include:

- Degree of prematurity — Mortality rises with increasing immaturity (ie, decreasing birthweight and gestational age)
- Maternal ethnicity
- Level of neonatal care
- Congenital anomalies

Gestational age and birth weight — Mortality rates amongst premature infants correlate with birthweight and gestational age with decreases in both associated with poorer survival [1,4]. Thus infants born with the lowest gestational age and birthweight have the largest impact on infant mortality because they have the greatest risk of death. As an example, although infants who weigh less than 1000 g account for only 0.8 percent of births in the United States, they accounted for 55 percent of all infants deaths in 2005 [1].

In 2004, infant mortality rates per 1000 live births based upon birth weight were as follows (figure 2) [7]:

- 2500 g — 2.3
- < 2500 g — 56
- < 1500 g — 245
- < 500 g — 850

A similar relationship with increasing mortality rates per 1000 live births and decreasing gestational age (GA) was also noted:

- 37 to 41 weeks GA — 2.43
- 34 to 36 weeks GA — 7.3
- 32 to 33 weeks GA — 17
- Less than 32 weeks — 183

Mortality data for infants born at or below 25 weeks gestation who are at the limit of viability are reviewed separately. (See "Limit of viability".) Overall, more than two-thirds of infant deaths occur during the neonatal period defined as less than 28 days of age. The risk of dying within this neonatal period increases with decreasing gestational age. In addition, lower birth weights due to fetal growth restriction increase mortality at a given gestational age in premature infants born at or below 31 weeks gestation [8]. (See "Small for gestational age infant", section on 'Mortality'.)

Extremely preterm infants — Although infants born at or before 25 weeks of gestation have the highest mortality rate, about 50 percent [9-11], it appears that the survival rate of infants between 24 and 26 weeks gestation has improved with advances in neonatal care [10,11]. (See 'Trends over time' below and "Limit of viability".)

Risk factors for death or severe neurosensory impairment in extremely low birth weight (ELBW) infants (birth weight less than 1000 g) include bronchopulmonary dysplasia, brain injury, severe retinopathy of prematurity, and infection (eg, meningitis, sepsis, and necrotizing enterocolitis) [12]. (See "Short-term complications of the premature infant" and "Long-term neurodevelopmental outcome of premature infants".)

Late preterm infants — Late preterm infants (born between 34 weeks, and 36 weeks and 6 days gestation) are an "at risk population" with a three to five-fold greater risk of mortality than term infants. The mortality of later preterm infants is discussed separately. (See "Late preterm infants", section on 'Mortality'.)

Ethnicity — Mortality rates of premature infants vary among ethnic groups as demonstrated by infant mortality data from the United States in 2004 (figure 3) [7]. The highest mortality rate is in black infants at any given gestational age or birthweight compared to other ethnic groups.

For example, the infant mortality rates per 1000 live births for premature infants with birth weights <1500 g (very low birth weight infants) based upon maternal ethnicity were as follows:

- Overall — 244.5
- White — 231.9
- Black — 274
- Asian or Pacific Islander — 222.7

Similar differences in infant mortality rate based upon gestational age were reported among ethnic groups. The infant mortality rates per 1000 live births for premature infants with gestational age <32 weeks based upon maternal ethnicity were as follows:

- Overall — 182.5
- White — 168.4
- Black — 216.2
- Asian or Pacific Islander — 173.2

Health care disparities may in part explain the higher mortality rate of black infants versus other ethnic groups [13].

Level of neonatal care — Variation in neonatal care impacts on mortality rate and include:

- Changes in care over time with the introduction of new therapeutic interventions and changes in management.
- Delivery of care based upon hospital resources and experiences.

Trends over time — Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality rates of preterm infants, except in those who are at the limit of viability [10,14-17]. (see "Antenatal use of corticosteroids in women at risk for preterm delivery", section on 'Evidence of clinical efficacy' and "Treatment and complications of respiratory distress syndrome in preterm infants" and "Limit of viability")

This was demonstrated by the improved survival rate for VLBW infants (birth weights between 500 and 1500 g) reported by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network over four time periods (74, 80, 84, and 85 percent in 1988, 1990 to 1991, 1995 to 1996, and 1997 to 2002) [14,15]. However, there was little change in the survival rate of infants with birth weights between 501 and 750 g (about 55 percent) from the time periods between 1995 to 1996, and 1997 to 2002 [15].

In a study of extremely premature infants defined as GA at or below 25 weeks born in the Trent region of Great Britain, survival rates were compared from 1994 to 1999 and 2000 to 2005 [10].

- Survival rates increased from 24 to 41 percent in infants with GA of 24 weeks and from 52 to 63 percent in those with GA of 25 weeks.
- There was no change in the survival rate of infants with GA of 23 weeks between the two study periods (18 versus 19 percent).
- None of the 261 infants at or below 22 weeks gestation survived to discharge from the hospital during the entire study period from 1994 to 2005.

A regional population-study of two birth cohorts separated by 20 years (1985 to 1986, and 2005 to 2006) also demonstrated increased survival without severe neurodevelopment impairment [16].

Standard of neonatal care — Survival rates for VLBW infants are higher in centers that deliver a high volume of VLBW infants and provide the highest level of neonatal care (ie, level 3 neonatal intensive care unit [NICU]), as illustrated by the following:

- In a study from California that linked birth and death certificate data from 48,237 VLBW infants born between 1991 and 2000 [18], the highest survival rates for VLBW were in hospitals that had a level 3 NICU and an annual delivery rate of VLBW infants greater than 100 deliveries. In comparison, the lowest survival rate occurred in hospitals with level 1 care (no NICU) and an annual delivery rate of VLBW infants less than 10 (OR 2.72, 95% CI 2.37-3.12).
- A meta-analysis of 41 articles including the above study demonstrated a risk-adjusted increased death rate for VLBW and VPT (gestational age ≤ 32 weeks) infants born at centers without a level 3 NICU compared with those born centers with a level 3 NICU [19]. Calculated risk-adjusted odds ratio based on data from studies determined to be of adequate or high quality demonstrated higher mortality rates for infants born in non-level 3 hospitals for VLBW (adjusted OR, 1.62, 95% CI, 1.44-1.83) and VPT infants (adjusted OR, 1.55; 95% CI, 1.21-1.98). Unadjusted pooled mortality rates comparing infants born at non-level 3 centers to those born at level 3 centers were 38 versus 23 percent in VLBW infants and 15 versus 17 in VPT infants. Subgroup analysis of ELBW infants demonstrated similar results with increased death rates for those born at a non-level 3 center for both unadjusted mortality (59 versus 32 percent) and calculated risk-adjusted odds ratio (adjusted OR 1.8; 95% 1.31-2.46).

These results support perinatal regionalization with maternal transport of women at-risk to deliver a VLBW infant to a center that delivers a high volume of VLBW infants and provides level 3 neonatal care.

In the United States, about three-quarter of VLBW infants are admitted to a NICU based on representative data from 19 states [20]. Data did not distinguish between infants admitted at the facility of birth and those who were transported to a NICU from another facility. Using multivariate analysis, preterm delivery, multiple births, and cesarean delivery were associated with a greater likelihood of NICU admission among VLBW infants.

Substandard neonatal care is associated with increased mortality. A case-control study of the Confidential Inquiry into Maternal and Child Health Program (CEMC) in Great Britain, which matched all neonatal deaths (excluding those due to lethal malformations) in infants born at 27 to 28 weeks gestation in the United Kingdom during a two year period (1998 to 2000) with randomly selected survivors, showed increased infant mortality was associated with substandard neonatal care and early neonatal factors including fetal compromise but not maternal characteristics [21]. Areas where poor neonatal care were associated with an increased risk of dying included:]

- Hypothermia — Infants who died were more likely to be hypothermic (temperature $\leq 36^{\circ}\text{C}$) on admission to the neonatal intensive care unit (NICU) (73 versus 59 percent).
- Substandard ventilatory and cardiovascular management — Infants who died compared to survivors received substandard ventilatory (20 versus 7 percent) and cardiovascular care (15 versus 7 percent). Substandard care was defined as a failure to monitor or properly document blood gases and/or blood pressure, and make therapeutic adjustment to maintain blood gases and/or blood pressure within standard limits.

Congenital anomalies — Premature infants with major congenital anomalies have higher mortality and morbidity rates. In a study from the NICHD Neonatal Research Network, ELBW infants with congenital anomalies (eg, cardiac, renal, central nervous system anomalies, and chromosomal abnormalities) who survived the first 12 hours of life compared to those without any congenital abnormality had a higher mortality rate in the first 18 to 22 months of corrected age [22]. Premature survivors with major congenital anomalies were twice as likely to have neurodevelopmental impairment, have poor growth, and were at three-time greater risk of rehospitalization when compared with ELBW infants without major anomalies.

Time of death — In VLBW infants, about 50 percent of deaths occur in the first three days after delivery. This was illustrated by a study based on information from the National Inpatient Sample Database from 1997 to 2004 that included 115,350 VLBW infants [23]. Patients with congenital anomalies were excluded from the analysis. In this cohort, the distribution of birth weights was 10.6, 18.4, 16.9, and 54.1 percent for infants weighing <500 g, 500 to 749 g, 750 to 999 g, and 1000 to 1499 g, respectively. The following findings were noted:

- The overall survival rate was 77.5 percent. On the first day, 35 percent of the deaths occurred. By the end of the first three days and the 28th day, 58 and 90 percent of the deaths occurred.
- Deaths were more frequent for ELBW infants during the first day of life. Morality increased with decreasing birth weights as follows:
- For infants with birth weights <500 g, only 8 percent survived. Most of the deaths (72 percent) occurred in the first day of life and by the end of the third day 86 percent of deaths had occurred.
- For infants born between 500 and 749 g, the overall mortality rate was 49.2 percent, with 19.6 and 31.4 percent mortality at the end of the first and third day of life.
- For infants born between 750 and 1000 g, the overall mortality was 14.9 percent, with 3.1 and 6.4 percent mortality at the end of the first and third day of life.

In a study from the NICHD of 9575 VLBW infants, the overall mortality rate was 28 percent, and the highest mortality rate occurred in the first 12 hours of life [24].

Long-term mortality — Survivors of prematurity beyond the first year of life still remain at risk for early death compared to those born at term. In a population-based study from Norway of over one million individuals born between 1967 and 1988 and followed through 2002, those born prematurely (5.2 percent of the overall group) had an increased risk of death throughout childhood compared to individuals born full-term [25]. Mortality rates were greater for those born extremely premature (gestational age 22 to 27 weeks) and were generally higher for boys compared to girls at the same gestational age.

SUMMARY AND RECOMMENDATIONS

- Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. Premature infants are classified by birth weight or gestational age (table 1 and table 2). (See 'Definitions' above.)
- In the United States, about 12 to 13 percent of live births are premature and about 2 percent are born at a gestational age less than 32 weeks (figure 1). There has been a 21 percent rise in the overall proportion of preterm births since 1990, which is reflected in all stages of prematurity. Part of this increase in premature births is due to the increase of infants with multiple gestations. (See 'Incidence' above.)
- Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3). The four primary causes that lead to preterm labor and delivery are activation of the maternal or fetal hypothalamic-pituitary-adrenal axis, infection, decidual hemorrhage, and pathological uterine distention. (See "Pathogenesis of spontaneous preterm birth".)
- Risk factors associated with preterm birth include obstetric and sociodemographic factors (table 4). (See "Risk factors for preterm labor and delivery".)
- Low birth weight and prematurity are major contributors to infant mortality. In the United States, prematurity was associated with approximately 37 percent of infant deaths. (See 'Mortality' above.)
- Increased mortality rates in premature infants are associated with the following:

- Increasing immaturity (ie, decreasing birthweight and gestational age) (See 'Gestational age and birth weight' above.)
- Hospitals with lower levels of resource and experience in delivering neonatal intensive care (See 'Standard of neonatal care' above.)
- Congenital anomalies (See 'Congenital anomalies' above.)
- Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality rates of preterm infants, except in those who are at the limit of viability. (See 'Trends over time' above and "Limit of viability".)

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Prevention and treatment of neonatal pain

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INTRODUCTION — Advances in neonatal research demonstrate that newborns experience pain and controlling newborn pain has short-term and long-term benefits [1]. Care providers are expected to prevent infants from experiencing pain, if at all possible [2-4]. Varying degrees of neonatal discomfort or pain may occur during routine patient care (eg, gavage tube placement, bladder catheterization, or physical examination) [5], moderately invasive procedures (eg, suctioning, phlebotomy, or peripheral intravenous line placement), or more invasive procedures (eg, chest tube placement, circumcision, or central venous line placement).

Pain is most common and intense in infants admitted to the neonatal intensive care unit (NICU). Infants admitted to the NICU frequently experience acute pain from skin-breaking procedures, established pain following surgery, and prolonged (chronic) pain from diseases like necrotizing enterocolitis or meningitis. (See "Assessment of neonatal pain".)

In 2006, the American Academy of Pediatrics and the Canadian Pediatric Society (AAP/CPS) published new guidelines recommending that each health care facility that treats neonates establish a neonatal pain control program [2]. These recommendations include:

- Routine assessments for the detection of pain
- Reduce the number of painful procedures
- Prevent/reduce acute pain from invasive procedures performed at the bedside
- Anticipate and treat postoperative pain following surgery
- Avoid chronic pain/stress during neonatal intensive care

Prevention, control, and treatment of neonatal pain will be reviewed here. The assessment of neonatal pain is discussed separately. (See "Assessment of neonatal pain".)

APPROACH — An ethical approach to neonatal intensive care must include evidence-based and effective measures to reduce, control, or prevent pain in newborns, which includes: [6-8]:

- Preemptive analgesia for any anticipated painful procedure.
- Elimination of unnecessary noxious stimuli or painful procedures.

- Nonpharmacologic methods, pharmacologic agents, or a combination of these interventions, may be used to prevent and reduce neonatal pain. (See 'Analgesia for specific procedures' below.)

ANALGESIA FOR SPECIFIC PROCEDURES — Preemptive analgesia before and during elective painful procedures should be provided to all neonates. Analgesia often includes a combination of non-pharmacologic and pharmacologic techniques.

In our institution, we use a combination of measures for frequently performed neonatal procedures in a stepwise manner with increasing analgesia as the degree of anticipated procedural pain increases (figure 1) [7,9]. This approach is similar to the World Health Organization analgesic ladder for pain management in adults and guidelines published by the Italian Society of Neonatology [10]. (See "Evaluation and management of pain in children", section on 'Principles of management'.)

- Step 1 — Nonpharmacologic measures including pacifier use, administration of sucrose, swaddling, kangaroo care, and sensorial saturation. (See 'Nonpharmacologic analgesia' below.)
- Step 2 — Topical anesthetics (ie, topical lidocaine, lidocaine-prilocaine cream, amethocaine gel, tetracaine gel). (See 'Topical anesthetics' below.)
- Step 3 — Oral, intravenous, or rectal administration of acetaminophen. (See 'Acetaminophen' below.)
- Step 4 — Slow intravenous infusion of opioids (eg, fentanyl or morphine).
- Step 5 — Subcutaneous infiltration of lidocaine or specific nerve block.
- Step 6 — Deep sedation (eg, combination of opioids and other drugs) or general anesthesia.

The application of these steps to specific invasive procedures at the bedside depends upon the clinician's choice and hospital-specific policies and procedures.

Our analgesic management is detailed in the accompanying table for common procedures performed in the NICU (table 1) [11].

REDUCTION OF PAINFUL EVENTS — The most effective method to reduce neonatal pain or discomfort is to reduce the number of procedures performed and episodes of patient handling. NICUs and nurseries should develop strategies that limit handling and procedures but do not compromise the care of the infants.

With forethought and planning, the number of bedside disruptions and procedures can be reduced as follows, commonly referred to as "clustered care" [2,6,12]:

- Decrease the number of bedside disruptions by timing routine medical interventions (daily physical examinations by physician) with other care procedures (eg, diaper change or suctioning).
- Anticipate needed blood studies to minimize the frequency of blood studies. For example, nonchemical photometric devices can perform several analyses (eg, pH, PaO₂, electrolytes, calcium, and bilirubin) from a single small blood sample, thereby reducing the number of venipunctures or heel sticks required for laboratory testing.
- For newborns who need more than two to three heel sticks a day, a peripheral arterial catheter can be placed for frequent blood sampling and/or a central venous catheter in patients who need intravenous access. These procedures should be performed with appropriate analgesia. (See 'Analgesia for specific procedures' above.)
- If clinically appropriate, use noninvasive monitoring such as transcutaneous monitoring (eg, oxygen saturation or bilirubin levels), or near infra-red spectroscopy (NIRS) to avoid the need for blood sampling.
- Consider the use of noninvasive therapeutic approaches for achieving analgesia in newborns [13].

NONPHARMACOLOGIC ANALGESIA — The following nonpharmacologic approaches can effectively reduce pain and discomfort from minor procedures in neonates.

- Oral sucrose or glucose
- Breastfeeding
- Non-nutritive sucking

- Skin to skin contact (eg, kangaroo care)
- Swaddling including facilitated tucking (defined as maintaining the arms and legs in a flexed position)
- Sensorial saturation — Use of touch, massage, voice, smell, and sight

Nonpharmacologic approaches are generally more effective when used in combination than when used alone [14-18]. As discussed above, in our practice we use combinations of nonpharmacologic and pharmacologic measures depending upon the clinical setting (table 1). Combinations of nonpharmacologic measures (eg, sucrose and skin-to-skin contact) have additive or synergistic effects [17]. In some settings, these combinations may eliminate pharmacologic use or reduce drug dosage or frequency of doses required, and consequently, the risk of pharmacologic side effects [14-16,19].

Oral sucrose — Oral sucrose and other sweet-tasting liquids, such as glucose or saccharin, appear to be effective analgesics in both term and preterm infants [20]. This was illustrated in a systematic review of 44 published randomized controlled trials that included 3496 infants with gestational ages from 25 to 42 weeks [21]. In neonates undergoing skin-breaking procedures (eg, heelstick or venipuncture), sucrose was associated with the following findings:

- Reduced crying — Sucrose compared to placebo reduced crying behavior (ie, the percentage of time spent crying, total cry duration, and duration of the first cry) in both term and preterm infants.
- Dampened physiologic responses — Sucrose compared to placebo reduced the changes in heart rate, oxygen saturation, or vagal tone at heel lance.
- Reduced facial expressions — In eight of 10 studies, sucrose compared to placebo was associated with a lower pain score on unidimensional pain measures based on facial expression or the presence of crying.
- Improved composite pain scores — Six of seven studies that used multidimensional pain assessment tools reported lower pain scores in the groups who received sucrose compared to controls. (See "Assessment of neonatal pain", section on 'Pain assessment tools'.)

It remains unclear whether sucrose suppresses the neurophysiologic responses to pain.

- In a randomized trial of 44 term infants, although patients assigned to sucrose therapy versus placebo had lower pain scores (using the Premature Infant Pain Profile) following a heelstick, there were no differences in brain and spinal cord activity using brief electroencephalographic (EEG) and electromyographic (EMG) recordings between the two groups [22]. Several concerns about the study design and analysis have been raised including the small sample size, exclusion of more than 30 percent of the enrolled subjects in the sucrose group (9 of 29 patients), limitations regarding the electrophysiological monitoring to specific domains and amplitudes, and the timing of the EMG and EEG within one second after the heel lance, and the uncertainty of whether the time-limited EEG (one second) and EMG (two seconds) recordings actually measure pain, which the neonate was not able to express, or a withdrawal or nociception response, which the neonate did not perceive as pain [23-27]. These reservations have limited the applicability of these findings.
- In contrast, another trial reported sucrose given prior to a heelstick suppressed the electroencephalographic changes occurring in the right frontal lobe of control infants who received water [28].

Based upon animal studies, it was proposed that sucrose mediated its effect by activating endogenous opioid mechanisms in the brainstem [29-31]. In human infants, however, one study showed no changes in plasma beta-endorphin levels with sucrose analgesia, while another study demonstrated that intravenous naloxone appeared to potentiate the effects of sucrose administration [32,33]. Currently available evidence suggests that the analgesic effects of sucrose or glucose are mediated through activation of opioid receptors in the brainstem.

Sucrose may not provide enough analgesia to reduce the pain caused by intramuscular injection [34]. However, sucrose in combination with topical anesthetic appears to reduce pain from eye examinations screening for retinopathy of prematurity (ROP) [35-39]. A meta-analysis of five studies demonstrated infants who received sucrose had lower pain scores than those assigned placebo therapy during ROP screening. However, scores remained high even with sucrose therapy indicating the need for better pain reduction strategies [39].

Glucose appears to be as effective as sucrose in providing analgesia in preterm infants undergoing minor invasive procedures [19].

Dosing and administration — No optimal dose for oral sucrose has been established and dosing to treat neonatal pain ranges from 0.012 to 0.12 g (0.05 to 0.5 mL of a 24 percent sucrose solution) [2,29,40-42]. Current data indicates that sucrose is not effective after three months of age [43,44].

Sucrose can be administered orally via a syringe or onto the tongue by allowing the infant to suck on a pacifier that has been previously dipped in 24 percent sucrose solution.

Although repeated doses are effective [41,45], one study has reported adverse neurodevelopmental effects in preterm infants less than 32 weeks gestation who received more than 10 doses over a 24 hour time period [42,46]. A recent review also questioned the long-term developmental effects of repeated sucrose exposure in preterm neonates [47].

In our practice, we administer oral sucrose as a 24 percent sucrose solution via pacifier, given two minutes before painful procedures and repeat the sucrose administration as needed for pain relief. For intubated infants, we place sucrose directly on the infant's tongue based upon gestational age as follows:

- 27 to 31 weeks gestation — 0.1 mL
- 32 to 36 weeks gestation — 0.3 mL
- Greater than 37 weeks gestation — 0.5 mL

We monitor for changes in vital signs as well as any clinical signs of choking or gagging.

We use sucrose for minor procedures such as heelstick, venipuncture, venous catheterization, nasogastric insertion, arterial puncture, bladder catheterization, intramuscular or subcutaneous injections, eye examination for ROP assessment, dressing change, or tape removal. Sucrose is combined with other analgesic agents for moderately painful procedures such as lumbar puncture, circumcision, chest tube insertion, percutaneous central venous catheter insertion, or intraosseous access [34,40,48].

Sucrose may be used for distress unrelated to invasive procedures to reduce crying activity and heat loss [43,49], but an evaluation and documentation of its effectiveness is essential when sucrose is used outside the procedural pain setting.

Breastfeeding or breast milk — Breastfeeding or oral administration of breast milk appears to have similar analgesic effects as those elicited by oral sucrose. This was illustrated in a meta-analysis that included 11 trials of breastfeeding or supplemental breast milk [50]. One major limitation of this meta-analysis was the significant variability in study design among trials. Infants who were breastfed or received breast milk were compared to control groups receiving placebo or interventions such as sucrose or swaddling. The following main findings were noted:

- Neonates in the breastfeeding group had reduced crying and smaller increases in heart rate during a painful procedure compared to infants in the control groups.
- Breastfeeding and oral glucose administration were compared in two studies, which showed no differences in neonatal pain responses. (See "Assessment of neonatal pain", section on 'Pain assessment tools'.)
- Supplemental oral breast milk was associated with lower increases in heart rate and decreased crying when compared to placebo. However, infants treated with breast milk had higher increases in heart rate and longer duration of crying compared to those who received oral glucose/sucrose.

Breastfeeding has greater analgesic effects than non-nutritive sucking on a pacifier, with or without sucrose [51,52], but it is unclear whether combining breastfeeding and sugar solution increases the analgesic effects. In one study, there were additive analgesic effects when the two were combined [53]; however, another trial found no additional benefits of combining breastfeeding with sucrose [54].

Breastfeeding is a developmentally superior alternative to oral sucrose or glucose for pain control in infants, but it may not be applicable to intubated or very preterm neonates undergoing painful procedures [52]. If oral sucrose or glucose, or breastfeeding is unavailable, supplemental breast milk is a reasonable option for providing neonatal analgesia [55].

Non-nutritive sucking — Infants treated with non-nutritive sucking with pacifiers have lower increases in heart rate and decreased duration of crying in response to a painful stimuli compared to those who received no intervention [56], swaddling alone [57], rocking alone [58], or sensory stimulation [54]. However, pain relief was poorer in infants who received pacifiers only as compared to those receiving sucrose dipped pacifiers [56]. As a result, oral sucrose or breastfeeding is preferred to non-nutritive sucking or swaddling for infants undergoing minor painful procedures [51,53,54].

Other measures

- **Swaddling or facilitated tucking** — Restricting the movement of an infant's limbs activates proprioceptive, tactile, and thermal systems, facilitates self-soothing behaviors (eg, hand-to-mouth movement, and non-nutritive sucking), and is developmentally supportive. This can be achieved by swaddling in a blanket or manually by facilitated tucking (holding the infant's extremities flexed and contained close to the trunk). Both approaches compared to no intervention can reduce responses to invasive procedures (eg, endotracheal suctioning and heel stick) in term [57,59,60] and preterm infants [60-65]. Of note, swaddling has been associated with an increased risk of developmental dysplasia of the hip (DDH). (See "Epidemiology and pathogenesis of developmental dysplasia of the hip", section on 'Epidemiology'.)
- **Skin to skin contact** — Skin to skin contact, which includes kangaroo care (with infant resting between the mother's breasts) stimulates ventral tactile and proprioceptive systems and reduces neonatal pain responses. Several randomized trials have demonstrated that kangaroo care reduced pain compared to standard within the crib positioning when undergoing heel sticks [66-69]. In a recent clinical trial, 95 preterm neonates (gestational age 28 to 36 weeks) were randomly assigned to receive skin-to-skin contact or 25 percent glucose (1 ml), or no treatment during heel lancing. Skin-to-skin contact reduced changes in heart rate ($p=0.0001$), oxygen saturation ($p=0.0012$), facial pain expressions (brow bulge, eye squeeze, nasolabial furrowing; $p=0.0001$), and lowered their Premature Infant Pain Profile (PIPP) scores ($p=0.0001$) [70].
- **Sensorial saturation** — Sensorial saturation is the use of sensory input (eg, touch, massage, taste, voice, smell, and sight) during a painful procedure. Several studies from the same research group have shown reduction of pain in infants who received a combination of sensorial saturation and oral sucrose during painful procedures compared to oral sucrose alone [14,71,72]. This approach is labor-intensive and has not been replicated in other settings.

LOCAL ANALGESIA — Local analgesics, such as topical anesthetics and injectable lidocaine, can reduce procedural pain in neonates and are widely used. (See 'Topical anesthetics' below and "Infiltration of local anesthetics".)

Topical anesthetics — Several topical anesthetics are available, including EMLA® cream, an eutectic mixture of lidocaine (2.5 percent) and prilocaine (2.5 percent) in a cream base, Ametop® or Pontocaine® (2 or 4 percent tetracaine cream, respectively), L.M.X-4® or L.M.X-5® (4 or 5 percent liposomal lidocaine cream, respectively), and S-caine®, a eutectic mixture of lidocaine (7 percent) and tetracaine (7 percent). EMLA is the most frequently used preparation, and the one most extensively studied.

EMLA — The efficacy and safety of EMLA for procedural pain in newborns were evaluated in two systematic reviews [73,74]. The procedures assessed were circumcision [73], heelstick, venipuncture, arterial puncture, lumbar puncture, and percutaneous insertion of venous catheters [75]. The results were summarized as follows:

- Measures of pain during circumcision such as facial grimacing, duration of crying time, increased heart rates, and oxygen desaturations were significantly reduced with the use of EMLA compared to placebo.
- EMLA reduced the pain of venipuncture. It appeared to be more successful for venipuncture than arterial puncture.
- EMLA had no effect on lumbar puncture pain in one randomized trial.

- EMLA did not diminish pain associated with heel stick and may prolong the procedure because it produces vasoconstriction at the site of application.
- The effect of EMLA on the pain associated with percutaneous venous catheter placement was equivocal, with attenuation of increases in heart rate and respiratory rate, but no effects on blood pressure or oxygen saturation.

In a subsequent randomized trial of neonates undergoing lumbar puncture, EMLA reduced pain (detected by changes in heart rate and oxygen saturation, and facial expressions) compared to placebo at both needle insertion and withdrawal [74].

The most common side effect is mild, transient skin irritation, which is related to prilocaine contained in the formulation. Methemoglobinemia is a serious but rare side effect, and is more likely to occur in patients with a predisposing condition, such as glucose-6-phosphate dehydrogenase deficiency, or following the use of inappropriately excessive doses. In the above meta-analyses, application of EMLA appeared to be safe [73,75]. Methemoglobin concentration as a percent of hemoglobin concentration was similar in EMLA and control groups, and no study reported clinically significant levels. Plasma concentrations of lidocaine (four studies) and prilocaine (three studies) in treated infants were less than 0.3 and 0.1 µg/mL respectively, significantly below their toxic concentrations. (See "Clinical features, diagnosis, and treatment of methemoglobinemia".)

To attain adequate local anesthesia, 1 to 2 g of EMLA cream should be applied and covered with an occlusive dressing for 45 to 60 minutes. The safety of repeated doses, up to four times a day, has been suggested [76].

In our practice, if time permits for application, we use EMLA cream to reduce pain associated with venous, arterial, and lumbar punctures, and intravenous or arterial catheter insertion. EMLA is not effective in reducing pain from heel sticks because prilocaine causes vasoconstriction, and squeezing the heel for blood collection is the most painful part of the procedure.

The use of EMLA as a topical anesthetic is discussed in greater detail separately. (See "Procedural sedation and analgesia in children", section on "Topical agents".)

Lidocaine — Lidocaine can be injected locally to reduce the pain associated with venous or arterial puncture, percutaneous venous or arterial catheter placement, lumbar puncture, and circumcision. Lidocaine infiltration is also used during surgical operations to reduce the postoperative hyperalgesia and the need for postoperative analgesia.

Lidocaine is usually administered as either a 0.5 (5 mg/mL) or 1 percent solution (10 mg/mL) at a maximum dose of 3 to 5 mg/kg. In neonates, the combination of lidocaine with epinephrine should be avoided to minimize the risk of tissue necrosis and arrhythmias. Needle-free devices may be able to inject lidocaine subcutaneously, but these have not been tested in newborns [13].

For circumcisions, 1 percent lidocaine is administered either as a dorsal penile nerve block or circumferential subcutaneous local anesthesia (ring block) as the most effective therapy to reduce circumcision pain. Infants should also receive oral sucrose prior and during the circumcision, and acetaminophen for postprocedure pain. (See "Procedures for neonatal circumcision", section on 'Pain control'.)

The use of lidocaine as a local anesthetic is discussed in greater detail separately. (See "Infiltration of local anesthetics", section on 'Lidocaine'.)

SYSTEMIC ANALGESIA — Systemic pharmacologic agents that have been used in neonates to reduce pain and stress include nonopioid analgesics (eg, acetaminophen and ketamine), nonsteroidal anti-inflammatory agents, opioid analgesics (eg, morphine and fentanyl), and sedatives (eg, midazolam).

Opioids are the most effective therapy for moderate to severe pain in patients of all ages. They provide both analgesia and sedation, have a wide therapeutic window, and also attenuate physiologic stress responses. Morphine and fentanyl are the most commonly used opioids in neonates.

Acetaminophen — Acetaminophen is used in the management of mild to moderate procedural and post-operative pain. In both preterm and term infants, the clearance of acetaminophen is slower than older children, so oral dosing is required less frequently [77-79]. In neonates, recommended doses are 10 to 15 mg/kg given orally every six to eight hours and 20 to 25 mg/kg given rectally at the same time intervals. The maximum oral doses are 60 mg/kg per 24 hours in infants >32 weeks postconception age and 40 mg/kg per 24 hours for infants between 28 and 32 weeks postconception age [80]. These doses are primarily based upon antipyretic dose-response studies and may not be adequate for pain control.

In infants, both rectal [78,81,82] and intravenous formulations of acetaminophen [83] have been studied. There are minimal adverse effects in infants, and in contrast to its use in older children and adults, acetaminophen rarely, if ever, causes hepatic or renal toxicity in neonates [84,85]. In addition, intravenous administration of acetaminophen does not increase the risk of hypothermia in neonates [86].

Acetaminophen alone is not effective for pain reduction from circumcision [87] or heel sticks [88].

Nonsteroidal anti-inflammatory agents — Although nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively in older children and adults, there has been reluctance to use these agents because of their well-known adverse effects in newborn infants [89,90]. In studies that evaluated indomethacin and ibuprofen for treatment of patent ductus arteriosus in preterm infants, use of NSAIDs was associated with gastrointestinal bleeding, platelet dysfunction, and decreased glomerular filtration rate. As a result, NSAIDs are not generally used for analgesia because effective and safer agents are available. Use of NSAIDs during pregnancy may cause premature closure of the ductus arteriosus in utero, associated with severe pulmonary hypertension in the newborn [91]. (See "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants", section on 'Prostaglandin E2' and "Management of patent ductus arteriosus in premature infants", section on 'Cyclooxygenase inhibitors'.)

Opioid therapy — Opioids are the most effective therapy for moderate to severe pain in patients of all ages. They provide both analgesia and sedation, have a wide therapeutic window, and also attenuate physiologic stress responses. Morphine and fentanyl are the most commonly used opioids in neonates, although more potent (eg, sufentanil), shorter acting (eg, alfentanil, remifentanil), or mixed opioids (eg, tramadol) are being used with increasing frequency [92,93].

Morphine — Morphine is the most commonly used opioid for analgesia in the neonate. It has been used as a continuous infusion in ventilated infants or infants following major surgery, or intermittently to reduce the acute pain associated with invasive procedures. Whether it is an effective and safe neonatal analgesic in these clinical settings, however, remains under active investigation.

Ventilated neonates — Although morphine may improve ventilator synchrony [94] and sedate ventilated neonates [95,96], the following data suggest that routine continuous morphine infusions in ventilated preterm infants provide little or no clinical benefits compared to placebo.

A multicenter-blinded prospective trial (the NEOPAIN Trial) evaluated the outcomes of 898 ventilated preterm infants (gestational age ≤ 32 weeks) who were randomly assigned to continuous infusion of either morphine or placebo [97-99]. Open-label morphine was allowed and was administered based upon the clinical judgment of blinded care providers in each of the participating NICUs. The following findings were noted:

- There were no differences in the rates of mortality, severe intraventricular hemorrhage (IVH), or periventricular leukomalacia (PVL) between the two groups.
- Infants assigned to the morphine group compared to placebo appeared to have lower levels of pain as assessed by smaller increases in heart and respiratory rates, and lower scores on multidimensional neonatal pain assessment using the Premature Infant Pain Profile (PIPP). These differences were small, but reached statistical significance because of the large sample size.
- Although a higher proportion of control infants received open-label morphine, almost half of the patients in each group did not receive open-label morphine.
- Infants treated with morphine were more likely to develop hypotension [99], required longer duration of mechanical ventilation, and took longer to tolerate full-volume nasogastric feeds [97,98].

- The use of morphine did not increase the rate of gastrointestinal complications [98]. However, the morphine group had a delay in starting feeds and attaining full feeds. Other factors that were associated with a delay in starting feeds included lower birth weight, a higher score of neonatal morbidities, and the use of dexamethasone.

A smaller randomized clinical trial demonstrated that morphine had no additional analgesic effect compared to placebo using multiple measures of pain assessment [100]. In this trial of 150 preterm infants, there was a decrease in the rate of IVH in the morphine-treated group, but there was no difference in the likelihood of poor neurologic outcome between the two groups.

A systematic review on the use of opioids (primarily morphine) in ventilated infants selected 13 studies for analysis [101]. There was, however, significant variability of study design resulting in differences in the quality of the included studies. The following findings were noted:

- Pooled data from four high-quality studies (which used a validated pain assessment tool, PIPP, and included the above two trials [97,100]) demonstrated a trend towards reduced pain scores in the group of patients that received morphine compared to controls (-1.71, 95% CI -3.18 to -0.24).
- Other analyses demonstrated no differences in the rates of mortality (five trials), duration of mechanical ventilation (ten trials), and neurodevelopment outcomes evaluated at five to six years of age (two trials).
- There were no differences in secondary outcomes (eg, rates of necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, and hypotension requiring medical intervention), except patients in the morphine group took longer to reach full enteral feeds, especially very preterm infants.

Based upon the above studies, in preterm infants it appears that Morphine analgesia may be associated with significant side effects, including hypotension, delayed feeding, and it does not alter long-term outcomes [97,102,103]. The routine use of morphine infusions is, therefore, not recommended for ventilated preterm neonates.

In ventilated term infants, morphine analgesia may not be associated with the same risk of adverse effects as seen in preterm infants, but still may cause an increase duration of ventilation. This was illustrated in a retrospective study of 62 ventilated term newborns that found postoperative morphine infusions prolonged the need for mechanical ventilation, but were not associated with apnea, hypotension, or other complications [104].

Postoperative and procedural pain control — Observational studies and trials comparing intermittent bolus versus continuous morphine administration of morphine suggest that morphine is safe and effective in reducing postoperative pain in neonates [105-109]. However, there are currently no data from randomized trials comparing the safety of efficacy of postoperative morphine analgesia to placebo in preterm neonates.

Data also are conflicting regarding morphine's ability to reduce acute pain from procedures as demonstrated by the following randomized controlled trials [97,100,110,111].

- In the first study, ventilated neonates who required central venous line placement were randomly assigned topical anesthesia alone (tetracaine), morphine alone, or both tetracaine and morphine [110]. Infants who received no analgesic therapy because of parental choice were used as a no treatment group. Assessment of pain was based upon changes in heart rate and the duration of facial grimacing during different phases of the procedure. Morphine alone and morphine plus tetracaine groups had lower pain scores than the no treatment or tetracaine alone groups. However, patients who received morphine required an increase in ventilatory support within the first 12 hours following the procedure.
- The second study, nested within the NEOPAIN trial, evaluated the response to heel stick in preterm infants who were randomly assigned to continuous morphine infusion or placebo therapy [111]. Responses to pain using assessment tools based upon behavioral and physiological indicators demonstrated no difference in pain scores between the two groups.
- The third trial of ventilated preterm neonates assigned to either morphine or placebo therapy found no difference in the responses to tracheal suctioning between the two groups using multiple methods for pain assessment [100]. A detailed analysis of morphine pharmacodynamics in ventilated preterm

neonates also found no relationship between measured plasma morphine levels and the responses to tracheal suctioning [112]. (See "Assessment of neonatal pain", section on 'Pain assessment tools'.)

Birth asphyxia — Although data are limited, morphine analgesia may be beneficial in term infants following birth asphyxia. This was illustrated in an observational study of 52 term infants who had significant hypoxic-ischemic insults documented by elevated serum lactate levels or low five minute Apgar scored and underwent magnetic resonance imaging (MRI) [113]. MRI demonstrated less brain injury in infants who were treated with opioids than those who did not receive opioid therapy.

Fentanyl — In neonates, fentanyl is used because of its ability to provide rapid analgesia with minimal hemodynamic effects. There are no large trials of the use of fentanyl in neonates similar to those for morphine. Small randomized controlled trials have reported reduced stress hormone levels (eg, catecholamines and glucocorticoids), fewer episodes of hypoxia, and lower behavioral stress scores in ventilated infants treated with fentanyl compared to controls [114-116]. Although infants who received fentanyl required greater ventilatory support, there were no differences in clinical outcomes between the fentanyl- and placebo-treated groups [114,116].

Fentanyl or its shorter-acting derivatives (eg, alfentanil, remifentanil) are often used for achieving analgesia prior to tracheal intubation in preterm and term newborns [117-120]. A randomized controlled trial in 20 preterm newborns found that the overall intubating conditions were significantly improved in those receiving remifentanil rather than morphine prior to endotracheal intubation. However, there were no complications observed following either intravenous morphine or remifentanil use [117].

Compared to morphine, fentanyl analgesia is associated with less sedative or hypotensive effects, reduced effects on gastrointestinal motility or urinary retention, but greater opioid tolerance and withdrawal [121-124]. In one randomized trial comparing infusions of fentanyl (1.5 µg/kg per hour) versus morphine (20 µg/kg per hour) in ventilated neonates, similar pain scores, catecholamine responses, and vital signs were reported in the two groups. There were no adverse respiratory effects or difficulties in weaning from ventilation in either group, but lower beta-endorphin levels and decreased incidence of gastrointestinal dysmotility occurred in the fentanyl group [121].

In accordance with the American Academy of Pediatrics and the Canadian Pediatric Society (AAP/CPS) guidelines, we do not routinely use continuous infusions of fentanyl in ventilated preterm neonates. [2] We reserve the use of fentanyl when a rapidly acting opioid is required for analgesia in a controlled setting that can adequately address any associated potential side effects (eg, bradycardia, chest wall rigidity). Other indications include fentanyl analgesia for postoperative pain (particularly following cardiac surgery), or for patients with pulmonary hypertension (primary, or secondary to meconium aspiration, diaphragmatic hernia, or congenital heart disease). Further studies of fentanyl analgesia for ventilated preterm neonates, and for term and preterm neonates exposed to postoperative pain or procedural pain, are required to evaluate its safety and efficacy in these patients.

Our approach — Based upon the above discussion and clinical experience in our institution, we feel that routine use of morphine infusions in ventilated preterm infants cannot be recommended at this time, except for neonates undergoing tracheal intubation, central line placement, or surgery. Morphine analgesia may be used in ventilated term neonates following surgery, birth asphyxia, or those requiring moderately invasive procedures like central venous catheterization, tracheal intubation, or chest tube placement.

Extreme caution must be exercised if using opioid therapy in ventilated preterm neonates born at 23 to 26 weeks gestation or those with pre-existing hypotension at baseline because of the increased risk for associated adverse events [99,125].

Ketamine therapy — Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, was introduced as a “dissociative anesthetic” but is widely used for procedural, operative, or postoperative analgesia and sedation in neonates and small infants. Ketamine is the only analgesic that produces intense sedation and amnesia, while maintaining respiratory drive, producing bronchodilation, and improving hemodynamic function with mild increases in heart rate and blood pressure in critically ill neonates [126]. Although, in rodents and other animal models, prolonged exposure to high doses of ketamine was associated with increased apoptotic and/or necrotic

cell death in the developing brain, the clinical relevance of these data have been questioned [127,128]. In newborn rats, the use of ketamine analgesia in the setting of inflammatory pain reduced cell death in the developing brain areas and improved the animals' long-term neurobehavioral outcomes [129,130]

In preterm neonates undergoing central venous catheterization, no significant hemodynamic changes were associated with use of ketamine during the procedure [131]. High doses of 2 mg/kg of ketamine were associated with reduced heart rate [132], and even higher doses of 5 mg/kg reduced blood pressure without impairing cardiac output [131].

At our institution, we use ketamine (1 to 2 mg/kg per dose intravenously) for neonates with hemodynamic instability, such as those with congenital heart disease, congenital diaphragmatic hernia, or those requiring ECMO cannulation. Further research is needed to establish the safety and efficacy of ketamine analgesia/sedation for ventilated neonates or for other clinical indications.

Sedatives — These drugs (eg, benzodiazepines, barbiturates, and chloral hydrate) provide sedation, anxiolysis, muscle relaxation, and amnesia. However, sedatives do not provide analgesia and may even mask the clinical signs of pain in some neonates.

Midazolam is a short-acting benzodiazepine, but may cause prolonged sedative effects in sick preterm neonates. Three randomized trials have examined its use in ventilated preterm neonates [133-135]. However, differences in study design did not allow combining these results into a meta-analysis [136]. Two studies reported increased sedation with midazolam [134,135], and the third study reported an increase in poor neurologic outcomes among preterm neonates who received midazolam [133]. In addition, a randomized trial evaluating midazolam as pre-medication for endotracheal intubation was terminated early because of significant oxygen desaturations in treated versus control infants (86 versus 0 percent) [137]. Based upon these results, the use of midazolam is not recommended in preterm neonates.

In one animal study, midazolam increased the need for analgesia and provided poor sedation in newborn rats, which had comparable neurological maturity to preterm human neonates [138].

Long-term outcomes — Although data are limited, it appears that prolonged neonatal sedative and/or analgesic drugs have the potential to affect long-term neurological and behavioral outcomes [139]. However, in an analysis of data from a French population-based study (EPIPAGE cohort) of very preterm infants (gestational age below 33 weeks of age), after adjusting for gestational age and a propensity score (which included neonatal, pregnancy, and birth confounding factors), there was no difference in the five-year neurological outcome between patients who received sedative and/or opioid drugs for more than seven days as neonates compared to those without prolonged neonatal exposure to sedation and/or analgesia (RR 1.0, 95% CI 0.8 to 1.2) [140].

In another follow-up study of preterm survivors at five or six years, although there were no differences in cognition, behavior, movement and thyroid function between those randomly assigned to morphine and those assigned to placebo, although there was a trend towards better performance in the morphine group [103].

There is also indirect evidence that neonatal pain and stress may be associated with poorer neurodevelopmental outcome by altering the regulation of cortisol secretion in preterm infants with elevated basal cortisol levels and dampened stress reactivity until at least 18 months of age [141,142]. High cortisol levels during infancy contribute to greater risks of impaired neurodevelopment and poorer attention, modulated to some extent by maternal mood and caregiving [142-144].

SUMMARY AND RECOMMENDATIONS

- Neonates experience pain in a similar manner to older children and adults. Pain is most common and intense in infants who are cared for in the neonatal intensive care unit (NICU).
- Each health care facility that treats neonates should establish a neonatal pain control program that includes:
 - Routine assessment for the detection of pain. (See "Assessment of neonatal pain".)

- Reduction of the number of painful procedures and episodes of patient handling. (See 'Reduction of painful events' above.)
- Guidelines and protocols to prevent/reduce pain due to handling and procedures.
- Analgesia should be provided preemptively for any painful procedure. Nonpharmacologic measures (oral sucrose, breastfeeding, nonnutritive sucking, swaddling or facilitated tucking, and skin-to-skin contact) and pharmacologic agents (EMLA, lidocaine, and opioids) are used for neonatal pain control. Therapy including combination of interventions is dependent upon the specific procedure performed (table 1).
- We employ the following step-wise approach in the management of neonatal pain depending on the clinical setting, which is based on published data and our clinical experience.
- We suggest that facilitated tucking or skin-to-skin contact be used to improve analgesia for any painful procedure, when feasible (Grade 2B). (See 'Other measures' above.)
- For neonates undergoing a brief needlestick (eg, heelstick, venipuncture), we recommend oral sucrose (Grade 1B). Alternatives include breastfeeding, breast milk, or glucose. (See 'Oral sucrose' above.)
- For neonates undergoing a more prolonged or painful skin breaking procedure (arterial puncture, arterial or venous line placement, or lumbar puncture), in addition to oral sucrose, we suggest the use of a topical anesthetic cream (eg, EMLA®) (Grade 2B). (See 'Topical anesthetics' above.)
- For male neonatal circumcision, in addition to oral sucrose, we suggest ring block or dorsal penile nerve block rather than topical anesthetic cream (Grade 2B). (See "Procedures for neonatal circumcision", section on 'Pain control'.)
- For neonates who undergo more invasive procedures, such as central line placement, we suggest that nonpharmacologic measures be combined with local/topical anesthesia and/or systemic analgesia to provide adequate analgesia (Grade 2B). (See 'Systemic analgesia' above.)
- We recommend that neonates receive postoperative analgesia (Grade 1B). This is generally accomplished with a combination of nonpharmacologic approaches, acetaminophen, and opioid therapy. (See 'Systemic analgesia' above.)
- We recommend against the routine use of morphine for sedation in ventilated neonates (Grade 1B). Analgesia in such patients should be based on an individual assessment of their analgesic requirements. (See 'Morphine' above.)

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Long-term neurodevelopmental outcome of premature infants

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INTRODUCTION — Impaired neurodevelopmental outcome is a major long-term complication of surviving premature infants, especially extremely premature infants who are born at or below 25 weeks gestation. Survivors of premature birth need to be assessed for neurodevelopmental impairment and, if impairment is present, be referred to educational programs and subspecialty care in order to provide the best possible outcome.

The long-term neurodevelopmental outcome and care of survivors of premature birth will be reviewed here. An overview of the incidence, survival, and short-term complications of the premature infants is found separately. (See "Incidence and mortality of the premature infant" and "Short-term complications of the premature infant".)

DEFINITIONS — Different degrees of prematurity are defined by gestational age (GA) or birthweight.

The classification based upon GA is as follows:

- Late preterm birth — GA between 34 and less than 37 weeks
- Very preterm birth — GA less than 32 weeks
- Extremely preterm birth — GA at or below 25 weeks

Prematurely born infants are also classified by birth weight (BW):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

Percentiles of birth weights for the appropriate GA have been established (table 1). The above definitions are used throughout this review.

GENERAL ISSUES — In developed countries, advances in medical care have resulted in significant improvements in survival of premature infants, reaching a plateau in the late 1990s [1,2]. In particular, survival rates markedly improved for VLBW and ELBW infants who are at the greatest risk for neurodevelopmental disability [1]. In the United States, data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network noted survival rates of 72 percent for infants with gestational ages 22 to 28 weeks who were born between 2003 and 2007 [3].

In addition, there has been a 21 percent rise in the overall proportion of preterm births since 1990 in the United States, which peaked in 2006 with 12.8 percent of all live births born at a GA <37 weeks. (See "Incidence and mortality of the premature infant", section on 'Incidence'.)

The increase in premature births and the improved survival rate have outpaced any concomitant decrease in the rate of long-term neurodevelopmental sequelae. As a result, in the United States, survivors of premature birth account for approximately 45 percent of children with cerebral palsy, 35 percent of children with vision impairment, and 25 percent of children with cognitive or hearing impairment [4]. (See 'Trends over time' below.)

Outcome studies primarily from North America and Western Europe have demonstrated increased prevalence of the following neurodevelopment disabilities in survivors of premature birth compared to individuals who were born full term (FT):

- Impaired cognitive skills. (See "Specific learning disabilities in children: Clinical features", section on 'Risk factors'.) Motor deficits including mild fine or gross motor delay, and cerebral palsy. (See "Clinical features of cerebral palsy".)
- Sensory impairment including vision and hearing losses.
- Behavioral and psychological problems.

Although infants of any GA may have a neurodevelopmental deficit, the rates of neurodevelopmental disabilities increase with decreasing birthweight and GA. This has been well studied in prevalence studies of cerebral palsy (CP), where it is well established that the risk of CP increases with decreasing gestation and is discussed in detail separately. (See "Epidemiology and etiology of cerebral palsy", section on 'Epidemiology'.)

In the following sections, outcome data are presented for survivors of prematurity and include information on the prevalence of disabilities at school age and adolescence, subsequent academic performance, and capacity to function as adults.

Of note, caution should be used when comparing results among different outcome studies because of variations in study design. These include:

- Time of study as practice changes occur
- Population study based upon BW or GA
- Assessment tools used for evaluation
- Length of follow-up (ie, age at assessment)

With respect to the time of study, reports on adult outcome are often assessing survivors during a time period when the use of postnatal steroids for chronic lung disease was widespread, and prior to the universal use of antenatal glucocorticoids or surfactant, which have changed clinical practice. (See 'Trends over time' below.)

SCHOOL AGE AND ADOLESCENCE

Neurodevelopmental disability and academic achievement — Outcome studies at school age and adolescence have documented an increased risk of neurodevelopmental disability with decreasing GA and BW. The following discussion emphasizes the importance of early assessment of neurodevelopment function in survivors of prematurity.

Extremely preterm infant — Among the most immature survivors (ie, extremely preterm infants or extremely low birth weight [ELBW] infants), impaired cognition, and motor and neurosensory deficits occur frequently, are often severe, and persist into school age and young adulthood [5-10].

The rates of these complications have been reported from several different developed countries and are illustrated by the largest study with the most complete follow-up up to 11 years of age as follows [5-10]:

In the EPICure study (based upon gestational age) from Great Britain and Ireland of 308 surviving patients born in 1995 who were at or less than 25 weeks gestation, neurodevelopmental disability was evaluated in 283 of the 308 survivors at 30 months and reassessed in 241 survivors at six years of age [5,6]. Disability was detected by standardized neurologic examination and cognitive testing using the Bayley Mental Developmental Index (MDI) and Bayley Psychomotor Developmental Index (PDI). Disability was defined as one or more of the following findings: Bayley MDI and PDI 3 standard deviations (SD) below the mean; cerebral palsy; blindness, and/or hearing loss.

- At 30 months of age, 30 percent had developmental delay, which was severe (3 SD below the mean) in 19 percent and moderate (2 to 3 SD below the mean) in 11 percent [5]. Severe neuromotor impairment, hearing loss that was uncorrectable or required hearing aids, and severe vision impairment were seen in 10, 3, and 2 percent of patients, respectively.
- At six years of age, severe, moderate, and mild disabilities were noted in 22, 24, and 34 percent of patients, respectively [6]. Eighty-six percent of children with severe disability at 30 months continued to have moderate to severe disability at six years of age.

- At 11 years of age, 219 of the 308 survivors compared to controls born at term had lower test scores for cognitive ability, reading, and mathematics, as well as lower performance ratings by teachers [10,11]. About 40 percent of survivors had cerebral palsy, and moderate or severe impairment of neuromotor function, vision, and hearing were present in 10, 9, and 2 percent of children, respectively [10]. Overall, 45 percent of extremely premature children had serious functional disability compared to 1 percent of their classmates, and about half were free of serious disability.
- Thirteen percent of extremely premature children attended special schools, and about 60 percent of those in mainstream schools had special education needs [11]. Survivors in mainstream schools had a 10-fold greater use of special education resources than their classmates.

In a longitudinal study (based upon birth weight) from a large urban center in Cleveland, Ohio, an increase in neurodevelopmental impairment at eight years of age was demonstrated in 219 ELBW survivors born between 1992 and 1995 compared to 176 NBW controls [7]. These included higher rates of:

- Poor motor skills (47 versus 10 percent) and cerebral palsy (14 versus 0 percent)
- Intellectual quotient (IQ) less than 85 (38 versus 14 percent)
- Impaired vision of less than 20/200 (10 versus 3 percent)
- Limited academic skills (37 versus 15 percent)

The rate of ELBW survivors without any impairment is very low in the smallest neonates and increases with BW. This was illustrated in a study from the National Institute of Child Health and Human Development Neonatal Research Network that assessed the outcome of 5250 ELBW infants who were born between 1998 and 2001 at 18 to 22 months CA [12]. The following outcomes were noted:

- By 18 to 22 months CA, 40 percent of the cohort had died.
- Sixteen percent of the cohort had no impairment, which was defined as a Bayley Scales of Infant Development II score ≥ 85 , normal neurologic examination, and normal vision, hearing, and walking. The unimpaired survival rates varied from less than 1 percent for infants with BW ≤ 500 g to 24 percent for infants with BW between 901 to 1000 g. The mean BW for unimpaired survivors was 824 g.
- Twenty-two percent had mild impairment (Bayley score between 70 and 84, mild cerebral palsy, mild neurologic findings, or minor sensory impairment) and 22 percent had moderate to severe impairment (Bayley score < 70 , moderate/severe cerebral palsy, bilateral blindness, or bilateral hearing requiring amplification).
- Multivariate regression analyses demonstrated the following factors, in addition to birth weight, were associated with mortality and neurodevelopmental outcome; maternal (age, marital status, and private insurance) and infant characteristics (female, singleton, small for gestational age, and white), prenatal and delivery care (antenatal steroids and cesarean delivery), and the absence of major neonatal morbidities and interventions.

Similar results were reported from a prospective study of all infants born in Norway between 1999 and 2000 with gestational ages between 22 and 27 weeks or birth weights between 500 and 999 g [13]. At a mean age of 5 years and 10 months, the mean IQ was 94 ± 15 , and the incidence of cerebral palsy (CP) was 11 percent. The risk of moderate to severe disability was greater in children with gestational ages 25 weeks or less (28 of 87 children, 32 percent) compared with those born between 26 and 27 weeks (12 of 152 children, 8 percent).

Very preterm infant — Although less at risk for neurodevelopmental disability compared to extremely preterm or ELBW survivors, a significant number of very preterm or VLBW adult survivors have neurodevelopment deficits. In reviewing the literature, one must remember these VLBW studies include patients who are ELBW. Study outcomes may differ because the relative proportion of ELBW patients, who may contribute substantially to the morbidity, may vary within these studies.

The magnitude of risk was illustrated in the French EPIPAGE study that prospectively followed 2901 premature live births between 22 and 32 gestation weeks born in 1997 and a control group of 667 infants born at 39 and 40 weeks gestation [14]. Only 12 percent were born at or below 25 weeks gestation (ELBW). At five years of age, 1817 of the 2357 premature survivors (77 percent) and 396 controls (60 percent) were evaluated by medical

examination and cognitive assessment using the Kaufman assessment battery for children and recording mental processing composite (MPC) scores. The following findings were noted at five years of age:

- Cerebral palsy was present in 9 percent of survivors of prematurity, which was severe in 20 percent of the cases defined as an inability to walk.
- Premature survivors compared to controls had impaired cognitive function as demonstrated by a significantly increased likelihood of having low MPC scores between 70 and 84 (odds ratio [OR] 3.0, 95% CI 2.0-4.6) and between 55 and 69 (OR 3.4, 95% CI 1.8-6.4).
- Severe bilateral vision impairment was seen in 1 percent of premature survivors. Its prevalence increased with decreasing gestational age with 10 percent of infants born at or below 26 weeks gestation having severe bilateral vision impairment.
- Although disability rates were greatest in children who were born at or below 28 weeks gestation (49 percent), the absolute number of children with disabilities was greatest in the group of children born between 29 and 32 weeks gestation. Special health-care services were needed in approximately 40 and 30 percent of the infants with GA between 24 and 28 and between 29 to 32 weeks, respectively.

In separate analyses of the EPIPAGE cohort, premature survivors without moderate or severe neurologic disabilities at discharge remained at higher risk for global developmental delay and discrepancies in academic achievement compared with controls at two years of age [15] and five years of age [16]. At five years of age, the risk of mild and severe cognitive deficiencies in survivors without moderate to severe neurologic disabilities was 21 and 11 percent [16]. Factors that significantly impact developmental outcomes included lower gestational age at birth, presence of cerebral lesions on brain imaging, being born small for gestational age, lack of breastfeeding, and parental education, occupation, and socio-economic status. This suggests that early neonatal morbidities, as well as the postdischarge environment, play a vital role in the developmental trajectory of a preterm infant.

In an Australian cohort of preterm infants with a gestational age ≤ 32 weeks born between 2003 and 2006, significant motor and cognitive deficits were demonstrated at one year of life [17]. Overall, 30 percent of the 218 of the 310 patients evaluated had neurodevelopment delay detected by neurologic examination and testing using the Bayley Mental Developmental Index (MDI) and Bayley Psychomotor Developmental Index (PDI). Bayley PDI scores less than 85 and 70 were observed in 27 and 8 percent of patients, respectively, Bayley MDI scores less than 85 and 70 in 18 and 3 percent of patients. Five percent had abnormal neurologic examination, including three children with hearing loss and three with unilateral blindness.

Two meta-analysis reviewed neurobehavioral outcomes and motor development in very preterm (gestational age ≤ 33 weeks) and/or VLBW infants.

- The first study, which reviewed the literature between 1998 and 2008, demonstrated that very preterm and/or VLBW infants had more behavioral problems (inattention), poorer executive function (verbal fluency, working memory, and cognitive flexibility), and lower test scores in mathematics, reading, and spelling compared to term-born peers [18]. Poorer outcome was associated with lower birthweight and gestational age. Differences between very preterm or VLBW children, and those born at term in academic achievement, behavioral difficulties and neurocognitive problems persisted through adulthood.
- The second study, which reviewed the literature between 1992 and 2009, demonstrated that very preterm and/or VLBW infants had greater motor impairment from infancy to 15 years of age [19]. Lower gestational age and birthweight were associated with poor motor development in the first years of life, which persisted through adolescence. These motor deficits affected balance skills, ball skills, manual dexterity, and fine and gross motor development.

A Dutch study assessed 705 of 959 survivors at 19 years of age who were born before the use of antenatal glucocorticoids and surfactant [17]. Moderate to severe disability was present in 13 percent of survivors. These included neuromotor disability (8 percent), moderate to severe cognitive impairment (4 percent), and visual (2 percent), and hearing impairment (2 percent). The proportion of these patients with birth weights less than 1000 grams was not delineated.

Moderate to late preterm infants — Data, although limited, suggest that moderate to late preterm infants (gestational age between 34 and less than 37 weeks) compared to full term infants have a poorer long-term developmental outcome. This was illustrated in a retrospective Dutch study of 377 moderate to late preterm survivors (gestational age between 32 to 37 weeks) at eight years of age [20]. Of note, 42 percent of the original cohort was not evaluated. The following findings were noted:

- Children who were born moderately to late preterm were more likely to need special education than the general population (7.7 versus 2.8 percent).
- Of the preterm survivors who attended a mainstream primary school, the need to repeat a grade was greater in those born preterm (19 versus 8 percent).
- Adjusting for maternal education, the IQ score of the premature group was three points lower than the control term group (105 versus 108).
- Children who were born preterm were more likely to have behavior problems and attention-deficit hyperactivity disorder.

Further discussion on the long-term neurodevelopment outcome of late preterm (gestational age between 34 and 36 weeks) is presented separately. (See "Late preterm infants", section on 'Long-term outcome'.)

Neonatal brain injury — Preterm survivors with severe neonatal brain injury have the most severe neurodevelopment impairment and are the most likely to use school services. This was illustrated in a follow-up of infants (birth weights of 600 to 1250 g) born between 1989 and 1992 and enrolled in the Indomethacin Intraventricular Hemorrhage (IVH) Prevention Trial [21]. At 12 years of age, cognitive, language, behavioral and educational outcome of preterm survivors with severe brain injury (grade 3 or 4 IVH, periventricular leukomalacia, or severe ventriculomegaly) were compared to preterm survivors without brain injury and children born at term. The following findings were noted:

- Severe neonatal brain injury was the strongest predictor of poor intelligence at 12 years of age and was associated with a 20-point deficit in both verbal and full IQ scores.
- Preterm survivors with brain injury compared to preterm survivors without brain injury and controls born at term were most likely to require school services (76, 44, versus 16 percent, respectively), additional support in reading (47, 30, versus 6 percent), writing (44, 20, versus 4 percent), and mathematics (47, 30, versus 4 percent).

In a case series 21 children (age range 4 to 12 years) who were premature survivors with periventricular hemorrhagic infarction from an original cohort of 38 infants (15 who died), 13 had unilateral spastic cerebral palsy, 3 had bilateral cerebral palsy, 1 had minor neurologic dysfunction, and 4 were neurologically normal [22]. The overall mean and median total IQ was 83. Verbal memory and behavior were abnormal in about half of the children.

Behavior and psychological effects — ELBW and VLBW children are more likely than children born with normal birthweight (NBW) to have specific behavioral problems and psychological problems. These include attention deficit hyperactivity disorder, general anxiety, depression, and poor social interaction with peers [23-26]. However, premature adolescent and young adult survivors tend to engage in less-risky behavior and be shyer than those born full-term [23,24,27].

Extremely low birthweight — Children who are ELBW survivors are at increased risk for behavioral and school problems as illustrated by the following:

- In another report from the EPICure study (United Kingdom and Ireland) of premature infants born at a GA \leq 25 weeks, children who were extremely premature were more likely to have behavior problems at 6 years of age compared to those born at full term based upon reports from parents and teachers (19 versus 3 percent) [28]. These included difficulties in attention (33 versus 7 percent) and peer interaction (25 versus 5 percent), hyperactivity (30 versus 9 percent), and emotional (14 versus 4 percent) and conduct problems (13 versus 5 percent).
- In a Swedish report of 86 children born at a GA <26 weeks evaluated by parent and teacher surveys at a mean age of 11 years, 85 percent of children born prematurely were functioning in mainstream schools

without major adjustment problems [29]. However, children who were ELBW infants compared to full term controls were more likely to have internalizing behaviors (anxiety, depression, withdrawn, and somatic complaints) and attention deficit, and were less well adjusted at school.

ELBW survivors are also at-risk for autistic spectrum disorders:

- In a follow-up assessment of the EPICure cohort at 11 years of age, 16 of 219 survivors (7 percent) were diagnosed with autism spectrum disorders compared with none of their term-born classmate controls [30].
- In the ELGANs (extremely low gestational age newborns) study of infants born before 28 weeks gestation, 21 percent of the 988 survivors screened positive for autism at 24 months corrected age based on assessment using the Modified Checklist for Autism in Toddlers (M-CHAT) [31]. However, the M-CHAT appears to have low specificity in children who were born before 28 weeks' gestation because they have associated motor, cognitive, visual, and hearing impairments. (See "Screening tools for autism spectrum disorders", section on 'Modified CHAT'.)

Very low birthweight — Similar behavior and psychological changes have been reported in VLBW children and young adults as illustrated by the following observations from different time periods at different age of follow-up:

- In a follow-up report from the EPIPAGE study of ELBW infants born in 1997, the 1102 LBW survivors at five years of age were more likely to have behavioral problems compared to 375 control children born at term [32]. Although behavioral problems were strongly associated with low cognitive performance, LBW survivors still had a higher risk of behavior problems than children born at term after adjusting for cognitive performance, and other risk factors, including maternal age at birth, health of the child, maternal mental health, and parents' assessment of the child's development (OR 1.8, 95% CI 1.2 to 2.8). Behavior problems included hyperactivity, conduct problems, emotional symptoms, and problems with peers.
- In a study of 219 ELBW survivors born between 1992 and 1995 at a tertiary center in Cleveland, Ohio, attention deficit hyperactivity disorder was more common in the ELBW survivors than children born at term at eight years of age. The children who were ELBW infants were also more likely to have higher anxiety, and symptoms associated with Asperger syndrome and autism [33].
- In a longitudinal study from the same center in Cleveland, Ohio, psychopathology and behavioral outcomes at 20 years of age were examined in 242 VLBW survivors born between 1977 and 1979 compared to 233 NBW controls [23]. VLBW males compared to controls experienced fewer delinquent behaviors, similar rates of internalizing and externalizing behaviors, but had more frequent thought problems as reported by parents. VLBW females also had fewer delinquent behaviors but had more withdrawn and internalizing behavior by self-reports, and had higher parental reported scores of anxiety, depression, withdrawal, and attention problems than controls.
- In a study from the United Kingdom of 108 individuals who were born very preterm (VPT, gestational age less than 33 weeks) and 67 controls born at term between 1979 and 1981, assessment at age 18 to 19 years using the Eysenck Personality Questionnaire-Revised demonstrated that VPT women were more introverted and likely to be anxious, moody, depressed, and had lower self-esteem compared to controls [34].

Premature birth appears to be associated with an increased risk for significant psychiatric disorders in adolescent and young adult survivors [35,36]. This was demonstrated by a population-based Swedish study that reported hospitalization rates for a psychiatric disorder in preterm survivors (age range 8 to 29 years) of 5.2 percent for individuals born at 24 and 28 weeks gestation (hazard ratio of 1.68) and 3.5 percent for those born between 29 and 39 weeks gestation (hazard ratio of 1.21) [36].

ADULT OUTCOME — In adult survivors of prematurity, the risk of medical and social disabilities increases with decreasing gestational age.

This was best illustrated in a population-based outcome study of all infants born alive and without congenital anomalies in Norway between 1967 and 1983 [37]. The risk of the following medical disabilities was greatest in

very preterm adult survivors (gestational age between 23 to 27 weeks) compared to adults who were full term (gestational age ≥ 37 weeks):

- Cerebral palsy (9.1 versus 0.1 percent)
- Mental retardation (4.4 versus 0.4 percent)
- Schizophrenia (0.6 versus 0.1 percent)
- Autism spectrum (0.6 versus 0.05 percent)
- Other psychological, behavior, emotional disorders (2.5 versus 0.2 percent)
- Disability affecting ability to work (10.6 versus 1.7 percent)

In this study, prematurity was associated with achievement of a lower educational level, lower income, and increase likelihood of governmental subsidy.

Other studies have reported similar results of lower rates of educational achievement, independent living, lower net income, and permanent employment in premature survivors compared to those born full term [38-42]. These results are most likely due to poor cognitive skills leading to impaired learning, especially in adults with birth weights below 1500 g or below 32 weeks gestation [43,44]. Higher socioeconomic status appears to decrease the effect of GA upon cognitive test scores [43].

In contrast, some studies suggest that despite their increased risk of neurodevelopmental disability, patients who are preterm survivors may overcome these difficulties and become functional young adults at a comparable rate to those who were born full term.

This was demonstrated in a longitudinal prospective Canadian study of 166 patients who were ELBW (born between 1977 and 1982 and recruited at birth), and 145 matched controls with normal birth weight (sex, age, and social class) who were recruited at eight years of age [45]. Neurosensory impairment was higher in the ELBW compared to the NBW group (27 versus 2 percent). Evaluation at 23 years of age demonstrated no differences between the 149 of the 166 ELBW participants and the 133 of 145 NBW controls in the following activities:

- High school graduation: 82 versus 87 percent
- Pursuing postsecondary education: 32 versus 33 percent
- Employment: 48 versus 57 percent
- Independent living: 42 versus 53 percent
- Married or cohabiting: 23 versus 25 percent
- Parents: 11 versus 14 percent

In the previously discussed study from England, there were no differences between the individuals who were born very premature (VPT) from those born full term in school achievement (A level qualification), enrollment in postsecondary education, and employment rate even though the VPT group was relatively more disadvantaged in their socioeconomic status compared to controls [34]. The VPT group did receive more educational assistance than controls.

In a 31 year long-term study, there were no differences in 126 adults born preterm (34 weeks GA) compared to full term controls in marital status, educational attainment, socioeconomic status, cognitive function, working memory, and attention or psychological changes [46].

The differences in outcome among these outcome studies have been attributed to higher socioeconomic status, an increase in educational support, or benefit from a national health care system [7].

Quality of life — Both premature adolescent and young adult survivors, and their parents report a greater prevalence and complexity of functional limitations than control full term adolescents and their parents. Despite these limitations, premature survivors and their families place a high value upon their quality of life similar to those born full term [47-50].

As an example, in a subsequent report of the previously described cohort of 241 VLBW survivors and 232 matched normal birth weight controls from Cleveland [38], when assessed by the Child Health and Illness Profile: Adolescent Edition (CHIP-AE), the two groups self-reported similar health, well-being, and functioning at 20 years of age [51].

In addition, patients and their parents have a higher perception of their quality of life than health care professionals [52]. It is important for health care providers to be aware of this discrepancy so that they do not only focus narrowly on neurodevelopmental disabilities of their patients but also broaden their consideration of outcome to include the ability of adult survivors to overcome their limitations with a positive self-perception of their quality of life [45,53,54].

ASSOCIATED CONDITIONS — Other neonatal complications are associated with an increase risk of poor neurodevelopmental outcome [55,56]. These include the following:

- Bronchopulmonary dysplasia (BPD) [57]. (See "Outcome of infants with bronchopulmonary dysplasia", section on 'Neurodevelopment outcome'.)
- Necrotizing enterocolitis. (See "Management of necrotizing enterocolitis in newborns", section on 'Growth and neurodevelopment'.)
- Retinopathy of prematurity. (See "Retinopathy of prematurity".)
- Postnatal use of glucocorticoids to treat BPD is associated with an increased risk of cerebral palsy. (See "Postnatal use of glucocorticoids in bronchopulmonary dysplasia".)
- Intraventricular hemorrhage. (See "Management and complications of intraventricular hemorrhage in the newborn", section on 'Outcome'.)
- Poor growth — In very preterm infants, growth impairment has been shown to impair cognitive and motor performance at seven years of age [58]. Improved growth is associated with a better neurodevelopmental outcome as illustrated by a report from the NICHHD Neonatal Research Network that demonstrated increasing weight gain during NICU hospitalization was associated with decreasing incidence of cerebral palsy, Bayley MDI and PDI <70, abnormal neurologic examination, neurodevelopmental impairment, and need for rehospitalization when ELBW infants were evaluated at 18 to 22 months corrected age [59].
- Congenital anomalies — Premature survivors with congenital anomalies are more likely to have a cognitive impairment (Bayley MDI or PDI score less than 70), and motor and neurosensory deficit [60].
- Twin gestation [61]. Similar data on higher order gestation are not available.

TRENDS OVER TIME — Neonatal care has changed over time, resulting in improved survival, and possibly improved neurodevelopmental outcomes [62-64]. Possible changes in practice that have impacted on neurodevelopmental outcome include the use of antenatal glucocorticoids, surfactant, breast milk, and the decreased use of postnatal glucocorticoid therapy.

The following studies demonstrate improved survival and neurodevelopmental outcome in premature infants:

- In a report from the NICHHD Neonatal Research Network that assessed neurodevelopmental outcome for 3785 ELBW infants (BW 401 to 1000 g and GA between 22 to 32 weeks) born during three time periods (1993-1994, 1995-1996, and 1997-1998), both survival and neurodevelopmental outcome at 18 to 22 months adjusted age improved over the three time periods [62]. In this study, the risk of blindness and lower scores on cognitive and psychomotor testing (ie, Bayley Psychomotor/Mental Developmental Indices <70) decreased over time.
- A study from a single tertiary center in the United States demonstrated ELBW infants born in 2000 to 2002 had a better survival rate with less neurodevelopmental impairment (reduced risk of cerebral palsy) than those born during two earlier time periods (1982 to 1989, and 1990 to 1999) when evaluated at 20 months chronologic age [63].
- Improved neurodevelopmental outcome was also illustrated in a population study from the state of Victoria, Australia that compared infants with gestational age below 28 weeks born in 2005 compared to cohorts born in the 1990s [65]. Infants born in 2005 compared to those born in 1997 had lower rates of severe developmental delay (3.7 versus 14.8) and severe disability (3.7 versus 15.4 percent) at two years of age. Survival rates between the two cohorts were not significantly different between 2005 and 1997 (64 versus 70 percent).

- Improved survival and neurodevelopmental outcome at two years of age were observed in a regional study from East Anglia, United Kingdom in VLBW infants born from 1998 to 2002 compared with those born from 1993 to 1997 [66]. During the second time period, there was a decreased risk for blindness, hearing impairment, and hydrocephalus, and a trend towards a decrease in cerebral palsy.

In these studies, observed changes in practices overtime, such as administration of surfactant therapy and antenatal corticosteroids and decreased use of postnatal corticosteroids, were felt to be major contributors to both improved survival and neurodevelopmental outcome [62,63,65,66]. (See "Epidemiology and etiology of cerebral palsy", section on 'Epidemiology' and "Retinopathy of prematurity".)

However, neurodevelopmental outcome in infants <25 weeks gestation and/or birth weight ≤ 800 g appears not to have improved over time despite an increase in survival. This was illustrated by the following studies:

- In a large multicenter study from the NICHD Neonatal Research Network of patients born <25 weeks of gestation, there were no differences at 18 to 22 months' corrected age in mortality and the rates of cerebral palsy, neurodevelopment impairment, and a Bayley MDI score less than 70 between survivors born during two different time periods (1999 to 2001, and 2002 to 2004) [67].
- A study of extremely preterm infants with birth weights ≤ 800 g and a median gestational age of 25 weeks from a single tertiary NICU in British Columbia also demonstrated no change in the neurodevelopment impairment rate (30 percent) at school-age entry over a 20 year period (1983 to 2003), although there was improvement in survival rates [68]. In this cohort, the pattern of disabilities changed with increased rates of cognitive and hearing impairment, decreased rates of visual impairment, and a trend towards lower rates of cerebral palsy over the 20 year period.
- A study from a single tertiary NICU in the Netherlands demonstrated increased survival of infants with birth weights ≤ 750 g between two consecutive five year periods (1996 to 2000, and 2001 to 2005) [69]. This, however, was accompanied by an increase in the risk of impaired neurodevelopmental at two years corrected age during the second period (2001 to 2005).

In summary, some improvement in neurodevelopmental outcome measures has been seen in ELBW infants, however, neurodevelopmental outcome remains poor in the most immature of these infants (<25 weeks gestation or birth weight ≤ 800 g) who approach the limits of viability. In addition, some interventions, which may improve survival, appear to be associated with poor neurodevelopmental outcome. It is unclear whether these associations are direct effects of the intervention (eg, postnatal corticosteroids) or indirect markers for severity of illness (eg, prolonged ventilation).

NEUROIMAGING — Neuroimaging abnormalities detected in the neonatal period appear to be useful in predicting long-term neurodevelopmental outcome.

Ultrasonography — Cranial ultrasonography is the primary neuroimaging modality used to evaluate intracranial pathology in premature infants and predict long-term outcome. It can reliably detect germinal matrix and intraventricular hemorrhage (IVH), and periventricular leukomalacia. Ultrasonography is not as sensitive as magnetic resonance imaging (MRI) in detecting diffuse white-matter abnormalities or cerebellar abnormalities in the posterior fossa particularly during the first month of life [70]. However, extremely premature infants with normal ultrasounds at term equivalent are unlikely to have moderate or severe white matter or gray matter abnormalities on MRI [71].

Although patients with neonatal cranial ultrasound abnormalities compared to those with normal studies are more likely to have long-term neurodevelopmental outcome impairment, a significant number of patients with a normal ultrasound still have mental and psychomotor delay. This was illustrated in a prospective study of 1017 premature infants with a GA < 28 weeks [72]. Mental delay at 24 months of corrected age occurred in 26 percent of all patients including 23 percent of those with normal neonatal ultrasounds, and psychomotor in 31 percent of the entire group versus 26 percent with a normal study. Findings associated with an increase risk of mental delay included moderate/severe ventriculomegaly (RR 2.9, 95% CI 1.8 to 4.6), echolucency (RR 2.7, 95% CI 1.6 to 4.5), and echodensity (RR 1.7, 1.1 to 2.6). These three findings were also associated with an increased risk of psychomotor delay; moderate/severe ventriculomegaly (RR 3.6, 95% CI 2.3 to 5.6), echolucency (RR 4.6, 95% CI 2.7 to 7.8), and echodensity (RR 2.8, 1.9 to 4.2).

Severe IVH and periventricular hemorrhage and leukomalacia detected by ultrasonography are also associated with poor neurodevelopmental outcome. This was demonstrated in a retrospective study of 30 premature infants with periventricular hemorrhage, two-thirds of the patients had significant cognitive and/or motor abnormalities when assessed at 30 months of corrected gestational age [73]. (See "Periventricular leukomalacia", section on 'Prognosis' and "Management and complications of intraventricular hemorrhage in the newborn".)

MR imaging — Magnetic resonance imaging (MRI) studies have demonstrated significant structural brain changes in survivors of prematurity compared to those who were born full term. The following changes have been documented in premature survivors at school age, and in adolescence and adulthood compared to term infants [74-87].

- Thinning of the corpus callosum
- Increased ventricular volume
- Decreased relative volume of gray and white matter during brain growth throughout childhood

MRI appears to be useful in predicting neurodevelopmental outcome at the equivalent of term gestation (GA at 40 weeks) [83,84]. This was best illustrated in a study of 167 preterm infants (GA \leq 30 weeks) who had MRI performed at the equivalent of term gestation and underwent a comprehensive neurodevelopment assessment at two years of age (corrected for prematurity) [83]. The following findings were noted:

- At corrected age of two years, severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory impairment (hearing and vision) were seen in 17, 10, 10, and 11 percent of patients, respectively.
- At corrected age of two years, mild, moderate, and severe white matter abnormalities (eg, signal abnormalities, loss of volume, cystic abnormality, enlarged ventricles, thinning of the corpus callosum, and delayed myelination) were detected in 15, 30, and 50 percent of patients with severe cognitive delay, respectively.
- Patients with moderate to severe white matter abnormalities were at increased risk for severe cognitive delay (OR 3.6, 95% CI 1.5-8.7), severe psychomotor delay (OR 10.3, 95% CI 3.5-30.8), cerebral palsy (OR 9.6, 95% CI 3.2-28.3), and neurosensory impairment (OR 4.2, 95% CI 1.6-11.3).
- Gray matter abnormalities were seen in 49 percent of patients and were associated with an increased risk for severe cognitive delay (OR 3.0, 95% CI 1.2-7.1), severe psychomotor delay (OR 3.8, 95% CI 1.2-12.3), or cerebral palsy (OR 3.8, 95% CI 1.2-12.1), although less strongly than that observed in moderate to severe white matter abnormalities.

These results demonstrate that MRI changes are frequently seen in neonates with a GA \leq 30 weeks and that moderate to severe MRI changes are predictive of adverse neurodevelopmental outcome at two years of age.

Similar findings were noted in another study of very premature infants (gestational age $<$ 30 weeks) that demonstrated poor neurobehavioral performance correlated with white matter abnormalities and volume reduction, and a delay in gray matter gyral maturation at the equivalent of term gestation [88].

MRI abnormalities are more common in adult survivors with low birth weights than in normal control group [89]. Findings include prominent lateral ventricles, loss of white matter, and thinning of the corpus callosum.

MRI, however, can be more difficult (often requiring conscious sedation) and expensive to perform in the neonate compared to ultrasonography. In addition, it is not clear if there is a distinct advantage of MRI over ultrasonography for predicting outcome in these high-risk neonates. As a result, there is not enough evidence to recommend current routine clinical use of MRI as a predictor for neurodevelopmental outcome instead of ultrasonography [90].

PREDICTING OUTCOME — Neurodevelopmental outcome is assessed more accurately at school age than in early childhood because of the following factors:

- Cognitive recovery over time
- Lack of accurate predictive assessment tools in early childhood

Cognitive recovery — There is some evidence that the developing brain may recover some cognitive deficits due to premature birth. As an example, a prospective study of 296 premature infants (birth weight between 600 and 1250 g), who were serially evaluated at 36, 54, 72, and 96 months corrected age, showed improvement in verbal and IQ test scores over time [91]. Greater increases in test scores were associated with higher maternal education levels, two-parent family, and the use of early intervention services, especially in children from a socioeconomically disadvantaged background. Only children with early-onset intraventricular hemorrhage followed by significant central nervous system injury had declining test scores as they grew older.

Early childhood — In premature infants, neurological and development assessment at equivalent term of term gestation (GA at 40 weeks) is a poor predictor of neurodevelopmental outcome at school age and adolescence [92]. Prediction of school age outcome improves as the age at the time of assessment increases.

This was illustrated in a 10-year prospective study of 129 ELBW infants born between 1993 and 1998 who were evaluated at the equivalent of term gestation, and at 3, 6, 12, and 18 months corrected age, with follow-up evaluation between 5 and 10 years of age (mean 8.5 years) [92]. Assessment included neurologic examination, language and social development, behavior, and psychometric testing. The percentages of cases in which the neurodevelopmental status at school age was correctly predicted, were 49, 68, and 70 percent when the assessment was performed 'at term', and at two and four years of age, respectively. In contrast, patients with cerebral palsy were accurately identified by two years of age.

The Bayley Mental Developmental Indexes (Bayley MDI), the most commonly used measure of cognitive function in children less than two years of age, has been shown to poorly correlate with cognitive functioning tests at school age. In a study of 200 ELBW infants, cognitive impairment decreased from 39 percent (defined as a Bayley MDI score of less than 70) at 20 months corrected age to 16 percent at 8 years of age (defined as a Kaufman Assessment Battery for Children mental processing composite score of less than 70) [93].

In addition, it is important to use concurrent control data when using the Bayley scale to detect children at-risk for developmental delay. As an example, a population-based study from Australia demonstrated the mean values of the Bayley-III scale for extremely preterm infants (gestational age <28 weeks) at two-year corrected age approached the normative mean [94]. However, the mean values for term controls were also higher than expected with composite scores between 0.55 to 1.23 SD above the normative mean. When reference values were used to evaluate the extremely preterm patients, it appeared that the number of children with developmental delay was underestimated when compared to earlier studies from the same geographic location. In contrast, the proportion of developmental delay in the preterm group was in the expected range when the preterm group was compared to concurrent term controls. An editorial suggested that the use of reference values in this study would miss a significant number of children with developmental delay, and thereby would not receive early intervention [95].

However, it is unclear whether the improvement in cognitive function is a result of early interventions introduced to the ELBW survivor or because of the test's poor predictive value.

Our approach — We evaluate at-risk infants, including all ELBW infants and VLBW with a prolonged NICU course or conditions associated with poor neurodevelopmental outcome, for poor neurodevelopmental outcome [96]. (See 'Associated conditions' above.)

Until an accurate assessment tool to predict neurodevelopmental outcome in early infancy is developed, we continue to use the following to assess the neurodevelopmental status of the premature survivor in infancy and early childhood:

- Comprehensive physical examination including neurological examination to detect motor deficits and cerebral palsy. In particular, poor postnatal head growth is associated with poor neurodevelopmental outcome and cerebral palsy [97]. (See 'Cerebral palsy' below.)
- We continue to use the Bayley Mental Developmental Indexes in infants and toddlers as it is the best available tool to evaluate infants and young children for cognitive function, despite its poor correlation with cognitive testing at school age.

In older children, assessments include measures of IQ, academic achievement (standardized testing in mathematics, reading, and spelling), and neurophysiologic evaluation (attention, executive function, memory, and fine and gross motor function). (See "Specific learning disabilities in children: Clinical features".)

FOLLOW-UP CARE — Premature infants who survive to hospital discharge continue to have ongoing health issues. Optimal care is provided to the child and their family in a coordinated follow-up program that is familiar with the long-term sequelae of prematurity, can facilitate optimal growth and development of the child, help integrate the child into the family, school system, and targeted community services, and communicates effectively with the primary care provider.

In the United States, the Individuals with Disabilities Education Act (IDEA), a federal law, mandates early intervention for eligible patients between birth and three years of age. The individual states are responsible for the delivery of early intervention programs (EIP) and the primary care provider needs to be familiar with the state regulations of his/her community.

Each state is required to identify and evaluate patients at risk or who currently demonstrate developmental delays or disabilities. In most states, patients discharged from the neonatal intensive care unit (NICU) meet the eligibility criteria for diagnostic evaluation, which consists of a multidisciplinary set of assessments (eg, medical, nutritional, speech/language, hearing, vision, development, and family). However, eligibility for EIP differs from state to state and not all NICU graduates will qualify in some states.

Because of the need to provide optimal care to the infants discharged from the NICU, which are primarily premature infants, the American Academy of Pediatrics (AAP) has developed guidelines for the primary care provider in the management of these patients [96]. These guidelines include recommendation for screening, evaluation, and referral for hearing and vision loss, and neurodevelopmental disorders. (See "Care of the neonatal intensive care unit graduate".)

Hearing — Most NICU graduates are screened for hearing loss prior to discharge. Hearing screen should be repeated at five to six months corrected gestation age or sooner if there are concerns about hearing impairment. If an abnormal hearing screen is present, formal audiologic assessment should be performed. If the patient has sensorineural hearing loss, referral to a multidisciplinary team (audiologists, otolaryngologists, and speech pathologists) for management of the patient is recommended. (See "Screening tests in children and adolescents", section on 'Hearing screen' and "Treatment of hearing impairment in children".)

Vision — NICU graduates, especially VLBW and extremely low birth weight (ELBW) infants (birth weight <1500 g and <1000 g, respectively), are at increased risk for retinopathy of prematurity (ROP). Retinal screening by an ophthalmologist should be performed in all VLBW infants or a GA of less than 30 weeks, and in premature infants with birth weights greater than 1500 g or a GA >30 weeks whose clinical course places them at increased risk. The initial screen is performed at four to six weeks after birth with additional examinations at intervals of one to three weeks until the retinal vessels have fully matured. (See "Retinopathy of prematurity".)

Survivors of premature birth are at risk for other ophthalmologic abnormalities including reduced visual acuity, strabismus, myopia, and stigmatism, and should be screened by an ophthalmologist at 9 to 12 months of age. (See "Care of the neonatal intensive care unit graduate", section on 'Vision' and "Care of the neonatal intensive care unit graduate", section on 'Ophthalmologic conditions'.)

Cognitive and motor impairment — Screening for cognitive and motor impairment is imperative to identify survivors who would benefit from early intervention programs (EIPs) and special educational school programs. This should include screening for neurodevelopment problems that occur more frequently in survivors of prematurity such as cerebral palsy and learning disabilities.

EIPs appear to be effective at improving cognitive development in preterm infants. This was illustrated in a systematic review of 16 identified randomized or quasi-randomized trials that found EIPs improved cognitive outcome of children born preterm when evaluated during infancy or at preschool age [98]. However, this effect was not sustained in school-age children.

Cerebral palsy — As demonstrated by the outcome studies discussed above, cerebral palsy is seen in about 9 to 12 percent of ELBW and VLBW infant survivors. (See 'Neurodevelopmental disability and academic achievement' above.)

Clinicians should monitor NICU grads during office visits for physical signs of cerebral palsy such as initial hypotonia, spasticity, abnormal postural reflexes, increased tone, and deep tendon reflexes. Patients demonstrating any of these findings should be referred for evaluation by a pediatric neurologist. Patients who have cerebral palsy will require further evaluation and care from a multidisciplinary team including neurologists, and physical and occupational therapists. (See "Clinical features of cerebral palsy" and "Epidemiology and etiology of cerebral palsy" and "Management and prognosis of cerebral palsy".)

Learning and language delays — Learning and language delays are two of the most common complications of premature survivors and as discussed previously their prevalence increases with decreasing gestational age at birth. (See 'Neurodevelopmental disability and academic achievement' above.)

Screening for cognitive dysfunction, and learning and language delay is imperative to ensure early identification of problems and initiation of early intervention. Developmental evaluations should be based on the patient's post-menstrual age and not chronological age until at least 24 months of age. Referrals to high-risk development clinics and Early Child Intervention Programs should be made for all premature infants. (See "Evaluation and treatment of speech and language disorders in children" and "Specific learning disabilities in children: Clinical features", section on 'Clinical features'.)

SUMMARY AND RECOMMENDATIONS

- Premature survivors are at increased risk for impaired neurodevelopmental outcome compared to individuals who were born full term. These sequelae include cognitive abnormalities, motor deficits including mild fine or gross motor delay, and cerebral palsy, and vision and hearing losses. The risk of impairment increases with decreasing gestational age. (See 'General issues' above and 'Neurodevelopmental disability and academic achievement' above.)
- Premature survivors are more likely to have specific psychological and behavioral problems including attention deficit hyperactivity syndrome, general anxiety, and depression. In particular, female premature survivors have increased internalizing behavior (eg, anxiety, depression, and withdrawn behavior). (See 'Behavior and psychological effects' above.)
- Individuals with birth weights below 1500 g are at greater risk for poor academic performance than those born with normal birthweight because of their impaired cognition, neurosensory defects, and behavioral and psychological problems. (See 'Neurodevelopmental disability and academic achievement' above.)
- Despite their increased risk of neurodevelopmental disability, premature survivors may overcome these difficulties and become functional young adults at a comparable rate to those who were born full term. Patients and their parents place a high value on their quality of life, which is perceived at a higher quality than by health care professionals. (See 'Adult outcome' above.)
- Other neonatal complications are associated with an increased risk of poor neurodevelopmental outcome. These include bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage, poor growth, and the presence of congenital anomalies. (See 'Associated conditions' above.)
- Neonatal care has changed over time, resulting in improved survival, and possibly improved neurodevelopmental outcomes. (See 'Trends over time' above.)
- Cranial ultrasonography is generally the most commonly used neuroimaging modality to detect intracranial pathology and predict long-term outcome. Although magnetic resonance imaging is more sensitive in detecting diffuse white-matter abnormalities or cerebellar abnormalities in the posterior fossa, it is unclear whether it provides any more useful clinical information than ultrasonography. MRI is also more difficult to perform, requiring conscious sedation, and more expensive than ultrasonography. (See 'Neuroimaging' above.)
- Premature infants who survive to hospital discharge continue to have ongoing health issues including neurodevelopmental disabilities. Because of the need to provide optimal care to the infants cared for in the neonatal intensive care unit (NICU), which are primarily premature infants, the American Academy of Pediatrics (AAP) has developed guidelines for the primary care provider in the management of these

infants after hospital discharge. These guidelines include recommendation for screening, evaluation, and referral for hearing and vision loss, and neurodevelopmental disorders. (See 'Follow-up care' above.)

- Primary care clinicians should be familiar with his/her community resources and ensure the premature survivor is evaluated for neurodevelopmental disabilities including screening for hearing and vision. In the United States, LBW infants meet the eligibility criteria in most states for diagnostic evaluation by early intervention programs as mandated by the Individuals with Disabilities Education Act (IDEA). (See 'Follow-up care' above.)

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Periventricular leukomalacia

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INTRODUCTION — Periventricular leukomalacia (PVL) refers to injury of cerebral white matter that occurs in a characteristic distribution and consists of periventricular focal necrosis, with subsequent cystic formation, and more diffuse cerebral white matter injury [1]. PVL is the major form of brain white matter injury that affects premature infants, and is associated with the subsequent development of cerebral palsy, intellectual impairment, and visual disturbances. (See "Epidemiology and etiology of cerebral palsy".)

This topic will discuss the epidemiology, pathophysiology, pathology, diagnosis, and management of PVL.

HISTORY — The lesions of PVL were described more than 100 years ago [2]. Parrot recognized the periventricular lesions as infarcts called 'cerebral stéatose' [3]. Banker and Larroche used the term 'periventricular leukomalacia', described the neuropathological changes that corresponded to coagulation necrosis, and defined the clinicopathological correlations [4].

EPIDEMIOLOGY — PVL is more common in premature than term infants, and occurs more frequently with decreasing gestational age and size. The greatest period of risk for PVL is under 32 weeks of gestational age [5]. PVL also occurs in late preterm (late preterm) and term infants [6]. In the United States, infants born at less than 32 weeks account for about 2 percent of all live births, and very low-birth-weight infants (<1500 g) account for about 1 percent of all live births [7]. (See "Incidence and mortality of the premature infant", section on 'Incidence'.)

The incidence of PVL varies among centers and between survivors and nonsurvivors. The use of different ultrasonographic criteria (eg, echodensities or echolucencies) or MRI criteria contributes to this variability.

- The incidence of PVL based upon ultrasonographic findings ranges from 5 to 15 percent in very low-birth-weight infants [8]. In one study that evaluated the outcomes in approximately 4600 infants with birth weight <1500 g, PVL occurred in 6 percent of those who had sonograms at more than two weeks [8]. The incidence declined from 7 to 4 percent in the smallest (501 to 750 g) to largest (1251 to 1500 g) infants.
- The incidence of PVL based upon MRI findings is variable but generally higher than data based upon ultrasonography, as MRI is more sensitive than ultrasound for the detection of noncystic PVL in premature infants [9]. (See 'Magnetic resonance imaging' below.)
- Neuropathologic evidence of PVL is found in 25 to 75 percent of very low-birth-weight infants who die [1]. The incidence increases with longer postnatal survival. Infants who survived more than six days had higher rates of PVL than those who died earlier (60 versus 7 percent) [10]. Differences between living and autopsied infants occur in part because ultrasonography detects only overt forms of white matter injury.

Prenatal PVL — Among infants with PVL who die shortly after birth, the leukomalacia may have developed prenatally [11-14]. Many fetuses who die in utero after 20 weeks gestation have ischemic lesions that are associated with placental abnormalities [15]. (See "Placental pathology in cases of neurologically impaired infants".)

In addition, neuroimaging studies have detected PVL in many children with mild diplegia or hemiplegia who had uneventful term deliveries and neonatal periods, suggesting that the injury occurred prenatally [16,17].

PATHOPHYSIOLOGY — PVL can be caused by ischemia or infection. Because of changes in vascular and cellular factors during development, the brain is more vulnerable to these insults in premature than term infants [1,5,18].

While there are numerous animal models for prenatal and perinatal ischemic brain injuries, and while each model partially recapitulates human pathology, none of them fully mimic PVL [19].

Vascular anatomic factors — The anatomy of the developing cerebral vasculature renders the premature infant especially vulnerable to periventricular white matter injury. Incomplete development of vessels that penetrate the deep and subcortical white matter and those that supply the area near the ventricles result in a boundary zone around the ventricles with diminished vascularization. This area is therefore vulnerable to reduced flow [20,21].

Circulatory factors — Circulatory factors that increase vulnerability to PVL include impaired cerebral vascular autoregulation and vasoconstriction [1,18]. Autoregulation is needed to maintain adequate cerebral blood pressure despite systemic blood pressure variation, and impairment of autoregulation can result in reduced cerebral perfusion when systemic hypotension occurs.

Causes of impaired autoregulation include asphyxia, hypoxemia, hypocarbia, hypotension, excessive handling, and multiple gestations [1,15-17]. Hypoxemia and hypocarbia also cause cerebral vasoconstriction, decreasing cerebral blood flow. Prenatal circulatory disturbances can cause PVL in the fetus.

Cellular factors — In cystic PVL, which occurs predominantly in deep white matter, necrotic changes usually affect all cell components. In contrast, the pathology in diffuse noncystic PVL predominantly affects a specific cell lineage, that of oligodendrocytes.

The following observations from cell culture, animal model, and human development studies suggest that oligodendroglial (OL) cells are a particularly susceptible target:

- In cell culture, differentiating preoligodendrocytes (preOLs), in contrast with astrocytes, are vulnerable to death induced by the excitatory amino acid glutamate, which increases after ischemic injury [22]. Furthermore, cultured preOLs are sensitive to the toxic effect of cystine deprivation, a form of oxidative stress [23,24].
- In a rodent model of neonatal hypoxia-ischemia, late preOLs but not early or mature OLs are selectively vulnerable to hypoxia-ischemia [25].
- In developing human brains, late preOLs are the predominant form during the developmental window of vulnerability for PVL (23 to 32 gestational weeks) [26]. In addition, selective cell death of late preOLs occurs in the diffuse lesion of PVL, which is mediated by oxidative stress [27,28].

Sources of the oxidative stress are attributed to cerebral ischemia and reperfusion and/or maternal/fetal infection [18,29]. Expression of inducible nitric oxide synthase, a key enzyme in the production of nitric oxide, is increased in brains with PVL, suggesting an important role of nitrosative stress in the pathology of PVL [30]. Ischemic insults result in excessive extracellular levels of glutamate released from damaged axons, reactive astrocytes, and preOLs. Excessive glutamate leads to prolonged depolarization of AMPA and kainate receptors on preOLs, resulting in an influx of calcium into the cells, accumulation of reactive oxygen species, and cell death [31]. Evidence of N-methyl-D-aspartic acid glutamate receptors on preOLs also suggests the presence of an alternative signaling pathway for preOL cell death [32].

Axonal development — Axonal maturation studies suggest that axons may be particularly susceptible to damage at a time in development that coincides with the highest risk of PVL [33]. Beta amyloid precursor protein, a marker for axonal damage, has been identified in swollen axons around PVL lesions in the white matter [34,35]. One potential mechanism of ischemic axonal injury in PVL is that of N-methyl-D-aspartic acid (NMDA) glutamate receptor excitotoxicity. In support, a study using a cultured rat optic nerve found that damage to small premyelinated axons during oxygen-glucose deprivation required activation of NMDA receptors expressed on oligodendrocyte processes at sites of contact with the small premyelinated axons [36].

Infection — Antenatal factors increase the risk of premature birth and PVL. As an example, PVL occurs more frequently in premature infants born to mothers with chorioamnionitis, premature or prolonged rupture of the membranes, bacterial vaginosis, or antepartum hemorrhage [11,37-42]. In a meta-analysis, chorioamnionitis was associated with cystic PVL (relative risk 3.0) and cerebral palsy (relative risk 1.9) [43]. Funisitis (inflammation of the umbilical cord) or neonatal sepsis also increases the risk of PVL [37,44]. (See "Placental pathology in cases of neurologically impaired infants".)

Cytokines — Infection may be associated with PVL because the white matter is especially susceptible to damage mediated by cytokines produced as a consequence of maternal or fetal infection, even when the infection is asymptomatic [40,42,45,46]. Increased cytokines activate astrocytes and microglia in the white matter, which in turn release reactive oxygen species that result in injury to preOLs [29].

As an example, in a series of 94 preterm pregnancies in which amniocentesis was performed, 23 newborns had subsequent sonographic evidence of PVL [45]. Median amniotic fluid concentrations of tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 were higher in newborns with PVL than those without. All eight infants who later developed cerebral palsy had PVL and elevated amniotic fluid cytokine levels. In another study, overproduction of tumor necrosis factor-alpha was identified in the microglia of PVL lesions [47].

Inflammatory cytokines also may play a role in the development of white matter damage during or after ischemia [40,46]. In another study, preterm infants ≤ 32 weeks gestational age with genetic variation in the promoter region of the gene encoding interleukin-6 (CC genotype rather than GC or GG), possibly leading to enhanced IL-6 production, were at increased risk for PVL, intraventricular hemorrhage, and hemorrhagic infarction [48]. This functional polymorphism in the IL-6 gene also conveys susceptibility to cerebral palsy among term and near-term infants [49].

Genetics — Although PVL is not considered a genetic disease, individual genetic variations, either in the maternal or fetal genome, may contribute to a susceptibility to preterm birth and white matter injuries [48,50,51].

PATHOLOGY — PVL consists of periventricular focal necrosis, with subsequent cystic formation, and more diffuse cerebral white matter injury. Pathological changes in PVL include variable cell damage followed by cystic change, reduction in white matter, and ventriculomegaly. Ischemic injury initially results in focal necrosis with coagulative changes. These changes are followed by axonal swelling and proliferation of microglial cells, macrophages, and reactive astrocytes. The earliest microscopic changes, found within a few days, include astrocyte proliferation and microglia and macrophage accumulation [4]. Lesions may become cystic or hemorrhagic, with reduced white matter volume and ventriculomegaly [52,53].

Clinical correlation with pathology — The pathologic changes of PVL are associated with characteristic neurologic deficits. Damage to oligodendroglial cells can impair the myelination of projection and association fibers or interfere with cortical neuronal development [54,55].

The classic type of PVL with focal necrosis and cyst formation in deep white matter is more common in premature infants with gestational age between 24 to 32 weeks at birth. It is related to the development of cerebral palsy (CP) [1,5]. (See "Epidemiology and etiology of cerebral palsy".)

In contrast, a more diffuse cerebral white matter injury occurs in surviving smaller infants (less than 28 weeks) [34]. Their neurologic outcome is predominated by cognitive impairment, and they are less likely to manifest the typical spastic diplegia CP syndrome at school age [56].

In a study of childhood survivors (mean age 5.6 years) who were born prematurely with PVL, brain MRI using volumetric and diffusion tensor imaging measurements revealed atrophy with abnormal microstructure of the thalamus when compared with 74 term control children [57]. The authors speculated that the thalamus contributes to the cognitive deficits frequently observed in children with PVL.

Infants born with a very low birth weight (≤ 1500 g) are particularly prone to brain injury that involves PVL associated with "neuronal/axonal disease". The latter is a frequent accompaniment of PVL that is characterized by degeneration and volume loss of neurons and axons in the brainstem, basal ganglia, thalamus, cerebral cortex,

and/or cerebellum [58]. The constellation of PVL and neuronal/axonal disease has been termed "encephalopathy of prematurity." Common sequelae include cognitive, behavioral, attentional, or socialization deficits, while cerebral palsy (major motor deficits) is a less frequent outcome.

DIAGNOSIS — Periventricular leukomalacia (PVL) is detected in newborns by brain imaging using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Ultrasound is the initial standard method because it is portable and least expensive.

Ultrasound — Ultrasound findings in PVL consist of echodensities and cysts, but the criteria for diagnosis are not well defined. A standard examination includes coronal and sagittal views. In the coronal view, echodensities typically are seen adjacent to the external angles of the lateral ventricles and distributed throughout the periventricular region. In the parasagittal view, echodensities are apparent at the level of the foramen of Monro and trigone of the lateral ventricles [59-61].

The ultrasound findings evolve on repeated examinations. After one to three weeks, approximately one-half of the echodensities evolve into multiple small echolucent cysts (figure 1 and figure 2). The cysts commonly disappear after one to three months, and ventriculomegaly results. Detection of developing PVL during the first week using power and pulse wave Doppler ultrasound to estimate fluctuations of cerebral blood flow is under investigation [62].

Limitations — Ultrasound has limited sensitivity and specificity to detect PVL, especially if the lesions are less than 0.5 cm. Sonograms may detect only 30 to 40 percent of lesions identified at autopsy [63-65]. This incidence is illustrated by a study in which ultrasound identified only 11 of 39 hemispheres with histological evidence of hypoxic ischemic injury (sensitivity 28 percent) [64]. Serial ultrasound examination and the use of brain MRI improve detection.

In addition, while serial cranial ultrasound can detect cystic PVL, it has poor sensitivity for the detection of noncystic PVL. Brain MRI is the imaging modality of choice for the detection of diffuse noncystic PVL. (See 'Magnetic resonance imaging' below.)

With the increasing survival rate of extremely preterm infants, the noncystic form of PVL has become important in the current neonatal care of preterm infants [66].

Routine ultrasound screening — A practice parameter on neuroimaging of the neonate by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society made the following recommendations [60]:

- Routine ultrasound screening should be performed on all infants with a gestational age less than 30 weeks
- Screening should be performed at 7 to 14 days of age and repeated at 36 to 40 weeks postmenstrual age

This strategy is designed to detect clinically unsuspected intraventricular hemorrhage (IVH) that may influence monitoring and management, as well as PVL or ventriculomegaly, which provides information about neurodevelopmental outcome. (See "Clinical manifestations and diagnosis of intraventricular hemorrhage in the newborn" and "Management and complications of intraventricular hemorrhage in the newborn".)

Our practice is more inclusive, although we screen at similar intervals. We recommend routine cranial ultrasonography of all infants born before 33 weeks gestation or with birth weight <1500 g to identify intracranial abnormalities. Infants are screened at 7 to 14 days to detect intraventricular hemorrhage; an initial scan is obtained at three to five days in extremely low-birth-weight infants at high risk for abnormalities. PVL may not be seen on the initial scan. A sonogram performed at 4 weeks of age detects most cystic PVL and ventriculomegaly [67,68]. We also obtain a sonogram prior to discharge.

If abnormalities are detected by ultrasonography, more frequent examinations are performed to assess the progression of PVL. In this case, MRI frequently is used for better documentation of the extent of white matter injury. (See 'Magnetic resonance imaging' below.)

Computed tomography — CT scanning is less useful for the diagnosis of PVL in the very preterm infant because it detects fewer lesions than does MRI or ultrasonography [69]. The reduced sensitivity of CT scanning is due in part to the difficulty in differentiating periventricular hypodensities from areas of hypodensity that normally are present. However, in older infants, CT can identify the loss of periventricular white matter and ventricular enlargement.

Magnetic resonance imaging — Technological advances have enabled MRI to be performed on preterm infants. PVL is seen as hypointense periventricular lesions on T1-weighted MRI images and as hyperintensity on T2-weighted images [70]. Such changes can be detected early in the neonatal stage, even before cystic formation becomes evident on ultrasound [71].

MRI can detect the same well-defined pathologic lesions seen by ultrasound, including IVH and cystic PVL, with the additional advantage of detecting more subtle abnormalities, such as noncystic diffuse white matter injuries, with higher sensitivity. This advantage of MRI is important because noncystic diffuse white matter injuries are common in extremely preterm infants. Comparative studies in preterm infants revealed that cranial ultrasound showed high reliability in the detection of cystic PVL, germinal layer hemorrhage, and IVH, but had significant limitations in the detection of noncystic PVL or diffuse white matter injuries [72,73]. In addition, normal echogenicity in white matter on ultrasound does not always predict normal white matter signal intensity on MRI.

Diffusion-weighted imaging (DWI) is an MR technique that demonstrates motion of water in tissue and enables detection of abnormalities in white matter, providing a mechanistic insight into the imaging studies of preterm infants [70,74,75]. DWI enables earlier detection of PVL or white matter injuries [76,77].

DWI studies show that diffuse high signal intensities seen on T2-weighted MRI, whose interpretation was uncertain, likely represent oligodendrocyte or axonal abnormalities [78,79]. These findings suggest that diffuse high T2 signal intensity in white matter may be a neuroradiologic correlate of the pathologic findings associated with noncystic PVL [34].

MRI in older children — In older children with spastic cerebral palsy, MRI findings include increased periventricular intensity on T2-weighted scans, ventriculomegaly, a bumpy configuration of the lateral ventricles, high-intensity areas in the white matter adjacent to the trigone body of the lateral ventricles, and deep cortical sulci. These findings result from glial scarring and inadequate myelination of periventricular axons [80,81]. MRI findings in children with PVL are related to clinical outcome. (See 'Prognosis' below.)

DIFFERENTIAL DIAGNOSIS — In addition to ischemia and bacterial infections discussed above, other conditions cause periventricular white matter injury. They include malformations and genetic, metabolic, and infectious insults [52]. For example, toxoplasmosis and cytomegalovirus cause periventricular necrotizing lesions accompanied by calcification. PVL must also be distinguished from periventricular hemorrhagic infarction.

Periventricular hemorrhagic infarction — PVL is distinct from periventricular hemorrhagic infarction, although the two may coexist in premature infants. PVL is generally symmetric and rarely hemorrhagic [54]. In contrast, periventricular hemorrhagic infarction nearly always is unilateral or asymmetric and always is grossly hemorrhagic [54]. The pathogenesis of this lesion is uncertain, but probably results from infarction caused by venous obstruction after a germinal matrix-intraventricular hemorrhage [54]. The circulatory disturbance is thought to occur in the subependymal region where the medullary veins drain into the terminal vein, as demonstrated by Doppler ultrasound study [82].

In serial imaging studies, periventricular hemorrhagic infarction evolves into a single large cyst, in contrast with the multiple small cysts seen in PVL. This large cyst usually does not disappear and may become confluent with the lateral ventricle [54]. The clinical correlate of hemorrhagic infarction is a spastic hemiparesis or an asymmetric spastic quadriparesis that usually is accompanied by intellectual deficits.

MANAGEMENT — No specific cure exists for periventricular leukomalacia (PVL). Therapy is directed at teaching caregivers to handle, feed, dress, and toilet their children. Physical therapy also may prevent secondary deformities. However, a randomized controlled trial of 105 infants with abnormal cranial ultrasound scans

demonstrated no benefit of early physical therapy (started before clinical abnormalities developed) compared with standard treatment (delayed physical therapy, started when abnormal physical signs became apparent) [83].

After discharge, infants with PVL are monitored for the development of sequelae, including spastic cerebral palsy, cognitive impairment, and visual and ocular abnormalities. Parents are trained to identify and ameliorate gross and fine motor deficits and disorders of higher mental function and are supported in the care of a handicapped child [84].

PROGNOSIS — Cranial ultrasound and brain MRI may yield prognostic information in neonates and children with PVL. In addition, a meta-analysis of 51 studies with a total of 481,753 infants found that lower umbilical cord pH is significantly associated with intraventricular hemorrhage or PVL (odds ratio 2.9, 95% CI 2.1-4.1) in addition to other adverse outcomes [85].

Ultrasound studies — Cranial ultrasound findings and neurodevelopmental examinations in newborns correlate with later clinical outcome. Infants with more extensive white matter injury and persistent ventricular enlargement are more likely to have severe motor and cognitive deficits.

The sonographic detection of PVL with cyst formation in the neonatal period correlates with the subsequent development of cerebral palsy.

- In a review of 12 studies, 58 percent of 272 infants with periventricular echolucency developed cerebral palsy, compared with 2.6 percent of 655 infants with normal cranial ultrasound scans [86]. Similarly, premature infants with abnormal neurodevelopmental examinations were more likely to have cerebral palsy (38 versus 6 percent) or minor neuromotor dysfunction (27 versus 13 percent) at 1 year or older, compared with infants with normal examinations [87].
- In a study of 127 surviving preterm infants with periventricular echodensities or cyst formation, moderate or severe periventricular echodensities with large cyst formation had a positive and negative predictive value for cerebral palsy of 90 and 93 percent, respectively [43]. The contribution of periventricular echodensities without cysts to the development of neurologic sequelae is less well defined.

Abnormalities confined to the germinal matrix correlate with hemorrhage and do not predict poor outcome [88].

Another important determinant of long-term outcome is the presence of periventricular intraparenchymal echodensities that represent hemorrhagic necrosis. One report compared the outcomes in 75 infants with extensive or localized intraparenchymal echodensities [89]. Infants with extensive injury were more likely to die (79 versus 38 percent), have motor deficits (100 versus 70 percent), and have poor cognitive outcome (80 versus 57 percent) than those with localized lesions.

Although ultrasound has been most conventionally and widely performed to detect PVL in preterm infants, it is less effective in identifying infants who have noncystic PVL. In a study of 1749 infants with extremely low birth weight and normal ultrasound studies, 29 percent had either cerebral palsy or delayed mental development before 2 years of age [90]. Considering the increase in survival rate of extremely preterm infants, it would be reasonable to consider MRI to add more prognostic information for such high-risk infants.

MRI studies — Abnormal white matter and gray matter findings on brain MRI at term are predictors of adverse neurodevelopmental outcome, as illustrated by the following reports:

- In a study of 167 very preterm infants, moderate to severe cerebral white matter abnormalities on MRI performed at term equivalent (gestational age of 40 weeks) were found in 21 percent, and were associated with the following adverse neurodevelopmental outcomes at a corrected age of 2 years [9]:
 - Cognitive delay (odds ratio [OR] 3.6, 95% CI 1.5-8.7)
 - Motor delay (OR 10.3, 95% CI 3.5-30.8)
 - Cerebral palsy (OR 9.6, 95% CI 3.2-28.3)

- Neurosensory impairment (OR 4.2, 95% CI 1.6-11.3)

The same study found that gray matter abnormalities on MRI at term equivalent were present in 82 infants (49 percent), and were also significantly associated (but less strongly than white matter abnormalities) with cognitive delay, motor delay, and cerebral palsy [9].

- A similar study of 86 prematurely born newborns found that neurodevelopmental outcome among survivors at 18 months was normal, borderline, and abnormal in 59, 26, and 15 percent, respectively [91]. Increasing severity of white matter injury, ventriculomegaly, and intraventricular hemorrhage on early MRIs (at median age 32 and 37 weeks post-gestation) were associated with abnormal outcome.

Quantitative MRI studies have found a decreased volume of cortical gray matter in preterm infants at term [92-95] and later in childhood [96-99] in comparison with normal term infants. Such abnormalities in neuronal development may be associated with the cognitive dysfunction commonly observed in preterm infants [55]. In addition, precise quantification of human brain development demonstrates that cortical surface area grows faster than cortical volume in an allometric scaling relationship [100]. This rate of growth is dose-dependently reduced with earlier interruption of pregnancy and is proportional to the risk of later developmental delay.

White matter injuries appear to be a major risk factor for cortical abnormalities in preterm infants. In a volumetric MRI study of 119 preterm infants, those with severe or moderate white matter injury had a 17 percent reduction of cortical gray matter volume, 25 percent reduction of absolute myelinated white matter volume, and a 49 percent increase of absolute cerebrospinal fluid volume compared with infants without white matter injuries [93]. In subsequent studies from the same group, white matter injuries had a greater influence on reduction in gray matter at term than other variables (gender, gestational age, intrauterine growth retardation, bronchopulmonary dysplasia, and intraventricular hemorrhage) [101]. In addition, white matter injuries at term appear to be predictive of motor and cognitive impairment at 2 years of age [9].

MRI findings may also be useful to predict disability in older infants or children. For example, in a study of 30 children 6 to 14 years of age with spastic diplegia, the extent of white matter reduction, severity of ventricular dilatation, involvement of the optic radiation, and thinning of the posterior corpus callosum correlated with full scale and performance IQ, but not with verbal IQ [102]. In another series of 31 children with spastic cerebral palsy and PVL, lateral ventricular volumes measured on MRI were larger in those with than without cognitive impairment or in age-matched controls [103]. Ventricular volumes were also greater in children with moderate or severe motor deficits than in those with mild deficits. However, the extent of increased periventricular intensity on T2-weighted scans performed in the neonatal period was not as predictive, correlating somewhat with mental impairment but not with the severity of cerebral palsy [104].

PREVENTION — Strategies to prevent periventricular leukomalacia (PVL) emphasize the maintenance of cerebral perfusion. Systemic hypotension, cerebral vasoconstriction, or conditions that impair cerebrovascular autoregulation should be avoided by correcting abnormalities in blood pressure and blood gases (eg, hypocarbia, hypoxemia).

The role of neuroprotective agents in the prevention of PVL is being investigated. Antenatal exposure to betamethasone may be associated with a decreased risk of cystic PVL. In a retrospective, observational study of 883 preterm infants, the rate of cystic PVL was lower in infants whose mothers received antenatal betamethasone than in those who received dexamethasone (adjusted odds ratio 0.3) or no glucocorticoid treatment (adjusted odds ratio 0.5) [105]. Further study is needed to confirm these observations [106]. (See "Antenatal use of corticosteroids in women at risk for preterm delivery".)

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Retinopathy of prematurity

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INTRODUCTION — Retinopathy of prematurity (ROP), formerly known as retrolental fibroplasia because of its end-stage appearance, is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. Next to cortical blindness, ROP is the most common cause of childhood blindness in the United States. Other ophthalmologic disorders that occur frequently in preterm infants include amblyopia, strabismus, and refractive errors.

An overview of ROP will be provided below. Other common eye problems in premature infants are discussed separately. (See "Refractive errors in children" and "Overview of amblyopia" and "Evaluation and management of strabismus in children".)

OCULAR CHARACTERISTICS — The size and characteristics of the eye differ in premature and term infants:

- The globe diameter is approximately 10 to 14 mm at 28 weeks' gestation, compared with 16 to 17 mm at term.
- The cornea and vitreous may be hazy in premature infants and impede visualization of the fundus. Small peripheral lens vacuoles are common. In addition, an incompletely involuted hyaloid artery may appear as a white or red strand in the vitreous.
- The blood vessels in the anterior vascular capsule of the lens regress in a consistent pattern and correlate well with gestational age between 27 and 34 weeks [1].
- Pupillary size in premature infants is approximately 3 to 4 mm, slightly smaller than at term. Constriction of the pupils in response to light starts at approximately 30 to 32 weeks' gestation and is consistently present after 35 weeks [2].
- Tear production is reduced in premature infants and may result in drying of the corneas during an eye examination, increased absorption of topically applied medications, or masking the diagnosis of a congenital lacrimal duct obstruction [3].

PATHOGENESIS

Normal vascularization — The sequence of vascularization of the eye is important in understanding the pathogenesis of ROP. No blood vessels are present in the retina before approximately 16 weeks' gestation. From approximately the sixth week, the anterior segment of the eye receives its vascular supply from the hyaloid artery. This artery originates from the optic nerve, passes through the vitreous, and supplies vessels to both surfaces of the lens and iris. These vessels usually are resorbed by 34 weeks of gestation.

Retinal vascularization begins at 15 to 18 weeks' gestation. Retinal blood vessels extend out from the optic disc (where the optic nerve enters the eye) and grow peripherally. Vascularization in the nasal retina is complete at approximately 36 weeks. Vascular development usually is complete in the temporal retina by 40 weeks, although maturation may be delayed until 48 to 52 weeks' postmenstrual age in premature infants (figure 1).

Vascularization in ROP — The pathogenesis of ROP is not well understood. The mechanism is thought to involve two stages. An initial injury caused by factors such as hypotension, hypoxia, or hyperoxia, with free radical formation, injures newly developing blood vessels and disrupts normal angiogenesis. Following this disruption, vessels either resume normal growth or new vessels grow abnormally out from the retina into the vitreous. Increased permeability of these abnormal new vessels (neovascularization) can result in retinal edema and hemorrhage. Abnormal fibrovascular tissue may develop along with the neovascularization and later contract, producing traction on the retina. In some severe cases, this results in retinal distortion or retinal detachment. However, in most instances, the abnormal vascular tissue regresses with little residual effect.

Regulation of the expression of vascular endothelial growth factor (VEGF) and other cytokines may contribute to both normal retinal vessel growth and abnormal vascular disruption and subsequent neovascularization [4-10]. The mechanisms that determine whether initial disruption of normal angiogenesis in ROP will be followed by resumption of normal vascular development or progression of pathologic neovascularization are unknown.

Insulin-like growth factor-1 (IGF-1) supports normal retinal vascular growth and interacts with VEGF [11-13]. The possible role of IGF-1 in ROP has been evaluated in several series of preterm infants who had serial blood samples and retinal examinations. In each of these series, decreased serum concentrations of IGF-1 were associated with the development of ROP [14-18].

With low IGF-1, vessels cease to grow, the maturing avascular retina becomes hypoxic, and VEGF accumulates. Later, as IGF-1 levels rise during maturation and reach a critical level, neovascularization ensues.

Activation of a specific VEGF receptor may protect developing retinal vessels and prevent retinal ischemia induced by oxygen. This was investigated in a study in newborn mice, in which activation of the VEGF receptor VEGFR-1 by placental growth factor-1 (PlGF-1) decreased the obliteration of retinal vessels by hyperoxia (22 versus 5 percent) and did not induce neovascularization [19]. Stimulation of another VEGF receptor, VEGFR-2, had no effect on blood vessel survival.

Photoreceptor development — ROP appears to affect photoreceptor development. An observational study in which retinal sensitivity and retinal responsiveness were assessed by electroretinography between 30 and 72 weeks' PMA suggests that photoreceptor development is altered in prematurity (with or without ROP); that conditions that affect the photoreceptor cells (eg, ROP, ROP treatment) appear to reduce sensitivity; and that retinal neuronal behavior may be influenced by extrauterine experience [20,21].

EPIDEMIOLOGY — ROP affects a substantial number of premature infants worldwide. Both the incidence and severity increase with decreasing gestational age (GA) and birth weight [22-26].

In a study of 951 preterm infants born (<37 weeks' GA) at a single center between 1989 and 1997, ROP developed in 21 percent of patients and severe ROP in 5 percent (stage 3 or greater) [22]. No infant born at more than 32 weeks' GA developed the disorder, and no infant born later than 28 weeks' GA needed retinal surgery. (See 'Stage' below.)

In a multicenter study conducted in the United States between October 2000 and October 2002, the incidence of ROP in preterm infants (birth weights <1251 g) was 68 percent [27]. The overall incidence of severe ROP was 36 percent. The incidence of ROP was 8 percent, 19 percent, and 43 percent among infants born at ≥ 32 weeks', >27 to 31 weeks', and ≤ 27 weeks' gestation, respectively.

The increased incidence of severe ROP with decreasing GA also was demonstrated in a population-based cohort study from New Zealand and Australia [24]. The overall incidence of severe ROP among infants born at less than 32 weeks' GA was 10 percent. Severe ROP increased from 3 to 34 percent as gestational age decreased from 27 to 24 weeks, respectively.

The above studies, which were conducted in developed countries, suggest that infants born at ≥ 32 weeks are not at risk for developing ROP. In addition, most infants born at >28 weeks who develop ROP have mild disease that does not require treatment.

In developing countries, the infants who develop severe ROP are larger and are of a greater estimated GA than those in developed countries. A survey of ophthalmologists from low, moderate, and highly developed countries found that the mean birth weight of infants with severe ROP was greater in infants in developing than in developed countries (900 versus 750 gm) [28]. Similarly, the mean GA of infants with severe ROP was greater in developing than in developed countries (26 to 33.5 versus 25 weeks).

Risk factors — The most important risk factor for developing ROP is prematurity. However, more than 50 separate risk factors have been identified. On multivariate analysis, low birth weight, low gestational age, assisted ventilation for longer than one week, surfactant therapy, high blood transfusion volume, and cumulative illness severity were independently associated with higher rates of ROP [29-31].

Other possible risk factors include sepsis, fluctuations in blood gas measurements, intraventricular hemorrhage, bronchopulmonary dysplasia, systemic fungal infection, and early administration of erythropoietin for the treatment of anemia of prematurity [29,30,32]. The risk of developing ROP also appears to be related to longitudinal weight gain and serum concentrations of IGF-1 and IGFBP-3 [16,33,34]. (See 'Vascularization in ROP' above and 'Anemia of prematurity', section on 'Early EPO use'.)

Elevated arterial oxygen tension is also thought to contribute [35-37]. However, ROP is not the only consideration in determination of target oxygen concentration in preterm infants. Decreased target oxygenation saturation has been associated with increased mortality [37]. (See 'Oxygen monitoring and therapy in the newborn', section on 'High versus low SpO₂ target'.)

Infection may worsen the course of ROP. In one study of affected infants, those with candidemia were more likely to reach threshold ROP and require surgical intervention (OR 7.4, 95% CI 1.7-32.1) compared with those without candidemia [38]. Infection was also associated with poor outcome following laser photocoagulation.

CLASSIFICATION — The International Classification for Retinopathy of Prematurity (ICROP) provides a uniform approach to documenting the extent and severity of disease [39,40]. This system facilitates communication among care providers and promotes collaborative clinical investigation. Four features are evaluated: zone, stage, extent, and presence or absence of plus disease.

Features

Zone — The location of the retinopathy within the retina is defined by dividing the eye into three zones, centered on the optic nerve (figure 2):

- Zone 1, the central zone at the posterior pole of the eye, has a radius of twice the distance from the optic disc to the macula and subtending an arc of 60 degrees centered on the disc.
- Zone 2 forms a circle outside zone 1 with a radius from the optic nerve to the nasal ora serrata.
- Zone 3 is the remaining temporal crescent of retina.

Stage — The five stages indicate the increasing severity of disease:

- Stage 1 consists of a flat white line that demarcates the vascular and avascular retina (picture 1).
- In stage 2, a ridge of fibrous tissue protrudes into the vitreous in the region between the vascular and avascular retina (picture 2).
- In stage 3, new blood vessels and fibrous tissue grow along the ridge and often extend into the vitreous (picture 3).
- Stage 4 signifies a partial retinal detachment. It is further subdivided into stages 4A and 4B, depending upon whether the detachment excludes or includes the macula, respectively (picture 4).
- Stage 5 denotes a total retinal detachment (picture 5).

In the large natural history study mentioned above, stages 1, 2, and 3 occurred at a median postmenstrual age of 34.3, 35.4, and 36.6 weeks, respectively [23].

Extent — The extent of disease is described by dividing the retinal surface into 30° sectors, similar to the hours of a clock. As many as 12 clock hours can be affected, and the stage of retinopathy can vary among sectors.

Plus disease — Plus disease refers to dilation and tortuosity of the retinal arterioles and venules in the posterior pole of the retina as defined by a standard photograph (picture 6) [40]. This indicates severe ROP, perhaps caused by excessive shunting of blood through the neovascular tissue at the ridge, and often is followed by rapid progression to retinal detachment. Plus disease also may be a direct effect of excessive VEGF acting on retinal blood vessels. Vitreous haze, engorgement of the iris vessels, and poor dilation of the pupil sometimes accompany plus disease, and often heralds rapid progression with poor prognosis. This has been referred to as "rush disease," but the newer terminology, "aggressive posterior ROP," is more descriptive and probably preferred [40]. Pre-plus disease is defined as dilation and tortuosity of the posterior pole arterioles and venules that are insufficient for the diagnosis of plus disease [40]. It is the precursor to plus disease and, in one study, predicted progression to severe ROP that required treatment [41].

Threshold ROP — Threshold ROP is defined as five contiguous clock hours or eight total clock hours of stage 3 and plus disease in zone 1 or 2.

Prethreshold ROP — Prethreshold ROP is defined as one of the following:

- ROP at any stage less than threshold in zone 1
- Stage 2 and plus disease in zone 2
- Stage 3 without plus disease in zone 2

- Stage 3 with plus disease in zone 2 but with fewer clock hours of stage 3 than required to meet threshold

NATURAL HISTORY — The course of ROP is more correlated with postmenstrual age (PMA) than postnatal age. The condition typically begins about 34 weeks' PMA, although it may be seen as early as 30 to 32 weeks [23]. ROP advances irregularly until 40 to 45 weeks' PMA but resolves spontaneously in the majority of infants. In the natural history study, in which two-thirds of infants with birth weight ≤ 1250 g developed ROP, treatment for severe disease was needed in only 6 percent [23].

Regression of ROP also depends upon PMA and the location of disease. In one report of 766 children from the natural history study, involution began at a mean PMA of 38.6 weeks, and before 44 weeks in 90 percent of patients [42]. The outcome was favorable in 99 percent of infants when ROP resolved by moving from zone 2 to 3. Partial or total retinal detachment was never seen when ROP was limited to zone 3 in serial examinations.

Ocular outcome is poor in preterm infants with untreated severe ROP. This was evaluated at 5.5 years' corrected age in infants with birth weight ≤ 1250 g who were enrolled in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity [43]. Among untreated eyes, poor fundus structural outcomes (macular compromise by retinal folding or severe retinal detachment) occurred in 3.1 percent of eyes, and poor Snellen visual acuity (20/200 or worse) occurred in 5.1 percent of eyes. All poor structural outcomes and nearly all poor visual acuity outcomes had a history of severe ROP (zone 2 ROP involving >6 clock hours of stage 3+ disease or zone 1 ROP). Poor visual acuity occurred in only 2 of 110 eyes (1.8 percent) when ROP was observed only in zone 3.

SCREENING

Evaluation — The screening evaluation consists of a comprehensive eye examination performed by an ophthalmologist with expertise in neonatal disorders [44]. The pupil must be dilated in order to visualize the vitreous and retina. We recommend instillation in the eye of a combination eyedrop (Cyclomydril, which contains weak concentrations of phenylephrine and cyclopentolate) 30 minutes before the examination. Both manipulation of the eye and the drops used to dilate the pupil can produce systemic sequelae, most notably bradycardia and cardiac arrhythmias [45]. Therefore, careful monitoring of the infant throughout the examination procedure is essential. Topical anesthetic can be used if the examining clinician prefers.

The retina is examined by looking through the pupil with an indirect ophthalmoscope and a 20 or 28 diopter condensing lens while the eyelids are retracted with a speculum. ROP is most commonly visualized in the peripheral retina, which often is obscured by the iris. In order to completely view this area, a scleral depressor is used to indent the eye externally. ROP, if present, is described using the standardized classification. (See 'Classification' above.)

Screening criteria — We screen all infants with birth weight ≤ 1500 g or a gestational age (GA) of less than 30 weeks, as well as those with birth weight between 1500 g and 2000 g or a GA of more than 30 weeks whose clinical course places them at increased risk for ROP (as determined by the attending clinician) as per the 2006 Joint Statement of the American Academy of Pediatrics (AAP) Section on Ophthalmology, the American Academy of Ophthalmology (AAO), and the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) [44,46]. These screening criteria, however, are controversial. In a Canadian study, screening infants with a birth weight of 1200 g or less was the most cost-effective strategy [47].

Screening for ROP is a labor-intensive process with a relatively low yield; less than 10 percent of infants who are screened require treatment [48]. Incorporation of postnatal risk factors into the screening guidelines may increase the yield of screening. Models using various combinations of gestational age, birth weight, postnatal weight gain, and serum IGF-1 levels to predict increased risk of severe ROP have been developed [33,34,49,50]. In initial validation studies, the sensitivity of these models approaches 100 percent, but the specificity ranges from 32 to 84 percent. The use of such models to screen for increased risk of severe ROP has the potential to reduce the number of infants requiring ophthalmologic examinations. However, these methods require additional validation in other populations before changes to the current screening recommendations can be made.

Evaluation schedule — We initiate screening examinations at four to eight weeks after birth, depending upon the GA (at 30 weeks' PMA for infants born at 22 to 26 weeks and at 4 weeks of chronologic age for children born at

≥27 weeks). Our screening schedule conforms to evidence-based screening criteria, which were developed for infants with birth weight ≤1250 g or GA <31 weeks based upon natural history data from two large randomized trials (table 1) [51,52]. In these studies, retinal conditions that indicated a risk of poor outcome were not observed before 31 weeks postmenstrual age (PMA) or 4 weeks postnatal age in 99 percent of infants [53].

Additional examinations are performed at intervals of one to three weeks until the retinal vessels have completely grown out to the ora serrata. If ROP develops, the eyes are examined more frequently, depending upon the severity of disease and rate of progression. The AAP/AAO/AAPOS joint statement recommends follow-up examinations according to the following schedule [44].

Follow-up within one week is recommended for infants with [44,54]:

- Stage 1 or 2 ROP in zone 1
- Stage 3 ROP in zone 2

Follow-up within one to two weeks is recommended for infants with:

- Immature vascularization in zone 1, without ROP
- Stage 2 ROP in zone 2
- Regressing ROP in zone 1

Follow-up within two weeks is recommended for infants with:

- Stage 1 ROP in zone 2
- Regressing ROP in zone 2

Follow-up within two to three weeks is recommended for infants with:

- Immature vascularization in zone 2, without ROP
- Stage 1 or 2 ROP in zone 3
- Regressing ROP in zone 3

When an infant is discharged home before the retinal vasculature is mature, parents must understand the importance of timely follow-up [44,55].

Discontinuation — Screening examinations continue until ROP regresses and the vasculature matures or treatment is needed. Screening examinations can be discontinued when any of the three signs listed below is identified. In the two large randomized trials described above, these signs indicated that the risk of visual loss from ROP was minimal or had passed [51,52].

- Lack of development of prethreshold (stage 3 ROP in zone 2 or any ROP in zone 1) or worse ROP by 45 weeks' postmenstrual age
- Progression of retinal vascularization into zone 3 without previous ROP in zone 1 or zone 2
- Full vascularization

TREATMENT

Indications

Threshold — In the past, ablative therapy for ROP was recommended when threshold ROP (five contiguous clock hours or eight total clock hours of stage 3 and plus disease in zone 1 or 2) was reached. However, earlier intervention is now recommended, as described below [56,57].

In the natural history study, threshold ROP was reached at a median postmenstrual age of 36.9 weeks (5th and 95th percentiles of 33.6 and 42.0 weeks, respectively) [23]. If untreated, approximately 50 percent of eyes with threshold ROP progress to retinal detachment and severe visual impairment [58]. Once retinal detachment occurs, therapy restores useful vision in only a small number of patients. (See 'Retinal detachment' below.)

Prethreshold — Approximately one-third of infants with prethreshold ROP progress to threshold disease [59]. Prethreshold ROP is defined as one of the following: ROP at any stage less than threshold in zone 1; stage 2 with plus disease in zone 2; stage 3 without plus disease in zone 2; or stage 3 with plus disease in zone 2 but with fewer clock hours of stage 3 than required to meet threshold. Repeat examinations usually are performed more frequently because prethreshold ROP can worsen rapidly. (See 'Evaluation schedule' above.)

Using data from the Multicenter Trial for Cryotherapy for Retinopathy of Prematurity study, a computerized model was developed to identify the risk of poor outcome for eyes with prethreshold ROP [60]. The model takes into account demographic factors including birth weight, gestational age, and race, and clinical factors such as age of onset of ROP, rapidity of progression, and the presence of plus disease. The model was able to identify eyes with a high (>15 to 100 percent) or low risk of poor structural outcome without treatment. At three months' corrected age, an unfavorable outcome was more likely in the high- than low-risk group (36 versus 5 percent). The two major predictors of poor prognosis were:

- ROP present in zone 1 (odds ratio [OR] 9.1)
- Plus disease diagnosed at the first examination with prethreshold ROP (OR 8.6)

Early treatment may be beneficial in prethreshold ROP that is considered to be at greater risk for an unfavorable outcome. This was demonstrated in a multicenter trial in which eyes with "high-risk" prethreshold ROP (defined as >15 percent risk of unfavorable outcome without treatment) were randomly assigned to early treatment or conventional management [48]. Compared with conventional treatment, early treatment reduced unfavorable visual acuity (14.5 versus 19.5 percent) and unfavorable structural outcomes (9.1 versus 15.6 percent) at nine months' corrected age. At age six years, early-treated eyes continued to have fewer unfavorable structural outcomes (8.9 versus 15.2 percent) and relatively preserved peripheral vision [61,62]. However, visual acuity outcomes were no longer statistically superior (24.6 versus 29.0 percent unfavorable, $p=0.15$) in the early treatment group. In subgroup analysis, early treatment improved visual acuity outcome for "higher-risk" prethreshold eyes (as defined below).

Based upon further analysis of the results at nine months' corrected age, the recommendations for retinal ablative therapy or continued observation in prethreshold ROP were revised [48,56]. The results at six years support these revisions [62]. Retinal ablative therapy should be considered for eyes with "higher-risk" prethreshold ROP based on clinical findings [48,56]. These include:

- Zone 1, any stage ROP with plus disease
- Zone 1, stage 3 ROP without plus disease
- Zone 2, stage 2 or 3 ROP with plus disease

Close observation should continue for eyes with lower-risk prethreshold ROP based on clinical findings [44,63]. (See 'Evaluation schedule' above.)

Modalities — Standard treatment consists of ablation of the peripheral avascular retina by cryotherapy or laser photocoagulation. This intervention reduces the incidence of adverse structural and functional outcomes [59,64]. Unfortunately, despite appropriate treatment, threshold ROP progresses to retinal detachment in 15 to 20 percent of cases [59]. When threshold ROP is reached, treatment should be undertaken as soon as practicable, and almost always within 72 hours of diagnosis [44].

Cryotherapy — Cryotherapy was the only proven treatment for ROP until the early 1990s, but it has been replaced by laser photocoagulation as standard therapy. The procedure involves freezing the peripheral retina through the wall of the eye, including sclera and choroid, and is performed using local or general anesthesia.

The safety and efficacy of this technique were demonstrated in a large multicenter trial in which 291 infants with threshold ROP were randomly assigned to cryotherapy or no treatment [51]. Significantly fewer treated eyes had an unfavorable outcome, defined as posterior retinal detachment, posterior retinal fold, or retrolental tissue that obscured visualization of the posterior pole (31 versus 51 percent), at three months. The benefit was sustained at 12 months after randomization [58]. Continued benefit of cryotherapy was demonstrated at 15-year follow-up in 254 survivors of the original cohort [65]. Outcome measures included evaluation of ocular structure and visual acuity. Significantly fewer treated than untreated eyes had poor ocular structure, including new retinal folds, retinal detachments, and obstruction of the view of the posterior pole (30 versus 52 percent). In addition, significantly fewer treated than untreated eyes had poor visual acuity, defined as 20/200 or worse (45 versus 64 percent).

Cryotherapy often causes conjunctival chemosis and can result in anterior and posterior inflammation or, in rare cases, more serious complications, such as serous retinal detachment (fluid under the retina) or macular scarring. Some infants, especially those who have bronchopulmonary dysplasia or are given general anesthesia, may develop respiratory decompensation during or after the procedure and need assisted ventilation.

Photocoagulation — Laser photocoagulation, using the diode or argon laser, has become standard treatment for ROP. The laser, mounted on an indirect ophthalmoscope, is aimed through the pupil and focused on the avascular retina using a condensing lens like the one used for retinal viewing.

Structural and visual outcomes suggest that laser photocoagulation is at least as effective as is cryotherapy and most likely superior, although comparative data typically depend upon historical controls or smaller controlled trials [66–68]. As an example, cryotherapy and laser photocoagulation, which were performed during different time periods, were compared in a retrospective record review [66]. ROP resolved in more eyes evaluated in the laser than in the cryotherapy group (88 versus 56 percent), and visual acuity at 12 months of age was significantly better in the laser group.

The short-term observational data that functional and structural outcomes are better with laser than cryotherapy are supported by long-term follow-up of participants in a randomized trial comparing these treatments. In two reports, 44 eyes in 25 patients who were randomly assigned to cryotherapy or laser therapy for threshold ROP (of 118 eyes in 66 patients in the initial group [69–71]) were evaluated after 10 years [72,73]. Compared with cryotherapy, outcomes in the eyes treated with laser included:

- Better mean best-corrected visual acuity (20/66 versus 20/182 (Snellen equivalent))
- Smaller likelihood of developing retinal dragging
- Less myopia, demonstrated by a lower mean spherical equivalent (-4.48 versus -7.65 diopters)
- Greater mean axial length (22.9 versus 21.7 mm) and anterior chamber depth (3.42 versus 2.86 mm) and decreased lens thickness (3.95 versus 4.33 mm)

Laser treatment also appears to be better tolerated than is cryotherapy. Infants are less likely to have conjunctival chemosis, inflammation, pain, or apnea and bradycardia following the procedure.

Cataracts may develop after laser treatment, although the degree of risk is uncertain. Cataracts may be less likely to occur following photocoagulation with a diode than argon laser. In one study of 293 eyes, no visually significant cataracts occurred after diode laser treatment [74]. In contrast, cataracts formed in 1 to 6 percent of eyes following argon laser treatment [75,76]. A rare complication of laser treatment is angle-closure glaucoma seen two to five weeks after treatment [77]. (See "Cataract in children" and "Overview of glaucoma in infants and children".)

Bevacizumab — Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, is an investigational therapy for ROP. Bevacizumab is approved for the treatment of metastatic colon cancer. (See "Overview of angiogenesis inhibitors", section on 'Bevacizumab'.) It has also been used off-label to treat neovascular eye conditions, including age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity [78,79]. (See "Overview of angiogenesis inhibitors", section on 'Bevacizumab' and "Age-related macular degeneration: Treatment and prevention", section on 'Bevacizumab' and "Prevention and treatment of diabetic retinopathy", section on 'VEGF inhibitors for PDR'.)

Potential advantages of intravitreal bevacizumab over photocoagulation for the treatment of ROP include ease of administration typically at the bedside and rapid effect. In addition, bevacizumab may be used in infants for whom photocoagulation is not possible (eg, those with opaque cornea or lens, vitreous haziness, poor pupillary dilation) [80,81]. Potential disadvantages include the possibility of long-term systemic effects and the critical timing of the injection (too early may interfere with normal vascularization; too late may lead to early retinal detachment) [79,81-83]. (See 'Pathogenesis' above.)

In a multicenter randomized trial comparing bevacizumab and conventional laser therapy in 150 infants with stage 3+ ROP in zone I or posterior zone II, bevacizumab was associated with decreased rates of recurrence and fewer structural abnormalities (eg, macular dragging, retinal detachment) at 54 weeks' postmenstrual age [80]. No systemic or local toxic effects were observed; however, the study was too small to adequately assess ocular and systemic safety. Recurrence occurred later among infants treated with bevacizumab than infants treated with laser therapy (mean of 16.0 versus 6.2 weeks after treatment), suggesting that infants treated with bevacizumab may require prolonged follow-up.

Although this trial suggests that bevacizumab is efficacious in the treatment of ROP prior to the onset of retinal detachment, additional trials are necessary to determine the optimal timing, dose, and duration of effect; whether bevacizumab should be used alone or in conjunction with other treatment modalities; the long-term effect of bevacizumab on visual acuity and visual fields; the duration and frequency of follow-up; and the management of recurrence [79-81,84].

Retinal detachment — When ROP progresses to partial or total retinal detachment (stage 4 or 5), surgical intervention is attempted to promote reattachment and preserve vision. The procedures typically used are scleral buckling or vitrectomy. In one series, these techniques resulted in light perception or better vision in 72 percent of eyes and achieved visual acuity of 20/300 or better in 15 percent [85].

With scleral buckling, a silicone band is placed around the eye and tightened so that the retina is reapposed to the wall of the eye, allowing reattachment to occur. Vitrectomy involves surgical removal of the vitreous, and excision of the fibrous tissue that is placing traction on the retina. The lens sometimes is sacrificed during the procedure to promote retinal reattachment. The retina then is placed against the wall of the eye and held there by injecting perfluorocarbon gas or silicone oil to replace the vitreous. Despite successful reattachment of the retina, many patients have extremely poor vision or are blind [56,86-89].

Predictors of retinal detachment after laser treatment at threshold were identified in a retrospective case series of 262 eyes in 138 infants [90]. Retinal detachment developed in 14 percent of eyes by 6 to 12 weeks [91]. Retinal detachment was more frequent in eyes with vitreous hemorrhage severe enough to completely obscure visualization of the retina and clinically important vitreous organization. Vitreous organization was defined by the presence of white, fibrous-appearing opacification of the vitreous above the vascular/avascular junction. It was considered clinically important when it spanned ≥ 2 contiguous clock hours or was dense enough to moderately or severely reduce visualization of the retina, but also to have been unassociated with retinal detachment at the time of initial discovery. The development of retinal detachment was not associated with prolonged activity of stage 3 disease or plus disease more than 21 days after treatment.

Follow-up — After treatment, follow-up examinations are typically performed every one to two weeks for one to two months and then at less frequent intervals depending upon the clinical course. Infants who develop ROP are at increased risk for abnormalities, including myopia, astigmatism, anisometropia, and strabismus and should be followed by an ophthalmologist [92-94]. These problems are discussed separately. (See "Overview of amblyopia" and "Evaluation and management of strabismus in children", section on 'Evaluation'.)

PREVENTION — Interventions to prevent or limit the progression of ROP have been unsuccessful, although further evaluation may be needed. Because oxidant injury contributes to ROP, antioxidant therapies, such as vitamin E, D-penicillamine, and limited exposure to light, have been tested.

In a meta-analysis of randomized trials of supplemental vitamin E, the treatment group was less likely than was the control to develop stage 3 or greater ROP (2.4 versus 5.3 percent) [95]. However, vitamin E increased the rate of sepsis and necrotizing enterocolitis in one study, and the overall risk-benefit ratio is uncertain [96].

D-penicillamine reduced the incidence of ROP in two randomized trials evaluated in a systematic review (relative risk 0.09; 95% confidence interval (CI) 0.01-0.71) [97]. However, no intravenous preparation is available, and further studies are needed to evaluate adverse effects. In a controlled trial, reduced exposure to ambient light did not change the incidence of ROP [52].

Supplemental oxygen therapy has been tested in infants with severe ROP because retinal hypoxia contributes to neovascularization. In the STOP-ROP trial, 649 infants with prethreshold ROP were randomly assigned to maintain oxygen saturation at 96 to 99 (supplemental) or 89 to 94 (conventional) percent [98]. The rate of progression to threshold was similar in the two groups (odds ratio, 0.72; 95% CI 0.52-1.01). Further analysis suggested that the treatment may be more effective in infants without plus disease (32 versus 46 percent rate of progression). However, adverse pulmonary effects occurred more frequently in the supplemental group. Treated infants were more likely to have pneumonia and/or exacerbations of chronic lung disease (13.2 versus 8.5 percent) and to remain hospitalized, on oxygen, and on diuretics at 50 postmenstrual weeks.

Based upon the available evidence, we recommend prompt detection and treatment of ROP. In addition, episodes of physiologic instability that may increase the risk of ROP should be avoided if possible. Additional preventive measures await further study. (See 'Screening' above.)

SUMMARY AND RECOMMENDATIONS

- Retinopathy of prematurity (ROP) is a developmental proliferative vascular disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. It is a common cause of childhood blindness in the United States. (See 'Introduction' above.)
- The incidence and severity of ROP increase with decreasing gestational age (GA) and birth weight. (See 'Epidemiology' above.)
- The International Classification for ROP provides a uniform approach to documenting the extent and severity of disease. It is based upon four features: zone (figure 2), stage, extent, and presence or absence of plus disease. (See 'Classification' above.)
- ROP typically begins about 34 weeks' postmenstrual age (PMA), but may be seen as early as 30 to 32 weeks. It advances irregularly until 40 to 45 weeks' PMA, but resolves spontaneously in the majority of infants. (See 'Natural history' above.)
- We screen for ROP in all infants with birth weight ≤ 1500 g or a GA of <30 weeks, as well as those with birth weight between 1500 g and 2000 g or a GA of ≥ 30 weeks whose clinical course places them at increased risk for ROP. The screening evaluation consists of a comprehensive eye examination performed by an ophthalmologist with expertise in neonatal disorders. (See 'Screening' above.)
- We initiate screening examinations at four to six weeks after birth, depending upon the GA (table 1). Additional examinations are performed at intervals of one to three weeks until the retinal vessels have completely grown out to the ora serrata. If ROP develops, the eyes are examined more frequently, depending upon the severity of disease and rate of progression. Screening examinations continue until ROP regresses and the vasculature matures or treatment is needed. (See 'Evaluation schedule' above and 'Discontinuation' above.)
- Treatment for ROP is indicated in infants with threshold disease; it also may be beneficial for those with high-risk prethreshold disease. (See 'Indications' above.)
- Treatment consists of ablation of the peripheral avascular retina by cryotherapy or laser photocoagulation. (See 'Modalities' above.)
- After treatment, follow-up examinations are performed every one to two weeks for one to two months and then at less frequent intervals depending upon the clinical course. (See 'Follow-up' above.)

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Refractive errors in children

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INTRODUCTION — This topic will review refractive errors in children. Vision assessment, strabismus, cataracts, and amblyopia are discussed separately. (See "Visual development and vision assessment in infants and children" and "Evaluation and management of strabismus in children" and "Cataract in children" and "Overview of amblyopia".)

Refractive errors in adults are discussed separately. (See "Visual impairment in adults: Refractive disorders and presbyopia".)

NORMAL REFRACTION — Refraction is the bending of light rays as they pass from one transparent medium to another medium with a different density. During vision, light that is reflected from an object is refracted by the cornea and lens and focused on the retina.

In emmetropia (an eye with normal refractive error), parallel light rays from a distant object are brought into focus precisely on the retina, and a clear image is perceived (figure 1). Perfect emmetropia rarely exists. The majority of individuals have some degree of refractive error, although most do not require correction.

REFRACTIVE ERRORS — Refractive errors are present when the optical image does not accurately focus on the retina. There are three types: myopia, hyperopia, and astigmatism (figure 1 and figure 2).

Refractive errors requiring correction are uncommon in preschool children [1]. However, nearly 20 percent of children develop refractive errors that require the use of eyeglasses before late adolescence [2]. Risk factors for refractive error include retinopathy of prematurity and family history of high refractive error [3]. (See "Retinopathy of prematurity".)

Myopia — Myopia (nearsightedness) occurs when the refracting power of the eye is too strong. It commonly occurs when the anterior-posterior diameter of the eye is too long relative to the refracting power of the cornea and lens. The focal point of the image is anterior to the retina and the image that reaches the retina is blurred (figure 1). Patients with myopia have better near vision than distance vision when they are uncorrected.

The prevalence of myopia increases during and after puberty, when the eye undergoes its adolescent growth phase. (See "Normal puberty".) The prevalence of myopia among children and adolescents in the United States is approximately 30 percent [4].

The prevalence of myopia varies with ethnicity and is particularly high among Asians; one study reported a prevalence of 84 percent among 16- to 18-year-olds in Taiwan [5]. In the United States, Asian children have the highest prevalence of myopia (18.5 percent), followed by Hispanic children (13.2 percent) [6]. The rates of myopia in Caucasians (4.4 percent) and African-Americans (6.6 percent) were not significantly different.

Myopia is corrected with a concave spherical lens to focus the light rays on the retina. Mild myopia does not require correction. However, myopia of any magnitude should be corrected if it alters a child's education or social function. Severe myopia (approximately >5 diopters) should be corrected, even in an apparently asymptomatic child, because of the risk of developing refractive amblyopia. The absolute threshold for when a child should be corrected varies by the caretaker's preference, age of the child, and other factors. (See 'Corrective lenses' below and "Overview of amblyopia", section on 'Anisometropic amblyopia'.)

Several randomized trials have demonstrated the potential for topical anticholinergic agents (atropine, pirenzepine) to slow the progression of myopia in children [7-9]. Additional studies are necessary before such treatments can be routinely recommended [10].

Hyperopia — Hyperopia (farsightedness) is the opposite of myopia. Hyperopia occurs when the refracting power of the eye is too weak. Most commonly, the hyperopic eye is too short relative to the refracting power of the cornea and lens. The focal point of the image is posterior to the retina, and the image that reaches the retina is blurred (figure 1). High degrees of hyperopia are associated with amblyopia and accommodative esotropia. (See "Causes of horizontal strabismus in children", section on 'Accommodative' and "Overview of amblyopia", section on 'Anisometropic amblyopia'.)

Mild hyperopia is the normal refractive state for infants and children. Children have the ability to "accommodate" or focus by contracting the ciliary body, which changes the shape and power of the lens and focuses the image appropriately on the retina. Without the ability to accommodate (eg, after cycloplegic drops), patients with hyperopia have better distance vision than near vision.

Hyperopia is corrected with a convex spherical lens to focus the light rays on the retina. Mild hyperopia generally does not require optical correction in children. Higher degrees of hyperopia (ie, >4 diopters) should be corrected in asymptomatic children because of the risk of developing refractive amblyopia and/or accommodative esotropia. Any degree of hyperopia may warrant correction if the child is symptomatic. (See 'Corrective lenses' below.)

Astigmatism — Astigmatism (from Greek: "a" = lack of, "stigma" = point) occurs when the optical system of the eye, particularly the cornea, is not perfectly spherical. The refractive power of the eye is different in different meridians, and the light rays cannot be brought to a single point (figure 2). Astigmatism may occur with myopia or hyperopia. Children with moderate or more severe astigmatism have difficulty performing visual tasks at both distance and near fixation.

Astigmatism is corrected with a cylindrical lens. Astigmatism should be corrected in symptomatic children and in asymptomatic children with large degrees of astigmatism (ie, approximately >1.75 to 2 diopters) [11]. The threshold for correcting astigmatism is lowered as the child gets older and visual demands increase. (See 'Corrective lenses' below.)

CORRECTIVE LENSES — Refractive errors are treated with corrective lenses. Myopia and hyperopia are corrected with spherical lenses (concave and convex lenses, respectively). Concave lenses are minus or divergent; convex lenses are plus or convergent. Astigmatism is neutralized with cylindrical lenses. Spectacle prescriptions reflect the spherical and cylindrical components necessary for correction.

REFRACTIVE SURGERY — Refractive error can be reduced with extraocular surgical procedures and intraocular surgical procedures. The extraocular procedures include excimer laser procedures (photorefractive keratectomy [PRK], laser in situ keratomileusis [LASIK], and laser-assisted subepithelial keratectomy [LASEK]) and intrastromal corneal rings (INTACS). The excimer laser emits an ultraviolet beam that has sufficient energy to break intermolecular bonds within the cornea ("photoablation"), which results of changing the shape and thus refracting power of the cornea.

The intraocular procedures include phakic intraocular lens implantation and refractive lensectomy or lens exchange. Phakic intraocular lens implantation is a procedure in which an artificial lens is inserted into the eye (anterior chamber or posterior chamber) while preserving the natural crystalline lens. Refractive lensectomy is a procedure that is essentially the same as cataract surgery except that the crystalline lens is being replaced because of high refractive error rather than lens opacity.

Refractive surgical procedures are typically performed in adults. (See "Laser refractive surgery".) However, in select conditions, refractive surgery may be performed in children to prevent amblyopia or as a component of the treatment of amblyopia (eg, severe anisometropia and bilateral severe abnormal refraction [isoametropia] with amblyopia in children who cannot or will not wear refractive correction) [12]. (See "Overview of amblyopia", section on 'Refractive surgery for amblyopia'.)

SUMMARY

- Refractive errors are present when the optical image does not accurately focus on the retina. Risk factors for refractive error include retinopathy of prematurity and family history of high refractive error. (See 'Refractive errors' above.)
- Myopia (nearsightedness) occurs when the refracting power of the eye is too strong, most commonly when the anterior-posterior diameter of the eye is too long relative to the refracting power of the cornea and lens (figure 1). The prevalence of myopia increases during and after puberty. Myopia is corrected with a concave spherical lens. (See 'Myopia' above.)
- Hyperopia occurs when the refracting power of the eye is too weak, most commonly when the eye is too short relative to the refracting power of the cornea and lens (figure 1). High degrees of hyperopia are associated with amblyopia and accommodative esotropia. Hyperopia is corrected with a convex spherical lens. (See 'Hyperopia' above.)
- Astigmatism occurs when the optical system of the eye, particularly the cornea, is not perfectly spherical (figure 2). Astigmatism is corrected with a cylindrical lens. Astigmatism should be corrected

in symptomatic children and in asymptomatic children when it is ≥ 1.75 -2 diopters, and sometimes even lower. (See 'Astigmatism' above.)

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Anemia of prematurity

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INTRODUCTION — Erythropoiesis decreases after birth as a result of increased tissue oxygenation due to the onset of breathing and closure of the ductus arteriosus, and a reduced production of erythropoietin (EPO) [1]. In term infants, the hemoglobin level typically reaches an average nadir of 11 g/dL at approximately 8 to 12 weeks after birth.

In preterm infants who are already born with a lower hematocrit, this decline referred to as anemia of prematurity (AOP) occurs earlier and is more pronounced in its severity than the anemia seen in term infants. The anemia of prematurity (AOP) will be reviewed here.

PATHOGENESIS — The primary cause of AOP is the impaired ability to increase serum erythropoietin (EPO) appropriately in the setting of anemia and decreased tissue availability of oxygen [2,3]. Circulating and bone marrow red cell progenitors respond to EPO, if present, indicating that the impaired erythropoiesis is due to lack of EPO, not a failure to respond to the hormone [4-6]. Other hematopoietic growth factors (eg, granulocyte-macrophage colony-stimulating factor) are not affected.

Impaired EPO production — Erythropoietin (EPO) is produced by the fetal liver and the cortical interstitial cells of the kidney in response to hypoxia. Its production is regulated by the transcription factor hypoxia inducible factor-1 (HIF-1). Its primary function is to regulate erythrocyte production. EPO does not cross the placenta in humans, and fetal production increases with gestational age [7-10].

Production of EPO in adults depends on the oxygen saturation of hemoglobin and tissue oxygen delivery, and is inversely proportional to central venous oxygenation. Although EPO levels in preterm infants with AOP increase slightly with hypoxia, they are lower than those seen in older children and adults with the same level of anemia [2,11]. (See "Regulation of erythropoiesis".)

In AOP, the specific mechanisms leading to the discrepancy between serum EPO concentration and the severity of the anemia are uncertain. Proposed pathogenetic pathways involve the site of EPO production and the developmental regulation of transcription factors in the liver versus the kidney.

- The liver is the principal site of EPO production in the fetus [12,13]. The feedback increase in hepatic EPO mRNA in response to anemia, and hypoxia may be less than that of the kidney [14]. EPO mRNA expression in the kidney is present in the fetus, and increases significantly after 30 weeks gestation, suggesting that the switch to the kidney as the main site of EPO production is developmentally regulated.
- The fetal or neonatal environment may alter the response to hypoxic signals by the liver. Support for this hypothesis comes from the observation that hepatic transplantation from fetal and neonatal lambs into adult sheep increased EPO production by the transplanted liver [15].
- Transcriptional regulatory factors, such as HIF-1, may contribute to low levels of EPO in premature infants. These factors activate target genes, including those encoding EPO, in response to decreased cellular oxygen concentration [16,17]. They appear to be developmentally regulated in some fetal tissues, which might account for the decreased expression of EPO in response to anemia in preterm infants [1,18].

Other factors — Although AOP is directly due to impaired EPO production, several other factors can contribute to anemia in preterm infants, including blood loss from phlebotomy, reduced red blood cell life span, and iron depletion.

Blood loss from phlebotomy — Premature infants frequently develop an early anemia that is primarily due to iatrogenic blood loss due to phlebotomy for blood tests. The volume of blood loss increases with illness severity and decreasing gestational age. In one report, withdrawal of blood in excess of that required for laboratory studies contributed to iatrogenic blood loss by 2 to 4 mL/kg per week [19]. However, efforts to reduce blood loss from phlebotomy have resulted in changes in clinical practice to limit blood sampling for essential testing and the use of microtechniques, which have reduced iatrogenic blood loss.

The impact of clinical practice on phlebotomy and blood testing was illustrated in a study of very low birth weight (VLBW) infants (birth weight <1500 g) cared for in two neonatal intensive care units (NICUs) [20]. Phlebotomy losses increased with decreasing gestational age and increasing illness severity, as measured by the Score for Neonatal Acute Physiology (SNAP). The average losses due to phlebotomy differed between the two NICUs and resulted in increased average blood transfusion requirements in the NICU with the greater volume of blood loss. However, this difference was not associated with differences in the days of oxygen therapy or mechanical ventilation, risk of bronchopulmonary dysplasia, or growth rate by day 28 of life. These findings suggest that the additional use of blood in one of the NICUs was discretionary rather than necessary, as clinical outcomes did not differ.

These studies indicate that blood loss due to phlebotomy in preterm infants may be greater than is necessary for the care of the neonate. They emphasize the need for nursery policies to ensure that only the minimal volume required for testing is drawn, and unnecessary tests are avoided.

Reduced red blood cell life span — Red blood cell survival in newborn term infants is approximately 60 to 80 days but decreases with decreasing gestational age to a range of 45 to 50 days in extremely low birth weight infants (birth weight below 1000 g). [21]. The reduced red cell life span contributes to the severity of anemia. Increased susceptibility to oxidant injury may contribute to shortened red cell survival in the neonate [22,23]. (See "Red blood cell survival: Normal values and measurement".)

Iron depletion — Although it is not involved in its pathogenesis, iron depletion may impair recovery from AOP. Because of their rapid growth rate, premature infants have increased utilization and depletion of iron stores and, as noted above, blood loss from phlebotomy. The administration of iron does not inhibit the fall in hemoglobin concentration due to AOP. However, in term infants, it reduces the incidence of iron deficiency anemia in the first year of life [2]. (See "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Low levels of other nutrients, such as vitamin B12 or folate, do not appear to contribute to neonatal anemia [1]. In one randomized trial, the combination of folate, vitamin B12, iron, and EPO compared to control therapy improved the ELBW infant's chance of remaining transfusion free (38 versus 5 percent) [24].

OXYGEN DELIVERY — Oxygen delivery is the rate at which oxygen is transported from the lungs to the microcirculation. It is determined by the product of cardiac output and arterial oxygen content. The arterial oxygen content is the amount of oxygen bound to hemoglobin plus the amount of oxygen dissolved in arterial blood. (See "Oxygen delivery and consumption".)

Oxygen delivery is dependent upon:

- Cardiac output
- Hemoglobin concentration
- Oxygen carrying capacity (affinity) of hemoglobin
- Arterial oxygen saturation and oxygen tension

In preterm infants with anemia, physiologic changes, which aim at maintaining adequate oxygen delivery, compensate for a significant decrease in hemoglobin, and are similar to those seen in older children and adults. These include increases in heart rate and stroke volume, which improve cardiac output [25].

However, anemic preterm infants may be less able to maintain oxygen delivery because of the following:

- Concomitant respiratory disease, such as respiratory distress syndrome and bronchopulmonary dysplasia, resulting in hypoxia.
- Limitations on maximum arterial oxygen saturation and oxygen tension for infants requiring respiratory support, because hyperoxia increases the risk of bronchopulmonary dysplasia and retinopathy of prematurity. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia", section on 'Oxygen toxicity' and "Neonatal resuscitation in the delivery room", section on 'Supplemental oxygen'.)
- Hemoglobin F (HbF)-containing red cells in the premature infant have a considerably higher oxygen affinity than adult red blood cells, resulting in reduced delivery of oxygen to tissues (figure 1).

HbF binds poorly to 2,3 diphosphoglycerate (2,3-DPG), a potent modulator that diminishes the affinity of hemoglobin for oxygen. Decreased binding increases oxygen affinity and shifts the oxyhemoglobin dissociation curve to the left, resulting in decreased peripheral oxygen delivery (figure 1). (See "Structure and function of normal human hemoglobins".)

The proportion of HbF increases with decreasing gestational age, and is regulated developmentally so that HbF levels are similar at the same postmenstrual age [26-28]. The concentration of HbF in an infant born at 28 weeks gestation is approximately 90 percent, and decreases to approximately 60 percent at 10 weeks after birth, a value that is similar to that of an infant newly born at 38 weeks gestation [26].

CLINICAL AND LABORATORY FEATURES — AOP typically occurs at 3 to 12 weeks after birth in infants less than 32 weeks gestation. The onset of AOP is inversely proportional to the gestational age at birth [1,29,30]. The anemia typically resolves by three to six months of age.

In a study of 40 VLBW infants, average hemoglobin concentrations fell from 18.2 g/dL at birth to a mean nadir of 9.5 g/dL at six weeks of age [31]. Values of 7 to 8 g/dL were common even in the absence of significant phlebotomy losses. Hematocrit values were lowest in the smallest infant with average nadirs of 21 percent in infants with birth weights (BW) less than 1000 g, and 24 percent in infants with BW between 1000 and 1500 g.

Many infants are asymptomatic despite having hemoglobin values less than 7 g/dL [32,33]. However, other infants with AOP are symptomatic at similar or even higher hemoglobin levels because of a reduced capacity to maintain adequate oxygen by other means in compensation for AOP. (See 'Oxygen delivery' above.)

Symptoms associated with AOP include tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased episodes of apnea or bradycardia.

The following laboratory findings in addition to anemia are characteristic of AOP:

- Peripheral blood smear demonstrates normocytic and normochromic red blood cells.
- The reticulocyte count is low, and red blood cell precursors in the bone marrow are decreased [2].
- Serum concentrations of EPO are low in premature infants during the first postnatal month compared to adults (9.7 versus 15.2 mU/mL) and remain inappropriately low for the extent of anemia through the second postnatal month [3].

MANAGEMENT — Clinicians who care for premature infants should anticipate the development of AOP. Optimal nutrition (eg, iron supplementation) should be provided and patients monitored for signs of anemia. Blood sampling should be limited to essential testing, and microtechniques should be used to minimize blood loss due to phlebotomy [19,34]. (See 'Blood loss from phlebotomy' above.)

Red blood cell transfusions are primarily used to treat infants with AOP. Human EPO appears have limited benefit in decreasing exposure to different blood donors and is NOT recommended for routine use.

Iron supplementation — The iron content at birth is lower in preterm infants than term infants, and the iron stores of preterm infants often are depleted by two to three months of age. As a result, all preterm infants who are breastfed should receive iron supplementation of 2 to 4 mg/kg per day through the first year of life [35]. Infants who receive iron-fortified formula need less additional supplementation than those who are exclusively breastfed, because for a given volume, iron-containing formula contains a higher concentration of iron than

breast milk. (See "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Although iron supplementation does not prevent AOP, the use of iron-fortified formula compared to nonfortified formula allows for greater iron substrate when erythropoiesis is stimulated [36]. Iron supplementation does reduce iron-deficiency anemia, which both premature and term infants are at high risk for developing in the first year of life. (See "Nutritional composition of human milk and preterm formula for the premature infant" and "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Laboratory monitoring — The hematocrit (HCT) or hemoglobin (Hb) concentration should be monitored on a weekly basis in extremely low birth (ELBW) infants (birth weight less than 1000 g) in the first weeks of life. Thereafter, in healthy, growing premature infants, it is not necessary to routinely monitor HCT/Hb. Infants with persistent illness (eg, bronchopulmonary dysplasia) or surgical issues may require monitoring.

In asymptomatic infants, measuring a reticulocyte count at approximately four to six weeks after birth is used to evaluate whether a red blood cell (RBC) transfusion may be needed. Although no clearly defined biological markers have been identified to indicate when a RBC transfusion should be given in a premature infant, an absolute reticulocyte <100,000/microL (<2 percent) is often used as a criterion for RBC transfusion in asymptomatic infants with a low HCT (less than 20 percent) or Hb (less than 7 g/dL). The indications for neonatal RBC transfusion are discussed in greater detail separately. (See "Red blood cell transfusions in the newborn".)

Transfusion — RBCs transfusion is the most rapidly effective treatment for AOP. However, transfusion is a temporary measure and has the disadvantages of further inhibiting erythropoiesis and being associated with risks of transmitted infection, graft-versus-host disease, and toxic effects of anticoagulants or preservatives. (See "Transfusion-associated graft-versus-host disease" and "Immunologic blood transfusion reactions".)

RBC transfusion is performed when the level of anemia becomes symptomatic or is thought to compromise adequate oxygen delivery. Guidelines for RBC transfusion are based upon the patient's hematocrit (hemoglobin), their requirement for respiratory support, and the presence of symptoms consistent with anemia (eg, tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased episodes of apnea or bradycardia). The indications for transfusions, specific blood products available for transfusion, and the administration of transfusion in the neonate are discussed in detail separately. (See "Red blood cell transfusions in the newborn" and 'Oxygen delivery' above.)

Erythropoietin — The pathogenetic importance of impaired erythropoietin (EPO) production in AOP provides the rationale for the therapy with recombinant human EPO. However, this approach has not been accepted widely because it appears to have limited efficacy in decreasing the number of blood donors to which the infant is exposed via transfusion, whether EPO is administered early (within the first week of life) or late (at or after eight days of life). Data on the outcome of early and late EPO administration are presented in the following two sections.

A more effective approach to reduce the number of donor exposures for the preterm infant than routine administration of EPO is to limit the amount of blood drawn, follow restrictive guidelines for red blood cell transfusion, and to use satellite packs [37]. Satellite packs involve dividing one unit of donor blood into multiple smaller aliquots, which allows repeated transfusions from the same donor to the individual infant. (See "Red blood cell transfusions in the newborn", section on 'Target hemoglobin or hematocrit' and "Red blood cell transfusions in the newborn", section on 'Administration'.)

In retrospective studies, early administration of EPO has been associated with an increased risk of retinopathy of prematurity (ROP). In addition, EPO is a costly intervention. As a result, the routine use of EPO in neonates is NOT recommended because the potential limited benefits are outweighed by the costs and possible risks of the intervention.

Early EPO use — Although early administration (within the first eight days of life) of EPO appears to reduce the number of transfusions required in preterm infants, the small reduction may be of limited clinical importance,

because EPO does not decrease the number of donor exposures due to the use of satellite packs. In addition, some trials suggest that early EPO administration increased the risk of retinopathy of prematurity (ROP).

These findings were best illustrated in a meta-analysis of 23 trials (2074 preterm infants) that evaluated the effect of early administration of EPO (given before eight days of age) compared to placebo or no intervention [38]. Many of these infants had received blood transfusions prior to enrollment in the trials. The following findings were noted:

- In 18 trials of 1825 infants, EPO reduced the risk of receiving one or more red blood cell transfusions (RR 0.80, 95% CI 0.75-0.86).
- In 13 trials of 1115 infants, EPO slightly reduced the number of red blood cell transfusions (weighted mean difference of -0.27, 95% CI -0.42 to -0.12).
- In 10 trials of 1425 infants, EPO increased the risk of ROP (RR 1.18, 95% CI 0.99-1.40). In a sub-analysis of 6 trials of 930 infants in which information was available, EPO appeared to increase the risk of severe ROP, defined as stage 3 or greater (RR 1.71, 95% CI 1.15-2.54).
- There were no differences between the EPO and placebo groups in the rates of mortality, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hypertension, length of hospital stay, or long-term neurodevelopmental outcome.

In a follow-up study from one of the trials included in the meta-analysis, EPO and placebo-treated infants at 18 to 22 months corrected age with birth weights <1000 g had similar weight and length, number of rehospitalizations, transfusions after discharge, and developmental outcomes [39].

In summary, early EPO is associated with only a small reduction in the number of transfusions, but no reduction in exposure to the number of donors, and has no impact on clinical outcomes.

Although the meta-analysis also demonstrated a trend for an increased risk of ROP, this could be a chance finding because development of ROP was one of many secondary outcomes evaluated [38]. In addition, the sub-analysis that reported early administration resulted in an increased risk of severe ROP must be interpreted with caution, given that the overall effect on all grades of ROP was substantially lower. Among the studies included in the analysis, there were no data regarding the gestational age of the patients and illness severity, which both directly impact on the risk of ROP. Further studies are required to demonstrate whether or not there is a clinically significant association between early EPO use and ROP.

Although it is difficult to determine the role of EPO in the multifactorial pathogenesis of ROP, the current evidence is sufficient to raise concerns about the early use of EPO given the limited benefit of reducing exposure to blood donors, its cost, and potential association with ROP. As a result, we recommend NOT to routinely administer EPO within the first eight days of life.

Late EPO use — Late administration of EPO reduces the number of transfusions, but the limited benefit does not justify its use. This was illustrated in a meta-analysis of 28 trials (1302 preterm infants) that evaluated the effects of late EPO administration (at or later than eight days of age) compared to placebo or no intervention [40]. Most of these infants had received blood transfusions prior to enrollment in the trials. The following findings were noted:

- EPO reduced the risk of receiving one or more red blood cell transfusions (RR 0.66, 95% CI 0.59-0.74).
- EPO reduced the number of red blood cell transfusions (weighted mean difference of -0.78, 95% CI -0.97 to -0.59).
- EPO had no effect on the rates for ROP, mortality, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hypertension, length of hospital stay, or long-term neurodevelopmental outcome.

Late administration of EPO reduced the mean number of transfusions by a little less than one transfusion per infant. This small benefit of EPO was diminished due to the exposure of previous blood transfusions before eight days of life, and the use of satellite packs that would mitigate against additional donor exposure in the control

group. As a result, we recommend NOT to routinely administer EPO after eight days because its limited benefit of limiting exposure to blood donors does not justify its cost.

Complications — Use of EPO in premature infants appears to be safe. Hypertension, rash, bone pain, seizures, or later development of anti-EPO antibodies have not been reported in premature infants. Complications include the following:

- A transient neutropenia that resolves with cessation of therapy is occasionally observed [41,42]. In one trial, mean absolute neutrophil counts after 20 days were lower in premature infants who received EPO compared to red blood cell transfusion (1.8×10^3 versus 3.9×10^3) [41].
- Iron deficiency occurs if supplementation is inadequate [42-44].
- As discussed above, early administration of EPO has been associated with increased risk of ROP. (See 'Early EPO use' above.)

Dose — If EPO is given, it can be administered intravenously (200 U/kg per dose once daily) or subcutaneously (400 U/kg per dose, 3 times per week) [45]. When given intravenously, EPO should be mixed in a protein-containing solution (5 percent albumin) and given over at least four hours, or, more commonly, is added to TPN and administered daily over 24 hours [46]. The undiluted drug (2000 U/mL) can be given subcutaneously in a volume of 0.2 mL/kg for infants less than 1000 g. EPO preparation with higher concentrations (up to 10,000 U/mL) can be used as the infant grows.

Infants treated with EPO require iron supplementation. A proposed regimen is a daily elemental iron dose of 6 mg/kg for infants on full enteral feedings, and 3 mg/kg for those taking at least 60 mL/kg per day [45]. For infants receiving total parenteral nutrition, iron dextran can be added to the solution (3 to 5 mg/kg weekly) [45].

The reticulocyte count, central hematocrit or hemoglobin concentration, and absolute neutrophil count are measured before as well as one to two weeks after starting EPO treatment. EPO is withheld if the absolute neutrophil count is less than 1000/microL. Serum ferritin levels may be useful in evaluating those infants who are not responding to therapy to detect iron deficiency [45].

SUMMARY AND RECOMMENDATIONS

- Newborn infants have a fall in hematocrit soon after birth due primarily to impaired production of erythropoietin. In preterm infants, the decline occurs earlier, is more pronounced, and is called anemia of prematurity (AOP). AOP typically occurs at 3 to 12 weeks after birth in infants less than 32 weeks gestation. (See 'Pathogenesis' above.)
- Other contributors to anemia in the preterm infant include iron depletion, blood loss due to phlebotomy, and a reduced red blood cell life span in preterm infants compared to that of full term infants and adults. (See 'Pathogenesis' above and 'Other factors' above.)
- Preterm infants are at particular risk for impaired oxygen delivery with anemia because of the increased likelihood of concomitant respiratory disease, high levels of hemoglobin F, and the need to avoid hyperoxia, which increases the risk of BPD and retinopathy of prematurity (ROP). (See 'Oxygen delivery' above.)
- Many infants remain asymptomatic despite having hemoglobin levels below 7 g/dL. However, other infants may be symptomatic at similar or even higher hemoglobin levels. Symptoms include tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased frequency of apnea or bradycardia. (See 'Clinical and laboratory features' above.)
- The laboratory findings characteristic of AOP include normocytic and normochromic red blood cells, low reticulocyte count, and low erythropoietin levels. (See 'Clinical and laboratory features' above.)
- AOP may require treatment with RBCs transfusion. However, transfusion is a temporary measure and has potential adverse effects, such as infection and graft-versus-host disease. Guidelines for RBC transfusion based upon a restrictive policy in the neonate are presented separately. (See "Red blood cell transfusions in the newborn", section on 'Indications'.)
- Administration of recombinant human erythropoietin (EPO) appears to have limited efficacy in decreasing the number of blood donors to which the infant is exposed. It is a costly intervention, and

early EPO use may increase the risk and severity of ROP. As a result, we recommend NOT to routinely administer EPO to preterm infants (Grade 1B). (See 'Erythropoietin' above.)

- A more effective approach to reduce the number of donor exposures for the preterm infant than routine administration of EPO, is combination of limiting the amount of blood drawn, a restrictive policy for red cell transfusions, and the use of satellite packs, which allow for repeated transfusions from the same donor to the individual infant. (See "Red blood cell transfusions in the newborn", section on 'Target hemoglobin or hematocrit' and "Red blood cell transfusions in the newborn", section on 'Administration' and 'Management' above.)

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Anemia of prematurity

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INTRODUCTION — Erythropoiesis decreases after birth as a result of increased tissue oxygenation due to the onset of breathing and closure of the ductus arteriosus, and a reduced production of erythropoietin (EPO) [1]. In term infants, the hemoglobin level typically reaches an average nadir of 11 g/dL at approximately 8 to 12 weeks after birth.

In preterm infants who are already born with a lower hematocrit, this decline referred to as anemia of prematurity (AOP) occurs earlier and is more pronounced in its severity than the anemia seen in term infants. The anemia of prematurity (AOP) will be reviewed here.

PATHOGENESIS — The primary cause of AOP is the impaired ability to increase serum erythropoietin (EPO) appropriately in the setting of anemia and decreased tissue availability of oxygen [2,3]. Circulating and bone marrow red cell progenitors respond to EPO, if present, indicating that the impaired erythropoiesis is due to lack of EPO, not a failure to respond to the hormone [4-6]. Other hematopoietic growth factors (eg, granulocyte-macrophage colony-stimulating factor) are not affected.

Impaired EPO production — Erythropoietin (EPO) is produced by the fetal liver and the cortical interstitial cells of the kidney in response to hypoxia. Its production is regulated by the transcription factor hypoxia inducible factor-1 (HIF-1). Its primary function is to regulate erythrocyte production. EPO does not cross the placenta in humans, and fetal production increases with gestational age [7-10].

Production of EPO in adults depends on the oxygen saturation of hemoglobin and tissue oxygen delivery, and is inversely proportional to central venous oxygenation. Although EPO levels in preterm infants with AOP increase slightly with hypoxia, they are lower than those seen in older children and adults with the same level of anemia [2,11]. (See "Regulation of erythropoiesis".)

In AOP, the specific mechanisms leading to the discrepancy between serum EPO concentration and the severity of the anemia are uncertain. Proposed pathogenetic pathways involve the site of EPO production and the developmental regulation of transcription factors in the liver versus the kidney.

- The liver is the principal site of EPO production in the fetus [12,13]. The feedback increase in hepatic EPO mRNA in response to anemia, and hypoxia may be less than that of the kidney [14]. EPO mRNA expression in the kidney is present in the fetus, and increases significantly after 30 weeks gestation, suggesting that the switch to the kidney as the main site of EPO production is developmentally regulated.
- The fetal or neonatal environment may alter the response to hypoxic signals by the liver. Support for this hypothesis comes from the observation that hepatic transplantation from fetal and neonatal lambs into adult sheep increased EPO production by the transplanted liver [15].
- Transcriptional regulatory factors, such as HIF-1, may contribute to low levels of EPO in premature infants. These factors activate target genes, including those encoding EPO, in response to decreased cellular oxygen concentration [16,17]. They appear to be developmentally regulated in some fetal tissues, which might account for the decreased expression of EPO in response to anemia in preterm infants [1,18].

Other factors — Although AOP is directly due to impaired EPO production, several other factors can contribute to anemia in preterm infants, including blood loss from phlebotomy, reduced red blood cell life span, and iron depletion.

Blood loss from phlebotomy — Premature infants frequently develop an early anemia that is primarily due to iatrogenic blood loss due to phlebotomy for blood tests. The volume of blood loss increases with illness severity and decreasing gestational age. In one report, withdrawal of blood in excess of that required for laboratory studies contributed to iatrogenic blood loss by 2 to 4 mL/kg per week [19]. However, efforts to reduce blood loss from phlebotomy have resulted in changes in clinical practice to limit blood sampling for essential testing and the use of microtechniques, which have reduced iatrogenic blood loss.

The impact of clinical practice on phlebotomy and blood testing was illustrated in a study of very low birth weight (VLBW) infants (birth weight <1500 g) cared for in two neonatal intensive care units (NICUs) [20]. Phlebotomy losses increased with decreasing gestational age and increasing illness severity, as measured by the Score for Neonatal Acute Physiology (SNAP). The average losses due to phlebotomy differed between the two NICUs and resulted in increased average blood transfusion requirements in the NICU with the greater volume of blood loss. However, this difference was not associated with differences in the days of oxygen therapy or mechanical ventilation, risk of bronchopulmonary dysplasia, or growth rate by day 28 of life. These findings suggest that the additional use of blood in one of the NICUs was discretionary rather than necessary, as clinical outcomes did not differ.

These studies indicate that blood loss due to phlebotomy in preterm infants may be greater than is necessary for the care of the neonate. They emphasize the need for nursery policies to ensure that only the minimal volume required for testing is drawn, and unnecessary tests are avoided.

Reduced red blood cell life span — Red blood cell survival in newborn term infants is approximately 60 to 80 days but decreases with decreasing gestational age to a range of 45 to 50 days in extremely low birth weight infants (birth weight below 1000 g). [21]. The reduced red cell life span contributes to the severity of anemia. Increased susceptibility to oxidant injury may contribute to shortened red cell survival in the neonate [22,23]. (See "Red blood cell survival: Normal values and measurement".)

Iron depletion — Although it is not involved in its pathogenesis, iron depletion may impair recovery from AOP. Because of their rapid growth rate, premature infants have increased utilization and depletion of iron stores and, as noted above, blood loss from phlebotomy. The administration of iron does not inhibit the fall in hemoglobin concentration due to AOP. However, in term infants, it reduces the incidence of iron deficiency anemia in the first year of life [2]. (See "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Low levels of other nutrients, such as vitamin B12 or folate, do not appear to contribute to neonatal anemia [1]. In one randomized trial, the combination of folate, vitamin B12, iron, and EPO compared to control therapy improved the ELBW infant's chance of remaining transfusion free (38 versus 5 percent) [24].

OXYGEN DELIVERY — Oxygen delivery is the rate at which oxygen is transported from the lungs to the microcirculation. It is determined by the product of cardiac output and arterial oxygen content. The arterial oxygen content is the amount of oxygen bound to hemoglobin plus the amount of oxygen dissolved in arterial blood. (See "Oxygen delivery and consumption".)

Oxygen delivery is dependent upon:

- Cardiac output
- Hemoglobin concentration
- Oxygen carrying capacity (affinity) of hemoglobin
- Arterial oxygen saturation and oxygen tension

In preterm infants with anemia, physiologic changes, which aim at maintaining adequate oxygen delivery, compensate for a significant decrease in hemoglobin, and are similar to those seen in older children and adults. These include increases in heart rate and stroke volume, which improve cardiac output [25].

However, anemic preterm infants may be less able to maintain oxygen delivery because of the following:

- Concomitant respiratory disease, such as respiratory distress syndrome and bronchopulmonary dysplasia, resulting in hypoxia.
- Limitations on maximum arterial oxygen saturation and oxygen tension for infants requiring respiratory support, because hyperoxia increases the risk of bronchopulmonary dysplasia and retinopathy of prematurity. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia", section on 'Oxygen toxicity' and "Neonatal resuscitation in the delivery room", section on 'Supplemental oxygen'.)
- Hemoglobin F (HbF)-containing red cells in the premature infant have a considerably higher oxygen affinity than adult red blood cells, resulting in reduced delivery of oxygen to tissues (figure 1).

HbF binds poorly to 2,3 diphosphoglycerate (2,3-DPG), a potent modulator that diminishes the affinity of hemoglobin for oxygen. Decreased binding increases oxygen affinity and shifts the oxyhemoglobin dissociation curve to the left, resulting in decreased peripheral oxygen delivery (figure 1). (See "Structure and function of normal human hemoglobins".)

The proportion of HbF increases with decreasing gestational age, and is regulated developmentally so that HbF levels are similar at the same postmenstrual age [26-28]. The concentration of HbF in an infant born at 28 weeks gestation is approximately 90 percent, and decreases to approximately 60 percent at 10 weeks after birth, a value that is similar to that of an infant newly born at 38 weeks gestation [26].

CLINICAL AND LABORATORY FEATURES — AOP typically occurs at 3 to 12 weeks after birth in infants less than 32 weeks gestation. The onset of AOP is inversely proportional to the gestational age at birth [1,29,30]. The anemia typically resolves by three to six months of age.

In a study of 40 VLBW infants, average hemoglobin concentrations fell from 18.2 g/dL at birth to a mean nadir of 9.5 g/dL at six weeks of age [31]. Values of 7 to 8 g/dL were common even in the absence of significant phlebotomy losses. Hematocrit values were lowest in the smallest infant with average nadirs of 21 percent in infants with birth weights (BW) less than 1000 g, and 24 percent in infants with BW between 1000 and 1500 g.

Many infants are asymptomatic despite having hemoglobin values less than 7 g/dL [32,33]. However, other infants with AOP are symptomatic at similar or even higher hemoglobin levels because of a reduced capacity to maintain adequate oxygen by other means in compensation for AOP. (See 'Oxygen delivery' above.)

Symptoms associated with AOP include tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased episodes of apnea or bradycardia.

The following laboratory findings in addition to anemia are characteristic of AOP:

- Peripheral blood smear demonstrates normocytic and normochromic red blood cells.
- The reticulocyte count is low, and red blood cell precursors in the bone marrow are decreased [2].
- Serum concentrations of EPO are low in premature infants during the first postnatal month compared to adults (9.7 versus 15.2 mU/mL) and remain inappropriately low for the extent of anemia through the second postnatal month [3].

MANAGEMENT — Clinicians who care for premature infants should anticipate the development of AOP. Optimal nutrition (eg, iron supplementation) should be provided and patients monitored for signs of anemia. Blood sampling should be limited to essential testing, and microtechniques should be used to minimize blood loss due to phlebotomy [19,34]. (See 'Blood loss from phlebotomy' above.)

Red blood cell transfusions are primarily used to treat infants with AOP. Human EPO appears have limited benefit in decreasing exposure to different blood donors and is NOT recommended for routine use.

Iron supplementation — The iron content at birth is lower in preterm infants than term infants, and the iron stores of preterm infants often are depleted by two to three months of age. As a result, all preterm infants who are breastfed should receive iron supplementation of 2 to 4 mg/kg per day through the first year of life [35]. Infants who receive iron-fortified formula need less additional supplementation than those who are exclusively breastfed, because for a given volume, iron-containing formula contains a higher concentration of iron than

breast milk. (See "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Although iron supplementation does not prevent AOP, the use of iron-fortified formula compared to nonfortified formula allows for greater iron substrate when erythropoiesis is stimulated [36]. Iron supplementation does reduce iron-deficiency anemia, which both premature and term infants are at high risk for developing in the first year of life. (See "Nutritional composition of human milk and preterm formula for the premature infant" and "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis".)

Laboratory monitoring — The hematocrit (HCT) or hemoglobin (Hb) concentration should be monitored on a weekly basis in extremely low birth (ELBW) infants (birth weight less than 1000 g) in the first weeks of life. Thereafter, in healthy, growing premature infants, it is not necessary to routinely monitor HCT/Hb. Infants with persistent illness (eg, bronchopulmonary dysplasia) or surgical issues may require monitoring.

In asymptomatic infants, measuring a reticulocyte count at approximately four to six weeks after birth is used to evaluate whether a red blood cell (RBC) transfusion may be needed. Although no clearly defined biological markers have been identified to indicate when a RBC transfusion should be given in a premature infant, an absolute reticulocyte <100,000/microL (<2 percent) is often used as a criterion for RBC transfusion in asymptomatic infants with a low HCT (less than 20 percent) or Hb (less than 7 g/dL). The indications for neonatal RBC transfusion are discussed in greater detail separately. (See "Red blood cell transfusions in the newborn".)

Transfusion — RBCs transfusion is the most rapidly effective treatment for AOP. However, transfusion is a temporary measure and has the disadvantages of further inhibiting erythropoiesis and being associated with risks of transmitted infection, graft-versus-host disease, and toxic effects of anticoagulants or preservatives. (See "Transfusion-associated graft-versus-host disease" and "Immunologic blood transfusion reactions".)

RBC transfusion is performed when the level of anemia becomes symptomatic or is thought to compromise adequate oxygen delivery. Guidelines for RBC transfusion are based upon the patient's hematocrit (hemoglobin), their requirement for respiratory support, and the presence of symptoms consistent with anemia (eg, tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased episodes of apnea or bradycardia). The indications for transfusions, specific blood products available for transfusion, and the administration of transfusion in the neonate are discussed in detail separately. (See "Red blood cell transfusions in the newborn" and 'Oxygen delivery' above.)

Erythropoietin — The pathogenetic importance of impaired erythropoietin (EPO) production in AOP provides the rationale for the therapy with recombinant human EPO. However, this approach has not been accepted widely because it appears to have limited efficacy in decreasing the number of blood donors to which the infant is exposed via transfusion, whether EPO is administered early (within the first week of life) or late (at or after eight days of life). Data on the outcome of early and late EPO administration are presented in the following two sections.

A more effective approach to reduce the number of donor exposures for the preterm infant than routine administration of EPO is to limit the amount of blood drawn, follow restrictive guidelines for red blood cell transfusion, and to use satellite packs [37]. Satellite packs involve dividing one unit of donor blood into multiple smaller aliquots, which allows repeated transfusions from the same donor to the individual infant. (See "Red blood cell transfusions in the newborn", section on 'Target hemoglobin or hematocrit' and "Red blood cell transfusions in the newborn", section on 'Administration'.)

In retrospective studies, early administration of EPO has been associated with an increased risk of retinopathy of prematurity (ROP). In addition, EPO is a costly intervention. As a result, the routine use of EPO in neonates is NOT recommended because the potential limited benefits are outweighed by the costs and possible risks of the intervention.

Early EPO use — Although early administration (within the first eight days of life) of EPO appears to reduce the number of transfusions required in preterm infants, the small reduction may be of limited clinical importance,

because EPO does not decrease the number of donor exposures due to the use of satellite packs. In addition, some trials suggest that early EPO administration increased the risk of retinopathy of prematurity (ROP).

These findings were best illustrated in a meta-analysis of 23 trials (2074 preterm infants) that evaluated the effect of early administration of EPO (given before eight days of age) compared to placebo or no intervention [38]. Many of these infants had received blood transfusions prior to enrollment in the trials. The following findings were noted:

- In 18 trials of 1825 infants, EPO reduced the risk of receiving one or more red blood cell transfusions (RR 0.80, 95% CI 0.75-0.86).
- In 13 trials of 1115 infants, EPO slightly reduced the number of red blood cell transfusions (weighted mean difference of -0.27, 95% CI -0.42 to -0.12).
- In 10 trials of 1425 infants, EPO increased the risk of ROP (RR 1.18, 95% CI 0.99-1.40). In a sub-analysis of 6 trials of 930 infants in which information was available, EPO appeared to increase the risk of severe ROP, defined as stage 3 or greater (RR 1.71, 95% CI 1.15-2.54).
- There were no differences between the EPO and placebo groups in the rates of mortality, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hypertension, length of hospital stay, or long-term neurodevelopmental outcome.

In a follow-up study from one of the trials included in the meta-analysis, EPO and placebo-treated infants at 18 to 22 months corrected age with birth weights <1000 g had similar weight and length, number of rehospitalizations, transfusions after discharge, and developmental outcomes [39].

In summary, early EPO is associated with only a small reduction in the number of transfusions, but no reduction in exposure to the number of donors, and has no impact on clinical outcomes.

Although the meta-analysis also demonstrated a trend for an increased risk of ROP, this could be a chance finding because development of ROP was one of many secondary outcomes evaluated [38]. In addition, the sub-analysis that reported early administration resulted in an increased risk of severe ROP must be interpreted with caution, given that the overall effect on all grades of ROP was substantially lower. Among the studies included in the analysis, there were no data regarding the gestational age of the patients and illness severity, which both directly impact on the risk of ROP. Further studies are required to demonstrate whether or not there is a clinically significant association between early EPO use and ROP.

Although it is difficult to determine the role of EPO in the multifactorial pathogenesis of ROP, the current evidence is sufficient to raise concerns about the early use of EPO given the limited benefit of reducing exposure to blood donors, its cost, and potential association with ROP. As a result, we recommend NOT to routinely administer EPO within the first eight days of life.

Late EPO use — Late administration of EPO reduces the number of transfusions, but the limited benefit does not justify its use. This was illustrated in a meta-analysis of 28 trials (1302 preterm infants) that evaluated the effects of late EPO administration (at or later than eight days of age) compared to placebo or no intervention [40]. Most of these infants had received blood transfusions prior to enrollment in the trials. The following findings were noted:

- EPO reduced the risk of receiving one or more red blood cell transfusions (RR 0.66, 95% CI 0.59-0.74).
- EPO reduced the number of red blood cell transfusions (weighted mean difference of -0.78, 95% CI -0.97 to -0.59).
- EPO had no effect on the rates for ROP, mortality, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hypertension, length of hospital stay, or long-term neurodevelopmental outcome.

Late administration of EPO reduced the mean number of transfusions by a little less than one transfusion per infant. This small benefit of EPO was diminished due to the exposure of previous blood transfusions before eight days of life, and the use of satellite packs that would mitigate against additional donor exposure in the control

group. As a result, we recommend NOT to routinely administer EPO after eight days because its limited benefit of limiting exposure to blood donors does not justify its cost.

Complications — Use of EPO in premature infants appears to be safe. Hypertension, rash, bone pain, seizures, or later development of anti-EPO antibodies have not been reported in premature infants. Complications include the following:

- A transient neutropenia that resolves with cessation of therapy is occasionally observed [41,42]. In one trial, mean absolute neutrophil counts after 20 days were lower in premature infants who received EPO compared to red blood cell transfusion (1.8×10^3 versus 3.9×10^3) [41].
- Iron deficiency occurs if supplementation is inadequate [42-44].
- As discussed above, early administration of EPO has been associated with increased risk of ROP. (See 'Early EPO use' above.)

Dose — If EPO is given, it can be administered intravenously (200 U/kg per dose once daily) or subcutaneously (400 U/kg per dose, 3 times per week) [45]. When given intravenously, EPO should be mixed in a protein-containing solution (5 percent albumin) and given over at least four hours, or, more commonly, is added to TPN and administered daily over 24 hours [46]. The undiluted drug (2000 U/mL) can be given subcutaneously in a volume of 0.2 mL/kg for infants less than 1000 g. EPO preparation with higher concentrations (up to 10,000 U/mL) can be used as the infant grows.

Infants treated with EPO require iron supplementation. A proposed regimen is a daily elemental iron dose of 6 mg/kg for infants on full enteral feedings, and 3 mg/kg for those taking at least 60 mL/kg per day [45]. For infants receiving total parenteral nutrition, iron dextran can be added to the solution (3 to 5 mg/kg weekly) [45].

The reticulocyte count, central hematocrit or hemoglobin concentration, and absolute neutrophil count are measured before as well as one to two weeks after starting EPO treatment. EPO is withheld if the absolute neutrophil count is less than 1000/microL. Serum ferritin levels may be useful in evaluating those infants who are not responding to therapy to detect iron deficiency [45].

SUMMARY AND RECOMMENDATIONS

- Newborn infants have a fall in hematocrit soon after birth due primarily to impaired production of erythropoietin. In preterm infants, the decline occurs earlier, is more pronounced, and is called anemia of prematurity (AOP). AOP typically occurs at 3 to 12 weeks after birth in infants less than 32 weeks gestation. (See 'Pathogenesis' above.)
- Other contributors to anemia in the preterm infant include iron depletion, blood loss due to phlebotomy, and a reduced red blood cell life span in preterm infants compared to that of full term infants and adults. (See 'Pathogenesis' above and 'Other factors' above.)
- Preterm infants are at particular risk for impaired oxygen delivery with anemia because of the increased likelihood of concomitant respiratory disease, high levels of hemoglobin F, and the need to avoid hyperoxia, which increases the risk of BPD and retinopathy of prematurity (ROP). (See 'Oxygen delivery' above.)
- Many infants remain asymptomatic despite having hemoglobin levels below 7 g/dL. However, other infants may be symptomatic at similar or even higher hemoglobin levels. Symptoms include tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased frequency of apnea or bradycardia. (See 'Clinical and laboratory features' above.)
- The laboratory findings characteristic of AOP include normocytic and normochromic red blood cells, low reticulocyte count, and low erythropoietin levels. (See 'Clinical and laboratory features' above.)
- AOP may require treatment with RBCs transfusion. However, transfusion is a temporary measure and has potential adverse effects, such as infection and graft-versus-host disease. Guidelines for RBC transfusion based upon a restrictive policy in the neonate are presented separately. (See "Red blood cell transfusions in the newborn", section on 'Indications'.)
- Administration of recombinant human erythropoietin (EPO) appears to have limited efficacy in decreasing the number of blood donors to which the infant is exposed. It is a costly intervention, and

early EPO use may increase the risk and severity of ROP. As a result, we recommend NOT to routinely administer EPO to preterm infants (Grade 1B). (See 'Erythropoietin' above.)

- A more effective approach to reduce the number of donor exposures for the preterm infant than routine administration of EPO, is combination of limiting the amount of blood drawn, a restrictive policy for red cell transfusions, and the use of satellite packs, which allow for repeated transfusions from the same donor to the individual infant. (See "Red blood cell transfusions in the newborn", section on 'Target hemoglobin or hematocrit' and "Red blood cell transfusions in the newborn", section on 'Administration' and 'Management' above.)

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Calcium and phosphorus requirements of newborn infants

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INTRODUCTION — Calcium (Ca) and phosphorus (P) are essential minerals for two reasons: they are critical for the structural integrity of bone; and calcium and inorganic phosphorus ions in the cellular and extracellular fluid play an important role in many biochemical processes. (See "Etiology of hypocalcemia in infants and children" and "Nutritional composition of human milk and preterm formula for the premature infant".)

CALCIUM HOMEOSTASIS — Calcium homeostasis is a function of dietary intake, intestinal absorption, skeletal accretion and resorption, and urinary excretion. Most of the body calcium and much of the phosphate exist as hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, the main mineral component of bone.

Within the plasma, both Ca and P circulate in different forms. Of the plasma Ca, for example, roughly 40 percent is bound to serum proteins, principally albumin; 10 percent is complexed with citrate, bicarbonate, sulfate, or phosphate; and 50 percent exists as the physiologically important ionized (or free) calcium [1].

Although only a small fraction of the total body Ca and P is located in the plasma, the plasma concentrations of ionized Ca and inorganic P are the ones under hormonal control. This function is mediated primarily by parathyroid hormone (PTH) and vitamin D metabolites, which affect intestinal absorption, bone formation and resorption, and urinary excretion [2-4]. (See "Chapter 6F: Hormonal regulation of calcium and phosphate balance".)

In addition to the effects of PTH and vitamin D, bone resorption of Ca is affected by certain medications. As an example, vitamin A and synthetic retinoids increase bone resorption.

The primary function of renal excretion of Ca is the maintenance of overall Ca balance, not the plasma calcium concentration, which is regulated by changes in bone resorption via the effects of PTH and vitamin D. Parathyroid hormone reduces urinary Ca excretion, an appropriate response if hypocalcemia has stimulated parathyroid hormone secretion. Diuretics also affect Ca excretion, which is increased by loop diuretics and reduced by thiazide diuretics. (See "Chapter 6F: Hormonal regulation of calcium and phosphate balance" and "Diuretics and calcium balance".)

CALCIUM AND PHOSPHORUS IN HUMAN MILK — Human milk has slightly greater concentrations of minerals after a term birth than after a preterm birth. Compared to preterm human milk, term human milk contains more Ca (7 versus 6.25 mmol/L [280 versus 250 mg/L]) and P (4.8 versus 4.5 mmol/L [150 versus 140 mg/L]) [5]. The Ca and P exist in ionized and complexed forms that are readily absorbed. (See "Nutritional composition of human milk and preterm formula for the premature infant".)

Estimation of dietary calcium requirement — The factorial method is used to determine the appropriate intake for a particular nutrient, such as calcium. This approach includes a summary of the nutrients provided and an estimate of nutrient losses [6]. It also accounts for the bioavailability of the particular nutrient, which may be affected by incomplete absorption.

In the following example, the factorial approach is used to estimate Ca intake in formula typical for very low-birth-weight (VLBW) infants.

- Net Ca deposition — 105 mg/kg per day
- Urinary losses — 5 mg/kg per day
- Cutaneous losses — 2 mg/kg per day

- Subtotal net Ca requirement — 112 mg/kg per day
- Interindividual variability — 10 percent
- Net absorption of dietary Ca — 50 percent
- Total calcium intake to meet requirement — 246 mg/kg per day

REQUIREMENTS IN PRETERM INFANTS — The accretion of Ca and P rises exponentially during the third trimester because of the high rate of intrauterine growth. Chemical analyses of fetal cadavers during the last trimester of pregnancy have been used to estimate the rate of nutrient accretion [7,8]. These data have been computed on a daily basis per kilogram body weight. The estimated intrauterine accretion rates for Ca and P are 105 mg/kg and 70 mg/kg per day.

The requirements for Ca and P intake in preterm infants attempt to meet the rate of intrauterine accretion and account for nutrient losses. Preterm infants who have inadequate mineral intake develop metabolic bone disease. (See "Nutritional composition of human milk and preterm formula for the premature infant" and 'Osteopenia of prematurity' below.)

Mineral inadequacy of human milk — The content of Ca and P in human milk is insufficient for VLBW infants to achieve intrauterine accretion rates or normal bone mineralization [6,9-12]. This condition was illustrated in a study of extremely low-birth-weight infants fed human milk; bone mineralization measured by photon absorptiometry was reduced, and one-third of the infants had rickets or fractures [13]. Biochemical markers of deficient mineral intake included low serum and urine phosphorus concentrations, elevated serum alkaline phosphatase activity, and elevated serum and urine calcium concentrations [10,11,14-16].

Most VLBW infants fed unsupplemented human milk have elevated serum alkaline phosphatase activity, indicating stimulation of bone resorption to normalize the serum Ca concentration. In one study of 865 preterm infants, infants fed unsupplemented human milk had elevated serum alkaline phosphatase activity, indicating stimulation of bone resorption to normalize the serum Ca concentration [15]. In this series, newborns with peak alkaline phosphatase activity >1200 IU/L had 1.6 cm less linear growth at 18 months and shorter stature at 9 to 12 years of age than those with lower levels [17].

Supplementation of human milk — Supplementation of human milk with Ca and P improves linear growth; increases bone mineralization during hospitalization and after discharge; and normalizes serum calcium, phosphorus, and alkaline phosphatase activity and urinary excretion calcium and phosphorus [15,16,18,19]. Net mineral retention and bone mineral content are improved with increased intake [20]. Bone mineral content was similar when Ca and P were added to a multivitamin fortifier or given alone, although the multivitamin formulation resulted in better linear growth [21].

For VLBW infants, we recommend the addition of Ca (2 to 3 mmol/kg per day or 80 to 120 mg/kg per day), and P (1.5 to 2 mmol/kg per day or 45 to 60 mg/kg per day) to human milk, so that infants receive the recommended intake of 200 mg/day of calcium and 100 mg/day after enteral feeding is established. Current commercial human milk fortifiers provide stable suspensions of these minerals. (See "Nutritional composition of human milk and preterm formula for the premature infant", section on 'Calcium and phosphorus' and "Human milk feeding and fortification of human milk for premature infants", section on 'Commercial fortifiers'.)

Premature formula — Premature formulas currently available in the United States administered to provide 120kcal/kg per day provide daily intakes of approximately 5 mmol/kg (200 mg/kg) Ca and 3 mmol/kg (100 mg/kg) P. Absorption of these minerals allows the infant to accrete minerals at the approximate intrauterine accretion levels [22]. However, quantities of Ca and P in formulas for term infants and other specialized (not premature) formulas are generally not adequate to meet the mineral needs of VLBW infants.

Absorption — The absorption of Ca from human milk or commercial formula is approximately 60 percent of intake [22], whereas the absorption of P is greater in human milk than in commercial formula (90 versus 80 percent). P retention is improved when the ratio of Ca to P intake is 1.6:1 to 1.8:1 compared to 2:1 [23]. Absorption of both minerals is affected by postnatal age and the intake of Ca, P, lactose, fat, and vitamin D [24]. However, vitamin D may contribute little to Ca absorption in premature infants in the first weeks of life [25].

Parenteral nutrition — Mineral accretion is inadequate in VLBW infants who are treated with total parenteral nutrition for more than two weeks. This is related in part to the need to limit mineral concentrations because of their solubility in parenteral nutrition solutions. However, increased administration of Ca and P improves mineral retention. As an example, in a study of 24 VLBW infants receiving total parenteral nutrition, administration of 17 mmol/L (680 mg/L) Ca and 20 mmol/L (660 mg/L) P resulted in net retention of 70 to 80 mg/kg per day Ca and P [26].

The recommended mineral concentrations for parenteral nutrition solutions depend upon the duration of therapy. When parenteral nutrition is given to VLBW infants for less than two weeks, solutions should contain Ca 15 mmol/L (600 mg/L) and P 15 mmol/L (465 mg/L) and be given at rates of 120 to 130 mL/kg per day [22]. Mineral concentrations are increased to Ca 20 mmol/L (800 mg/L) and P 20 mmol/L (620 mg/L) when parenteral nutrition is given at 120 to 130 mL/kg per day for more than two weeks. (See "Parenteral nutrition in premature infants", section on 'Calcium, phosphorus, and magnesium'.)

After discharge — Sufficient Ca and P must be provided for premature infants during hospitalization to maintain adequate bone mineral content. After discharge, continued supplementation may be needed. In a randomized trial, 59 premature infants who received formula with calcium content of 545, 660, or 1290 mg/L for eight weeks after discharge had greater gains in weight and length and lower serum alkaline phosphatase values than did those fed human milk [27]. Infants who received the formula with the highest calcium concentration had the highest bone mineral density. Infants who received human milk had the lowest bone mineral content. In another study, bone mineral content was greater at nine months corrected age in preterm infants taking formula with a Ca concentration of 700 mg/L compared to 350 mg/L [28].

The benefit of formula feeding on mineral status appears to dissipate over time, with a catch-up in bone mineral density by two years [29]. However, a mineral-enriched formula may be indicated after discharge in selected patients with elevated alkaline phosphatase and low serum phosphorus, especially in infants with birth weights <1500 g [30-32].

Growth is closely monitored in VLBW infants who are discharged feeding human milk exclusively. Possible mineral deficiency is assessed after four to eight weeks by measuring serum phosphorus concentration and alkaline phosphatase activity. If these values are abnormal, a radiograph of the long bones is obtained to assess mineralization. Mineral supplementation is provided if osteopenia is detected on the bone films. (See 'Osteopenia of prematurity' below.)

Supplemental minerals can be provided by several methods. One approach is to give formula with a high mineral content instead of human milk for multiple feedings each day. Typically, this is done for two to three feedings, but no studies have been done to evaluate different approaches. As an alternative, a human milk fortifier is added to the breast milk, which is given by bottle; this method has not been studied in infants after discharge. The last approach is less preferable because of concerns about the use of powdered infant formula and difficulties in accurately fortifying milk. In rare circumstances, such as cow milk protein allergy, use of special formulas or human milk fortifier is not feasible; in this setting, calcium and phosphorus supplements can be given.

OSTEOPENIA OF PREMATURITY — Osteopenia of prematurity, also called metabolic bone disease of prematurity, is defined as postnatal bone mineralization that is less than intrauterine bone density at a comparable gestational age [22,33,34]. Osteopenia occurs commonly in preterm infants; the incidence and severity increase with decreasing birth weight [35]. Characteristic radiographic changes are seen in 55 percent of infants with birth weight <1000 g [34]. High bone turnover appears to be more important than decreased bone formation in the pathogenesis of this disorder [36,37].

In addition to immaturity, the major predisposing factor is deficiency of Ca and P because of inadequate intake. Other risk factors include prolonged parenteral nutrition and medications that affect mineral metabolism, such as caffeine, loop diuretics, and corticosteroids [38]. Decreased bone mineralization also occurs in infants who are small-for-gestational age or are born to diabetic mothers [39,40].

Clinical features — Osteopenia typically develops in premature infants at 3 to 12 weeks of age. The condition is not clinically apparent and is detected by routine laboratory monitoring.

Laboratory features — The earliest indications of osteopenia are decreased serum phosphorus concentration, typically less than 3.5 to 4.0 mg/dL (1.1 to 1.3 mmol/L), and increased alkaline phosphatase activity. Alkaline phosphatase values >800 IU/L are worrisome, especially if combined with serum phosphorus values less than 4.0 mg/dL (1.3 mmol/L). However, distinguishing the normal rise in alkaline phosphatase activity associated with rapid bone mineralization from the pathologic increase related to early osteopenia often is difficult [41]. In this circumstance, decreased bone mineralization observed on a radiograph confirms the diagnosis.

Radiographic features — The radiographic feature characteristic of osteopenia is decreased lucency of the cortical bone with or without epiphyseal changes (picture 1). Most infants with decreased bone mineralization do not have fractures, even when osteopenia is severe. However, in rare cases, a fracture can be the earliest sign.

Diagnosis — We recommend routine monitoring of the serum phosphorus concentration and alkaline phosphatase activity in all infants with birth weight <1500 g. Studies are obtained at two week intervals until full feeds are achieved and stable values are demonstrated. Infants with additional risk factors for osteopenia, such as prolonged parenteral nutrition or inadequate enteral intake of Ca and P, are tested weekly. If these laboratory values are abnormal, we obtain radiographs of the wrist and/or knees to confirm the diagnosis.

Management — Osteopenia of prematurity is treated by providing adequate Ca and P for bone mineralization through feeding fortified human milk or premature formula (see above) [20,39]. Infants who do not tolerate human milk fortifiers or premature formula because of lactose intolerance or cow's milk protein allergy should be given supplements of calcium and phosphorus. The maximum allowable parenteral mineral concentrations should be provided to infants not receiving enteral feeding. Vitamin D supplementation is rarely indicated for this condition. Totally daily doses of 200 to 400 IU/day are adequate, although some prefer a higher dose of 800 to 1000 IU/d. Although the safety and efficacy of higher doses have not been established, they have been increasingly advocated [42].

Infants with severe cholestasis or other chronic illnesses may need prolonged supplementation with high doses of Ca, P and vitamin D. Vitamin D may need to be given as the active form, calcitriol (1,25 dihydroxy vitamin D) with appropriate monitoring of serum calcium to avoid hypercalcemia. Premature infants with fractures resulting from osteopenia are managed conservatively.

Most infants who receive increased enteral or parenteral mineral supplementation have improved radiographic findings after several weeks. Serum P concentration and alkaline phosphatase activity also become normal during this period.

CALCIUM REQUIREMENTS IN TERM INFANTS — Milk from their own mothers is the optimal nutritional source for term infants during the first year after birth and provides adequate amounts of Ca and P. The amounts of Ca and P retained by the term infant who is exclusively breastfed during the first six months and is supplemented with solid foods during the second six months result in appropriate bone mineralization.

Need for vitamin D supplementation — Although the amounts of Ca and P are adequate, human milk is not a primary source of vitamin D for infants. Rather, sunlight exposure is needed to provide for the cutaneous formation of vitamin D. As a result, rickets can occur in breastfed infants who have inadequate exposure to sunlight or are deeply pigmented.

Thus, the American Academy of Pediatrics recommends that breastfed infants receive supplementation of vitamin D in a dose of 400 IU per day [43]. Although infant formula is supplemented with vitamin D (400 IU/L), infants who ingest less than 1000 mL of vitamin D fortified formula also require supplementation in order to reach the recommended daily vitamin D dose of 400 IU [43,44]. In the United States, compliance with these vitamin D supplementation guidelines is poor and less than 15 percent of breastfed infants receive appropriate amounts of vitamin D [45]. (See "Vitamin D insufficiency and deficiency in children and adolescents", section on 'Vitamin D supplementation for infants'.)

Ca and P in formula — The concentrations of Ca and P in infant formulas are greater than in human milk to compensate for the possibility of reduced absorption of these minerals with formula feeding. Infants fed cow's milk-based formulas may have calcium retention, which considerably exceeds that of breast-fed infants [46]. The potential benefits of high levels of minerals in infant formulas on short and long-term bone mineralization are

uncertain [14]. There are no proven advantages to increasing bone mineralization or calcium retention in full-term infants relative to that achieved by breast-fed infants.

The bioavailability of Ca and P in the specialized formulas that contain soy or casein hydrolysates is less than in standard formulas. Thus, these special preparations have even greater concentrations of Ca and P.

SUMMARY AND RECOMMENDATIONS — Calcium (Ca) and phosphorus (P) are essential minerals as they play critical roles in the structural integrity of bone and growth, and in cellular and extracellular biochemical processes.

- Ca homeostasis is based upon the net effects of dietary intake, intestinal absorption, skeletal accretion and resorption, and urinary excretion. (See 'Calcium homeostasis' above.)
- The Ca concentration is greater in human milk from mothers after term delivery compared with preterm delivery. (See 'Calcium and phosphorus in human milk' above.)
- The requirement of both Ca and P is greater in preterm infants compared with term infants because of the high rate of accretion needed for growth. (See 'Requirements in preterm infants' above.)
- In preterm infants who are breastfed, Ca and P supplementation is required because preterm human milk is inadequate to meet the needs of these infants. We recommend the addition of Ca (2 to 3 mmol/kg per day or 80 to 120 mg/kg per day) and P (1.5 to 2 mmol/kg per day or 45 to 60 mg/kg per day) to human milk after enteral feeding is established. Current commercial human milk fortifiers provide stable suspensions of these minerals. (See 'Supplementation of human milk' above.)
- In preterm infants who are formula-fed, preterm formula in a volume of 120 to 150 mL/kg provide adequate Ca and P intake. However, formulas for term infants do not adequately meet the mineral needs of premature infants. (See 'Premature formula' above.)
- In preterm infants who receive parenteral nutrition, the requirement of Ca and P is dependent upon the length of parenteral nutrition. (See 'Parenteral nutrition' above.)
- After discharge, Ca and P supplementation may still be required. (See 'After discharge' above.)
- Inadequate Ca and P intake increases the risk of osteopenia of prematurity (ie, postnatal bone mineralization that is less than intrauterine bone density at a comparable gestational age). (See 'Osteopenia of prematurity' above.)
- Term human milk and term formula has adequate concentrations of Ca and P to meet the needs of term infants. However, in exclusively breast-fed infants, vitamin D supplementation (dose of 400 IU per day) is recommended because of the concern of inadequate vitamin D intake. (See 'Calcium requirements in term infants' above.)

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Epidemiology and etiology of cerebral palsy

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INTRODUCTION — Cerebral palsy (CP) consists of a heterogeneous group of nonprogressive clinical syndromes that are characterized by motor and postural dysfunction. These conditions, which range in severity, are due to abnormalities of the developing brain resulting from a variety of causes. Although the disorder itself is not progressive, the appearance of neuropathologic lesions and their clinical expression may change over time as the brain matures.

The epidemiology and etiology of CP are reviewed here. The clinical manifestations, diagnosis, management, and prognosis are discussed separately. (See "Clinical features of cerebral palsy" and "Diagnosis of cerebral palsy" and "Management and prognosis of cerebral palsy".)

EPIDEMIOLOGY — The precise prevalence of CP in the United States is uncertain because consistent information is lacking on follow-up of an entire population, especially for term and late preterm infants, which comprise the majority of births. A population-based surveillance study using data from three regions in the United States estimated a prevalence of 3.6 cases per 1000 children at eight years of age, but the study did not distinguish between children with and without a history of prematurity [1]. No data are available on CP prevalence in North America for term infants born since the mid-1980s [2]. In one report that used standard definitions and included 6000 children with CP from 13 geographically defined populations in Europe born from 1980 to 1990, the overall rate was 2.08/1000 live births [3].

The rate of CP is much higher in preterm than term infants, and increases with decreasing birth weight and gestational age. This is illustrated by the following studies:

- In a study from Europe, the rate was more than 70 times higher in infants with birth weight <1500 g than in those with birth weight >2500 g [3].

- In a population-based study from Sweden of 216 children with CP born between 1987 and 1990, the prevalence was 1.4, 14, 68, and 57 for birth weights ≥ 2500 g, 1500 to 2499 g, 1000 to 1499 g, and < 1000 g, respectively [4].
- Severe neuromotor disability was present in 10 percent of surviving infants born at ≤ 25 weeks gestation in 1995 in the United Kingdom and Ireland and evaluated at 30 months of age [5].
- In a review of 42 studies published after 1970, CP occurred in 12 percent of surviving infants born with gestational age ≤ 26 weeks and 8 percent of those with birth weight ≤ 800 g [6].

Even among infants born at term, small variations in gestational age are associated with risks for CP. In a population study of infants without congenital anomalies in Norway, the risk for CP was lowest among infants born at 40 weeks as compared with those born at 38 or 42 weeks [7]. The explanation for this association has not been established; it is possible that the presence of CP disrupts the timing of delivery or that the timing of the delivery causes the increased risk for CP.

The risk of CP increases at the extremes of birth weight across gestational ages. In the largest epidemiologic study on CP and birth weight, 4503 singleton children with CP born at 32 to 42 weeks gestation were compared to two reference standards for intrauterine growth [8]. The risk of CP was 4 to 6 times greater in infants with birth weight < 10 th percentile than those with birth weight between the 25th and 75th percentile. In those with birth weight > 97 th percentile, the risk was increased 1.6 to 3.1 times. The risk of CP was lowest in children with birth weight approximately one standard deviation above average. It is not known whether CP causes or results from abnormal growth [8,9].

The rate of CP and the extent of disability increased in preterm infants born in the 1960s through 1980s as survival improved for the most immature [10]. During the 1980s and 1990s, the rate of CP remained stable for term and late preterm babies, most of whom survive [2]. Although the risk is small for an individual, approximately one-half the cases of CP occur in infants born at or late preterm.

More recent data suggest a reversal of the trend in some areas. In Western Europe, there was a significant decrease in rates of CP among infants born at gestational age 28 to 31 weeks between 1981 and 1995, most likely because of improvements in perinatal care [11]. The study showed similar findings when the data were analyzed by birthweight: the birth prevalence of CP fell from 60.6 per 1000 liveborn very low birthweight infants in 1980 to 39.5 per 1000 in 1996. This improvement occurred despite overall increases in survival and multiple births, and decreases in mean birthweight among this group. Similarly, in Northern Alberta, the prevalence of CP among infants born between 20 and 27 weeks gestation began to decrease in the mid 1990s, in the setting of stable or decreasing mortality, reversing previous trends [12]. In that study, CP prevalence per 1000 live births decreased from 155 in 1992-1994 to 16 in the years 2001-2003.

ETIOLOGY — The etiology of CP is multifactorial. Known causes account for only a small proportion of cases [13]. Most cases are thought to be due to prenatal factors, although perinatal asphyxia plays a role in some; prematurity is a common association.

The multifactorial etiology was illustrated in a series of 213 children diagnosed with CP in Australia [14]. Major CP-associated pathologies other than acute intrapartum hypoxia were identified in 98 percent of cases; some children had more than one associated pathology:

- Prematurity (78 percent)
- Intrauterine growth restriction (34 percent)
- Intrauterine infection (28 percent)
- Antepartum hemorrhage (27 percent)
- Severe placental pathology (21 percent)
- Multiple pregnancy (20 percent)

Perinatal asphyxia — Although it is often suspected as a cause, perinatal hypoxia and/or ischemia likely accounts for only a small minority of cases of CP [15-17]. (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy" and "Etiology and pathogenesis of neonatal encephalopathy".)

Many studies that linked the development of CP to perinatal asphyxia used a low Apgar score at five minutes as a marker for asphyxia [15]. However, the use of Apgar scores alone is an inappropriate criterion, as they can be low due to maternal analgesia or prematurity when umbilical cord pH is normal, or normal in the presence of acute asphyxia or maternal metabolic acidosis. In the National Collaborative Perinatal Project that was performed in the 1960s and included approximately 49,000 subjects, the risk of CP at age seven years in infants with an Apgar score of 0 to 3 at five minutes was 4.7 percent, approximately 25 times the risk for those with scores of 7 to 10 [18]. In another study of children with birth weight >2500 g born in Norway in 1983 to 1987, the risk of CP with an Apgar score of 0 to 3 at five minutes was 6.8 percent [18]. In both studies, however, 93 to 95 percent of infants with Apgar scores of 0 to 3 at five minutes did not have CP [19].

Intrapartum abnormalities that may lead to asphyxia occur in children with and without CP but do not support a strong causative association [20]. In one study, tight nuchal cord was associated with spastic quadriplegia but not hemiplegia or diplegia, while placental abruption, placental previa, and prolapsed cord were rare and were not associated with development of CP. Intrauterine infection and coagulation disorders were more strongly associated with the development of spastic CP than was birth asphyxia [21,22].

In 2003, the American College of Obstetricians and Gynecologists, in collaboration with the American Academy of Pediatrics, convened a Task Force on Neonatal Encephalopathy and Cerebral Palsy that published a report illustrating the best scientific data and opinion on these issues [23]. According to the task force, four essential criteria are required to define an intrapartum asphyxial event sufficient to cause CP, as listed in the Table (table 1) [24]. In addition, the definition requires that at least three out of five other criteria be present to indicate that the timing of the insult is likely to have occurred during the peripartum period (within 48 hours of labor and delivery) (table 2). The latter criteria may be related to development of CP but are not considered to be specific for asphyxia.

In a retrospective study using these criteria, only 4 percent of children with CP who were born at full term had evidence of an acute hypoxic event during labor [14]. The criteria have not been prospectively validated.

Neonatal encephalopathy — In the term infant, severe perinatal asphyxia can cause parasagittal cortical injury and infarction in the brainstem and basal ganglia and lead to the development of spastic quadriplegia. Perinatal hypoxia-ischemia also can cause necrosis in the spinal cord gray matter, contributing to flaccidity, hypokinesia, and absent reflexes [25].

Infants with severe intrapartum hypoxia-ischemia have encephalopathy (eg, seizures, coma, hypotonia), dysfunction of another organ system, a persistently low Apgar score, and evidence of profound metabolic acidosis. The outcome depends upon the severity of the hypoxic-ischemic encephalopathy (HIE).

- Infants with mild HIE in the neonatal period have a very high probability (97 to 100 percent) of being completely normal at follow-up.
- Infants with moderate encephalopathy have a 20 to 35 percent risk of later sequelae from the insult, although those whose neurologic examinations are completely normal within one week have a good likelihood of normal outcome.
- Infants with severe encephalopathy have a 75 percent risk of dying in the neonatal period; among survivors, a universal risk of sequelae exists. (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy".)

Congenital abnormalities — The etiology of CP in term infants often is of prenatal origin [26,27]. This is supported by the observation that congenital abnormalities are more common in children with than without CP [28-30]. In a population-based case-control study in California, congenital abnormalities occurred in 19.2 percent of children with CP and 4.3 percent of controls (OR 5.2, 95% CI 2.8-9.7) [28]. This was attributable to a greater proportion of structural central nervous system (CNS) abnormalities in children with CP (14.5 versus 1 percent). The proportion of abnormalities outside the CNS was similar in the two groups. In another report, minor congenital anomalies were more frequent in children with ataxic CP than in related or unrelated controls [29].

Intrapartum events may be influenced by a preexisting abnormality [31,32]. In one report, birth defects (mostly non-CNS anomalies) occurred more often in term infants with neonatal encephalopathy, a risk factor for CP,

than in controls (27.5 versus 4.3 percent) [33]. The birth defect was considered the cause of the encephalopathy in approximately one-third of affected infants.

In a series of 150 affected patients, the etiology was attributed to congenital disorders in 53 and 35 percent of those with quadriplegic and nonquadriplegic CP, respectively [34]. Furthermore, many infants with anomalies have a breech presentation at birth, which also is a risk factor for CP [26,35].

Brain malformations — In some children, CP results from brain malformations. The biologic basis of most of these is unknown. Some result from abnormalities that occur during brain development and affect cell proliferation, migration, differentiation, survival, or synaptogenesis. Disorders of development occasionally result from exposure to radiation, toxins, or infectious agents during a critical period of gestation [36-39]. Some disorders (eg, schizencephaly) are genetic and follow mendelian inheritance patterns [40-44]. Chromosomal abnormalities are associated with some cerebral malformations, such as trisomies 13 and 18 and holoprosencephaly. Some neurocutaneous syndromes are associated with brain malformations (eg, hemimegalencephaly and hypomelanosis of Ito or the linear sebaceous nevus syndrome) [45].

Genetic susceptibility — The aggregation of CP in groups with high consanguinity, and observations of increased familial risk for CP suggests a genetic contribution to CP risk [46,47]. Several genetic polymorphisms have been associated with susceptibility for CP, including apolipoprotein E [48], genes associated with thrombophilias [49], and with inflammation (certain cytokines [50,51], inducible nitric oxide synthetase (iNOS), and lymphotoxin alpha (LTA, also known as TGF-beta) [51]).

Multiple births — The risk of CP is increased among multiple births [52-57]. Causes that may contribute to this risk include low birth weight, congenital anomalies, cord entanglement, and abnormal vascular connections [58]. In a study of births in Western Australia in 1980 to 1989, the prevalence of CP was 1.6, 7.3, and 28 per 1000 survivors to one year of age in singletons, twins, and triplets, respectively [52]. In this report, the increased rates of CP in multiples was limited to infants of normal birth weight, although multiples were more likely to have low birth weight.

Death of a co-twin greatly increases the risk of CP. In the report from Western Australia, the risk of CP among twins was greater when one twin died in utero (96 versus 12 per 1000 twin pairs) compared to both surviving [52]. The mechanism may include release of thromboplastin and emboli from the dead twin causing injury to the survivor. It is possible that some cases of CP in apparent singletons may be due to an unrecognized fetal death of a co-twin [59].

Postnatal death also increases the risk of CP in the surviving co-twin and monozygosity appears to influence this risk. In a report from England and Wales in 1993 to 1995, birth and death certificate data were analyzed for different sex (dizygotic) and same sex (dizygotic and monozygotic) twins [60]. Disability in the surviving twin after neonatal death of the co-twin was ascertained by a questionnaire sent to physicians. The risk of CP was significantly greater in same sex compared to different sex twin survivors (167 versus 21 per 1000) for infants of birth weight 1000 to 1999 g, although only marginally greater (224 versus 220 per 1000) for birth weight <1000 g.

Stroke — Stroke in the perinatal period contributes to CP, especially spastic hemiparesis. Thromboembolism and prothrombotic disorders contribute to the etiology of this disorder. Lesions typically are identified by cranial imaging studies following a neonatal seizure. However, some newborns with stroke are asymptomatic until hemiparesis or other abnormalities develop later in infancy or childhood. (See "Stroke in the newborn".)

Intracranial hemorrhage — Intracranial hemorrhage (ICH) in term infants is unusual but frequently results in neuromotor abnormalities. Most are recognized because of the sudden and dramatic onset of symptoms, including seizures, abnormal movements, apnea, lethargy, irritability, vomiting, and bulging fontanelle. Diagnosis is made by cranial imaging.

The incidence depends in part upon the method of ascertainment. In one series of 33 term infants with symptomatic ICH, the regional incidence was estimated to be 0.27 per 1000 live births [61]. Approximately one-third of cases were related to coagulopathies. In another report from Germany, ICH was diagnosed by ultrasound

scan in 54 of 2019 term infants (2.7 percent) treated in a newborn intensive care unit from 1989 to 1999 [62]. Neurologic impairment developed in 28 percent.

Thalamic hemorrhage with residual germinal matrix hemorrhage is a common source of ICH in this population. When no source is apparent, the ICH is thought to originate from the choroid plexus. In one report, thalamic hemorrhage was identified in 12 of 19 term infants younger than one month of age with ICH diagnosed by computed tomography [63]. Thalamic hemorrhage typically occurred in infants with uneventful birth histories and presentation after one week of age. Many had predisposing factors for cerebral vein thrombosis (eg, sepsis, congenital heart disease, coagulopathy, electrolyte disturbance). At 18 months of age, the majority had CP, predominantly hemiplegia, and other neurologic abnormalities such as hydrocephalus and seizures.

Intrauterine infection — Intrauterine infection is associated with an increased risk of CP. Congenital infections with organisms such as cytomegalovirus, syphilis, varicella virus, and toxoplasmosis play a role. Bacterial infections leading to chorioamnionitis are also associated with CP.

Chorioamnionitis is associated with an increased risk of CP in term infants, although few studies are available [21,64,65]. In one report, a population-based case-control study in California in 1983 to 1985 evaluated maternal infection in children with disabling spastic CP with birth weight >2500 g and no identified prenatal brain lesions [21]. The risk of CP was increased by maternal temperature >38 degrees in labor (OR 9.3) or a clinical diagnosis of chorioamnionitis. Indicators of maternal infection were more likely to occur in children with CP and spastic quadriplegic CP compared to controls (22 and 37 versus 2.9 percent). In addition, maternal infection was associated with birth depression and need for resuscitation and neonatal seizures.

In another case-control study in California of term singleton infants born at ≥ 36 weeks gestation between 1991 and 1998, chorioamnionitis occurred more often in children with CP than controls (14 versus 4 percent) [65]. Cerebral palsy could be attributed to chorioamnionitis in 11 percent of cases, and the odds ratio for developing cerebral palsy after a diagnosis of chorioamnionitis was 4.1 (95% CI, 1.6-10.1) in multivariable analysis. Other independent risk factors for CP included intrauterine growth restriction, maternal black ethnicity, maternal age >25 years, and nulliparity.

The role of intrauterine infection is supported by the presence of increased concentrations of inflammatory mediators (interleukins 1, 8, 9, tumor necrosis factor- α , and RANTES [regulated on activation normally T-cell expressed and secreted]) in neonatal blood samples of children with CP compared to controls [66]. In the same study, concentrations of antibodies to antithrombin, a translational product of factor V Leiden mutation, and proteins C and S also were higher in children with CP.

In preterm infants, perinatal infection appears to play a key role in the pathogenesis of periventricular leukomalacia (PVL) and subsequent CP [67]. PVL refers to necrosis of cerebral white matter in a specific distribution, dorsolateral to the external angles of the lateral ventricles and involving the region adjacent to the trigones and to the frontal horn and body of the lateral ventricles. In a meta-analysis of observational studies of the association of chorioamnionitis and CP and cystic PVL, clinical chorioamnionitis was significantly associated with CP (relative risk 1.9) and cystic PVL (RR 3.0) in preterm infants [68]. Histologic chorioamnionitis was also associated with these outcomes. (See "Periventricular leukomalacia".)

The development of PVL may be mediated by a fetal inflammatory response, as evidenced by increased concentration of cytokines in the amniotic fluid or umbilical cord blood. In one series of 94 preterm pregnancies in which amniocentesis was performed, 23 newborns had subsequent sonographic evidence of PVL [69]. Median amniotic fluid concentrations of tumor necrosis factor- α , interleukin-1 β , and interleukin-6 were higher in newborns with PVL than in those without. All eight infants who later developed cerebral palsy had PVL and elevated amniotic fluid cytokine levels. In another report, concentrations of interleukin-6, but not interleukin 1(β), interleukin-1 receptor antagonist, and tumor necrosis factor- α , were higher in umbilical cord plasma in preterm infants with than without PVL [70].

Prematurity — CP develops in approximately 5 to 15 percent of surviving very low birth weight infants. In this population, it is associated with the presence of PVL. In addition to perinatal inflammation and other etiologies discussed above, cerebral ischemia in a specific distribution contributes to PVL and leads to CP in preterm infants. (See "Periventricular leukomalacia", section on 'Pathophysiology'.)

Other conditions that primarily affect preterm infants and may lead to CP include severe intraventricular hemorrhage (IVH) and periventricular hemorrhagic infarction. (See "Management and complications of intraventricular hemorrhage in the newborn" and "Stroke in the newborn".) Posthemorrhagic hydrocephalus, a complication of IVH, frequently leads to CP [71].

The risk of motor impairment is greater in preterm infants affected by bronchopulmonary dysplasia (BPD). The mechanism is not known but may involve the use of corticosteroids to improve lung disease. A more detailed discussion of this issue is found elsewhere. (See "Prevention of bronchopulmonary dysplasia".)

An extrapyramidal movement disorder has been described in a series of 10 preterm infants with severe BPD [72]. This disorder became apparent at approximately three months of age. It persisted in three of the surviving seven infants and partially or completely resolved in the rest. A similar choreic disorder may occur in infants following cardiopulmonary bypass and profound hypothermia for repair of congenital heart defects [73]. Neuropathologic findings consisted of neuronal loss, reactive astrocytosis, and degeneration of myelinated fibers, primarily in the outer segment of the globus pallidus [74].

Acquired postnatal causes — Approximately 10 to 18 percent of cases of CP are acquired after the neonatal period [75]. Most of these patients have spastic CP. Causes include stroke, trauma, and severe hypoxic events such as near-drowning. Bacterial, viral, and fungal infections also may lead to CP.

Kernicterus — Infants with severe hyperbilirubinemia are at risk for kernicterus, permanent neurologic sequelae of bilirubin-induced neurotoxicity (BIND), that manifests itself as a type of CP characterized by choreoathetosis, with gaze abnormalities and sensorineural hearing loss. The disorder results when unconjugated bilirubin enters the brain and causes focal necrosis of neurons and glia. The regions most often affected include the basal ganglia and the brainstem nuclei for oculomotor and auditory function, accounting for the clinical features of this condition. (See "Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants", section on 'Kernicterus'.)

MAGNESIUM SULFATE — Because magnesium sulfate is neuroprotective in animals exposed to hypoxic-ischemic injury, it was hypothesized that CP might be reduced in offspring of mothers treated with magnesium sulfate for preeclampsia or preterm labor. There is increasing evidence from clinical trials that antenatal administration of magnesium sulfate to women with preterm labor decreases the incidence and severity of cerebral palsy in their offspring, without affecting mortality. (See "Neuroprotective effects of in utero exposure to magnesium sulfate".)

SUMMARY

- The prevalence of cerebral palsy (CP) is approximately 2 to 4 cases per 1000 children. The risk is markedly increased among infants with low birthweight, so the prevalence of CP in a given population also depends on rates of premature birth and survival of such infants. (See 'Epidemiology' above.)
- The etiology of CP is multifactorial. Most cases are thought to be due to prenatal factors. The most commonly identified prenatal risk factors for CP are prematurity, intrauterine growth restriction, intrauterine infection, antepartum hemorrhage, severe placental pathology, and multiple pregnancy. (See 'Etiology' above.)
- Perinatal hypoxia and/or ischemia likely accounts for only a small minority of cases of CP. (See 'Perinatal asphyxia' above.)
- Stroke in the perinatal period may cause CP, and is typically manifested as spastic hemiparesis. Thromboembolism and prothrombotic disorders contribute to the etiology of this disorder. (See 'Stroke' above and "Stroke in the newborn".)
- CP develops in approximately 5 to 15 percent of surviving very low birth weight infants. In this population, it is associated with the presence of periventricular leukomalacia, intraventricular hemorrhage and periventricular hemorrhagic infarction. (See 'Prematurity' above.)
- There is increasing evidence that antenatal administration of magnesium sulfate to women with preterm labor decreases the incidence and severity of cerebral palsy in their offspring, without affecting mortality. (See 'Magnesium sulfate' above and "Neuroprotective effects of in utero exposure to magnesium sulfate".)

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Red blood cell transfusions in the newborn

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INTRODUCTION — Red blood cell (RBC) transfusion provides an immediate increase in oxygen delivery to tissues and is an effective and rapid intervention to treat anemia. RBC transfusions can reduce the morbidity associated with anemia, especially anemia of prematurity, and may be life saving in neonates with severe blood loss.

However, transfusion is a temporary measure and has the disadvantages of further inhibiting erythropoiesis and being associated with risks of infection, graft-versus-host disease, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and toxic effects of anticoagulants or preservatives. In addition, deleterious effects specific to neonates such as transfusion related acute gut injury (TRAGI) [1] and intraventricular hemorrhage [2] have been reported. These potential adverse effects underscore the need to

carefully evaluate a neonate's ability to delivery oxygen to tissues prior to ordering a nonemergent transfusion, and to document benefit following the transfusion. (See "Transfusion-associated graft-versus-host disease" and "Immunologic blood transfusion reactions".)

It is often difficult to distinguish the neonate who is anemic and requires RBC transfusion from one who has adapted to a low hematocrit (Hct), and is best treated conservatively to avoid the associated risks of transfusion.

The indications for neonatal RBC transfusions and the selection of the proper blood product will be reviewed here. Anemia of prematurity and indications for red cell transfusion in infants and children are discussed separately. (See "Anemia of prematurity" and "Indications for red blood cell transfusion in infants and children".)

INDICATIONS — Anemia occurs when the RBC mass does not adequately meet the oxygen demands of the tissue.

Oxygen supply to the tissue is defined as the product of cardiac output and arterial oxygen content. The arterial oxygen content is dependent upon the hemoglobin concentration, arterial oxygen saturation, oxygen carrying capacity of hemoglobin (1.34 mL/gm hemoglobin), and to a minor extent, the solubility of oxygen. Oxygen supply is increased by increasing cardiac output, arterial oxygen saturation, or hemoglobin concentration.

The indications for neonatal RBC transfusions differ based upon the rate of fall in hemoglobin (acute versus chronic anemia). The need for transfusion in an infant with acute blood loss is generally dependent upon persistent clinical signs of inadequate oxygen delivery following intravascular volume restoration. In chronic anemia, the need for RBC transfusion is, likewise, based upon clinical signs of inadequate oxygen delivery (increased resting heart rate, acidosis, poor growth, and apnea) in addition to a specific hematocrit (hemoglobin) threshold (also referred to as hematocrit [hemoglobin] trigger) and the degree of respiratory support needed by the infant.

Acute blood loss — Neonates with significant acute blood loss require immediate fluid resuscitation, but may or may not require a RBC transfusion. For example, term infants may tolerate perinatal blood loss up to one-third of their total blood volume. Infants with a hemoglobin level ≥ 10 gm/dL following volume expansion usually have adequate oxygen delivery and generally only require iron supplementation to replace iron losses due to the hemorrhage.

Indications for a RBC transfusion in a term or preterm neonate after volume resuscitation with restoration of the effective circulating volume following an acute blood loss include:

- >20 percent blood loss
- 10 to 20 percent blood with evidence of inadequate oxygen delivery, such as persistent acidosis
- Ongoing hemorrhage

Prior to transfusion, it is critical to determine whether an infant born with a significantly low hematocrit was due to an acute fall near the time of delivery or was due to a chronic in-utero process because this may alter the type of transfusion administered (ie, simple versus exchange). For example, in the twin-twin transfusion syndrome or feto-maternal hemorrhage, the degree and timing of bleeding is variable. Bleeding may occur just before delivery or might have begun in the second trimester and be long-standing at the time of delivery, both of which may result in a hematocrit below 20 percent at birth. In the latter case, a partial exchange transfusion should be considered in an infant in whom an increase in tissue oxygen delivery is necessary, because a simple transfusion may cause a significant increase in blood volume resulting in heart failure because these infants often have elevated circulating blood volumes.

Chronic anemia — All newborn infants have a gradual fall in their hematocrit after birth due to impaired production of erythropoietin, referred to as physiologic anemia. In preterm infants, this decline occurs earlier and is more pronounced in its severity than in term infants. This hyporegenerative anemia associated with low erythropoietin concentrations is referred to as anemia of prematurity. (See "Anemia of prematurity", section on 'Pathogenesis'.)

In addition, infants cared for in the neonatal intensive care unit (NICU) are at risk for developing chronic anemia because of blood loss from phlebotomy. This is especially true for very low birth weight (VLBW) infants (birth weight <1500 g) who are often more severely ill and require frequent blood tests and who have a lower total blood volume than more mature, heavier neonates. In addition, RBCs in preterm infants have a reduced life span compared with full term infants, which contributes to the anemia of prematurity.

Target hemoglobin or hematocrit — Target hemoglobin and hematocrit, values below which a RBC transfusion is needed, have been used universally as clinical indicators for RBC transfusion in neonates, older infants, children, and adults. The clinical approach to transfusions in the newborn with chronic anemia has changed over time. The use of high hematocrit (hemoglobin) triggers (greater than 40 percent), referred to as liberal approach, was standard practice in the 1970s and 1980s. A more restrictive approach emerged in the 1990s and 2000s years, as concerns for the adverse effects of transfusions grew, particularly transmission of infections such as hepatitis B and C, and human immunodeficiency virus. This approach has decreased the transfusion rate in neonates. However, it remains unclear what the minimal target hematocrit or hemoglobin is in neonates that optimally balances the risk and benefits of this intervention.

The more restrictive approach was supported by results from a randomized trial studying the effects of erythropoietin (EPO) in preterm infants with birth weights below 1250, which was published in 1995 [3]. This study developed transfusion guidelines that used hematocrit triggers ranging from 20 percent in asymptomatic infants to 35 percent in infants who required respiratory support, including supplemental oxygen. Excellent short-term outcomes were noted in infants who were transfused based upon this protocol, demonstrating that premature infants were able to tolerate a gradual decline in hematocrit.

Three subsequent trials have been conducted to compare the risks and benefits of different hematocrit triggers in AOP. It is worth reviewing each of these as protocols and outcome measures varied among these trials.

In the first, which was only published in abstract form, 50 extremely low birth weight (ELBW) infants (birth weights below 1000 g) were randomly allocated to either a high hematocrit (hematocrit maintained above 32 percent by administration of EPO and RBC transfusions) or low hematocrit group (hematocrit maintained at or below 30 percent by RBC transfusions alone) [4,5]. The following findings were noted:

- At 36 weeks postmenstrual age (PMA), there were no differences in weight gain during hospitalization, the number of days on a ventilator, and the total number of hospital days between the two groups.
- At one year of age, both weight and head circumference were similar, and there was no difference in the neurodevelopmental outcome, which was assessed by Bayley Mental and Psychomotor Developmental Indices and by Infanib (neurologic screening test for infants between 1 and 18 months of age). In addition, there were no differences in these parameters in the eleven infants who had a hematocrit at or below 22 percent for more than three weeks compared with infants in the high hematocrit group.

The authors concluded that in ELBW infants, treatments aimed at maintaining hematocrit levels above 32 percent incurred additional cost without demonstrable benefit. Moreover, restrictive transfusion policies were not associated with adverse outcome.

In the next two trials, restrictive (low hemoglobin threshold) and liberal (high hemoglobin threshold) protocols were developed based upon hemoglobin thresholds for transfusion that vary with the postnatal age of the patient, the level of respiratory support required by the infant, and blood sampling technique (capillary versus central).

A single center study of 103 preterm infants (birth weight 500 to 1300 g) randomly assigned neonates to either a liberal or restrictive transfusion protocol based upon the degree of respiratory support needed by the infant [6]. The hematocrit triggers for intubated infants, infants receiving nasal continuous airway pressure or supplemental oxygen, and infants without respiratory support for the liberal protocol were 46, 38, and 30 percent, respectively, and for the restricted protocol 34, 28, and 22 percent. The following findings were noted:

- There were no differences in the length of time of ventilator or oxygen support, length of hospitalization, rate of severe retinopathy of prematurity (ROP) or chronic lung disease, or survival between the two groups.

- Infants in the liberal transfusion group had fewer and less severe episodes of apnea than the restricted group.
- At discharge, five infants in the restrictive group (10 percent) and eight infants (16 percent) in the liberal group had evidence of grade 3 to 4 IVH. However, the restrictive group had more infants with grade 4 IVH (four versus zero) and periventricular leukomalacia was demonstrated in four infants in the restricted group, but none in the liberal group.
- Although the infants in the liberal group received more transfusions, there was no difference between the two groups in the number of donors to whom the infants were exposed. There was no difference in the percentage of infants who avoided transfusion between the liberal and restrictive transfusion groups (12 versus 10 percent).

Although, this trial reported a less optimal neurologic outcome in preterm infants managed by a restrictive transfusion policy, it is unclear whether the differences in neurologic outcome between the two groups was more a reflection of antenatal or perinatal events as opposed to a direct influence of targeted hemoglobin. In addition, other concerns regarding this report included the broad range of birth weights of patients (500 to 1300 g) and the timing of subject enrollment, which may have precluded demonstrating abnormal ultrasound findings.

Long term follow-up of 56 infants enrolled in this study revealed lower performance scores on measures of associative verbal fluency, visual memory, and reading in the liberally-transfused group (n=33) compared with the restrictively-transfused group (n=23) [7], bringing into question the benefit of liberal transfusion guidelines. In a separate report, brain magnetic resonance imaging (MRI) performed in 44 of 55 patients (from the original 100 subjects enrolled) who participated in long-term evaluation at an average age of 12 years demonstrated smaller intracranial volume in the liberal versus restricted groups [8]. The total volume in the restricted group did not differ from that of normal control age-matched children who were born full term. However, cerebral white matter was decreased in both preterm groups compared with controls.

A larger multicenter study (PINT) did not find an increased risk of adverse neurological events with restrictive (low hemoglobin threshold) compared with liberal (high hemoglobin threshold) transfusion strategy [9]. In the PINT study, 451 preterm ELBW infants were randomly assigned by 48 hours of birth to either a high (liberal) or low (restrictive) hemoglobin transfusion protocol based upon the age of the patient and their level of respiratory support. For neonates requiring ventilatory support and in the high threshold group, central hemoglobin levels that triggered transfusion varied from a high of 12.2 gm/dL (hematocrit 37 percent) at one to seven days of life (DOL), 10.9 gm/dL (hematocrit 33 percent) at DOL 8 to 14, and 9 gm/dL (hematocrit 27 percent) at DOL 15 or later. For the low threshold group, corresponding triggering hemoglobin levels were 10.4 gm/dL, 9 gm/dL and 7.7 gm/dL (hematocrit of 31, 27, and 23 percent). Triggering hemoglobin levels for either the high or low threshold groups were lower for infants not requiring respiratory support. The following findings were noted:

- There were no differences in the rates of survival, bronchopulmonary dysplasia (BPD), severe ROP, or brain injury between the two groups. In particular, the incidence of brain injury detected by ultrasound was 12.6 percent in the low hemoglobin group versus 16 percent in the high hemoglobin group.
- Fewer infants in the low hemoglobin group compared with those in the high hemoglobin group required transfusions (89 versus 95 percent).
- The mean number of red blood cell donors to which infants were exposed to was significantly lower in the low hemoglobin group (2.1 versus 2.6). In addition, although there was a trend to significance, the mean number of transfusions received by infants in the low and high threshold groups (4.9 versus 5.7) was not significantly different.

In a follow-up study of 430 of the original 451 enrolled, there was no difference in the incidence of death or serious neurologic complications (cerebral palsy, cognitive delay [defined as a mental development index score less than 70], or severe visual or hearing impairment) between the low hemoglobin and high hemoglobin threshold groups at 18 to 21 months' corrected age (45 versus 38 percent). However, a posthoc analysis demonstrated the low hemoglobin group was more likely to have a mental development index score less than 85 [10].

This trial suggested that the threshold for transfusions in preterm infants can be reduced without increasing the risk of death or serious complications to a hemoglobin trigger of 10.4 g/dL in neonates in the first week of life, and to even lower levels in older infants.

In developed countries, the number of transfusions given to neonates has decreased from an average of seven transfusions in the late 1980s down to two transfusions per infant in 2009 during their initial birth hospitalization due to a more restrictive approach to transfusions [11,12]. Despite this decrease, the majority of ELBW infants still require blood transfusions based upon current protocols. For example, in the PINT study, only 11 percent of infants in the low threshold group and 5 percent in the high threshold group received no transfusions. It should be noted that none of the infants in the Iowa study or the PINT study received erythropoietin. For comparison, only 62 percent of preterm infants ≤ 800 grams birth weight enrolled in a randomized trial of erythropoietin, iron, folate, and B12 administration required transfusion, compared with 95 percent of the infants not receiving erythropoietin [13].

Search for other transfusion markers — Although hematocrit and hemoglobin have primarily been the triggers to indicate when transfusion is indicated in neonates, they are not adequate measures. This is illustrated by the observation that some infants remain asymptomatic at a given low hematocrit (hemoglobin), while others are symptomatic (tachycardia, poor weight gain, increased requirement of supplemental oxygen, or increased frequency of apnea or bradycardia) at a similar or higher concentration.

Research efforts have focused on identifying a more accurate indicator for transfusions; however, a reliable and sensitive marker has yet to be identified. Investigations to test a more accurate marker for transfusion have included studies of direct or indirect oxygen delivery (eg, peripheral fractional oxygen extraction and oxygen consumption) [14-16], echocardiographic changes in cardiovascular circulation [17-19], and the use of biochemical markers, such as serum lactate or vascular endothelial growth factor [20,21].

Our approach — Based upon the currently available data, the following transfusion guidelines have been adopted in several NICUs, = including our own (table 1).

- Acute blood loss that is greater than 20 percent of blood volume.
- Acute blood loss that is greater than 10 percent of blood volume with symptoms of decreased oxygen delivery, such as persistent acidosis after volume resuscitation.
- Transfusion should be given to any infant regardless of gestational age if there is an immediate need for increased oxygen delivery that cannot be met with increased respiratory support.
- The following guidelines for infants with chronic anemia suggest that transfusions should be considered based upon the respiratory support need by the infant. They are dependent upon a hematocrit (hemoglobin) value that is preferably measured from either a central venous or arterial sample. If a heelstick specimen is used, it should be obtained after adequate warming of the heel. The final decision for a transfusion is at the discretion of the neonatology team.
- For infants requiring moderate or significant mechanical ventilation, defined as fraction of inspired oxygen (FiO₂) >0.4 , and mean airway pressure (MAP) >8 cm H₂O on a conventional ventilator or MAP >14 on a high frequency ventilator, the hematocrit trigger is <30 percent (hemoglobin ≤ 10 g/dL).
- For infants requiring minimal mechanical ventilation, defined as fraction of inspired oxygen (FiO₂) <0.4 , and mean airway pressure (MAP) ≤ 8 cm H₂O on a conventional ventilator or MAP ≤ 14 on a high frequency ventilator, the hematocrit trigger is <25 percent (hemoglobin ≤ 8 g/dL).
- The hematocrit trigger is <25 percent (hemoglobin ≤ 8 g/dL) for infants requiring supplemental oxygen but not mechanical ventilation and one of or more of the following: tachycardia (heart rate ≥ 180 beats per minute) for ≥ 24 hours, tachypnea (respiratory rate ≥ 60 breaths per minute) for ≥ 24 hours, doubling of oxygen requirement from the previous 48 hours, metabolic acidosis as indicated by a pH 7.20 or serum lactate ≥ 2.5 mEq/L, weight gain <10 g/kg per day over the previous 4 days while receiving ≥ 120 kcal/kg per day, or if the infant undergoes major surgery within 72 hours. For infants requiring oxygen without any symptoms, a transfusion is not considered until symptoms occur.
- In asymptomatic infants, the hematocrit trigger is less than 18 percent (hemoglobin ≤ 6 g/dL) with an absolute reticulocyte $<100,000/\text{microL}$ (<2 percent). Infants without symptoms or oxygen requirements who are actively producing new red cells and have an elevated reticulocyte count likely do not require a red cell transfusion. This last threshold for transfusion is similar to criteria published in 2002 by the Canadian Paediatric Society. In their guideline, criteria for transfusion were for a symptomatic infant with a "hemoglobin falling below 6 gm/dL with an absolute reticulocyte count less than 100,000 to 150,000/microL, which suggests low plasma concentration of erythropoietin [22].

Other centers have transfusion guidelines with higher hematocrit (hemoglobin) triggers, which are based upon similar requirements for respiratory support [23,24].

SELECTION OF RED BLOOD CELL PRODUCTS — Once the decision to transfuse red blood cells (RBCs) has been made, the appropriate RBC product is chosen based upon the clinical setting. Donated whole blood used for transfusion may be modified in several ways that remove varying proportions of non-red cell components. These modifications are particularly important in the neonate because of their increased vulnerability to certain infections, such as cytomegalovirus, potential increased risk of graft versus host disease due to transfusion, and the possibility of alloimmune hemolytic disease of the newborn.

Products for acute blood loss — In the setting of acute blood loss, especially in life-threatening circumstances, any available RBC product that is compatible with the infant's blood type can be administered. If O negative packed RBCs (PRBCs) are available in the delivery room as an emergency transfusion for the mother, this blood also can be used in the neonate. O negative PRBCs are preferred over O negative whole blood, as the latter contains antibodies directed against A or B blood group, and against leukocytes. O negative whole blood should only be used as a last resort in critically ill neonates. In a sick infant cared for in the NICU, PRBCs are an alternative in an emergency situation.

Hemolytic disease of the newborn — Alloimmune hemolytic disease of the newborn (HDN) is a condition in which the red cells of the fetus or newborn are destroyed by maternally derived alloantibodies. These antibodies arise in the mother as the direct result of a blood group incompatibility between the mother and fetus. Infants often require exchange transfusion to remove the maternal alloantibodies, reduce the rate of hemolysis, and prevent significant hyperbilirubinemia. In some cases, a simple transfusion is administered because an exchange transfusion cannot be done in a timely manner. (See "Postnatal diagnosis and management of alloimmune hemolytic disease of the newborn", section on 'Management'.)

The different types of HDN include:

- **Rh(D)** — The most significant setup for HDN occurs in the Rh-positive infant (ie, D antigen positive) of an Rh-negative mother who has become sensitized and has produced Rh(D) antibodies. An infant who needs either simple transfusion or exchange transfusion because of HDN should receive Rh(D)-negative red cells of the appropriate ABO type.
- **ABO incompatibility** — Humans have four major blood groups in the ABO system (A, B, AB, and O) named for the antigen(s) on the red cell. The ABO system may cause HDN, although most cases are less severe than that caused by the Rh system. In infants with HDN due to ABO incompatibility, donor O cells are washed to remove any plasma that contains alloantibodies. These cells may be suspended in plasma that is compatible with both the infant's red cells and the transfused (donor) cells. AB plasma is compatible in all cases, since it does not contain anti-A or anti-B alloantibodies.
- **Other Rh antibodies** — Other antibodies including Rh antibodies in the C and E systems, and Kell antibodies can cause HDN or acute or delayed hemolytic transfusion reaction. In these cases, red cells that are negative for the antigen, against which the antibody is directed, are used.

Packed red cells — Packed RBCs are the blood products of choice for replacement during surgery, red blood cell loss, and sporadic transfusion therapy. The hematocrit of the unit varies depending upon the preservative solution. In the United States, commonly used solutions include CPDA-1 (citrate, phosphate, dextrose, adenine) with a Hct of 65 to 70 percent, and nutrient preparations, such as Adsol™ (AS-1; adenine, glucose, mannitol, and sodium chloride) and Nutricel™ (AS-2; citrate, phosphate, glucose, adenine, and sodium chloride), with a Hct of 50 to 60 percent. RBCs in the nutrient solutions (AS-1 and AS-2) can be used for 42 days after collection and those preserved in CPDA-1 for more than 28 days [25-27]. (See "Use of red blood cells for transfusion".)

Leukoreduced and irradiated red cells — Leukoreduction filters remove approximately 99.9 percent of white blood cells from PRBCs, which reduces febrile non-hemolytic transfusion reactions, prevents alloimmunization, and reduces (but does not completely prevent) the transmission of certain infections (notably CMV). However, leukoreduction does not eliminate all lymphocytes and cannot prevent transfusion-associated-graft-versus-host disease (TA-GVHD).

Irradiation prevents TA-GVHD in susceptible recipients. The dose of radiation is not sufficient to kill viruses and irradiation does not provide a CMV-safe product.

Leukoreduced PRBCs should be used in all neonates. In addition, most blood banks will also irradiate leukoreduced PRBCs prior to neonatal transfusion.

CMV-safe red cells — CMV-safe products (including CMV-seronegative and leukoreduced red cells) reduce the transmission of CMV in seronegative recipients. CMV-seronegative PRBCs should be used in the following populations, although many NICUs use CMV-seronegative PRBCs in all neonates:

- Infants awaiting or undergoing transplantation
- Immunocompromised infants
- Preterm infants of CMV seronegative mothers

Cord blood — Although cord blood has been suggested as a form of "autologous" blood donation, most birthing institutions are not prepared for the collection and storage of neonatal cord blood. Even with a program that collects and processes umbilical cord blood, autologous blood was only available in one-third of neonates that required transfusion [28].

An alternative to cord blood collection that may reduce erythrocyte transfusions is delayed clamping of the umbilical cord, especially in preterm infants. A 30 second delay in clamping promotes a placental blood transfer of 10 to 15 mL/kg [29]. In preterm infants, late compared with early cord clamping is associated with a significantly higher hematocrit four hours after birth, fewer transfusions for anemia or low blood pressure, less likelihood of intraventricular hemorrhage, and no increase in the need for treatment of jaundice. The effect of delayed umbilical cord clamping is discussed in detail separately. (See "Management of normal labor and delivery", section on 'Cord clamping' and "Management of normal labor and delivery", section on 'Cord blood'.)

ADMINISTRATION — The volume of transfusion is dependent upon the desired rise in hematocrit.

The volume of transfusion in mL is equal to the following calculation:

$$\text{Wt (kg)} \times \text{blood volume per kg} \times (\text{Desired Hct} - \text{Observed Hct}) / \text{Hct PRBCs}$$

In the newborn, the blood volume is about 90 cc/kg. Transfusions generally are given as PRBCs, in aliquots of 10 to 20 mL/kg, over two to four hours. In some circumstances, such as hemodynamic instability or hypovolemia due to blood loss, a smaller volume (10 mL/kg) is given more rapidly (over one to two hours).

In ELBW and VLBW infants, the small volumes, which may be as low as 7 mL of blood for a single transfusion, require the use of special equipment to maximize the use of a single unit from a donor. In addition, these systems allow for serial transfusions to an individual neonate from the same donor.

These include the following two systems:

- Small bags may come as part of a transfusion set (referred to as satellite packs) in which four or six aliquots can be made from a single red cell unit. If the blood bank has a sterile connecting device, the small bags can be connected to the large blood unit, and an appropriate amount withdrawn at any time.
- Another convenient device for small-volume transfusions is a syringe set in which the syringe is sterilely connected to the original unit. Blood is drawn through a filter into a syringe, and can be used within four hours without further filtration. Such systems have been shown to be safe [30] and can increase the numbers of transfusions from a single unit.

With both systems, the original expiration date of the unit is maintained if the sampling device remains connected to the original unit in a sterile manner. This period may be up to six weeks for use of a single unit in a nutrient solution such as Adsol™ (AS-1) and Nutricel™ (AS-2). If a single unit is designated for a premature

infant and is used until its expiration date, as many as 13 individual transfusions can be made from a single donor unit, which markedly decreases donor exposure [31].

SUMMARY AND RECOMMENDATION — Anemia occurs when the red blood cell mass does not adequately meet the oxygen demands of the tissue. Neonates may require red blood cell (RBCs) transfusions because of significant anemia due to acute blood loss or chronic anemia due to physiologic anemia and blood loss from phlebotomy. In particular, anemia in preterm infants (referred to as anemia of prematurity) is more severe and presents earlier in life.

- Neonates with significant acute blood loss require immediate fluid resuscitation. Indications for RBC transfusion in a neonate with acute blood loss following volume resuscitation include persistent acidosis indicating inadequate oxygen delivery, ongoing bleeding, and a blood loss greater than 20 percent of the infant's blood volume.
- In the acute setting of blood loss, especially in life-threatening circumstances, any available RBC product that is compatible with the infant's blood type can be administered. O negative packed RBCs (PRBCs) are preferred over O negative whole blood, as the latter contains antibodies directed against A or B blood group, and leukocytes. O negative whole blood should only be used as a last resort in critically ill neonates. (See 'Acute blood loss' above and 'Products for acute blood loss' above.)
- Target hemoglobin and hematocrit have been used universally as clinical indicators for RBC transfusion in neonates due to chronic anemia. Over the past three decades, clinical practice progressed from using high trigger levels (hematocrit of 40 percent referred to as a "liberal" approach) to lower levels (a "restrictive" approach). However, it still remains unclear what target hematocrit or hemoglobin for transfusion in neonates optimally balances the risk and benefits of this intervention. In our practice, we use a restrictive approach for neonatal transfusions that is based upon hematocrit triggers and the respiratory support required by the infant (table 1). (See 'Target hemoglobin or hematocrit' above.)
- Blood products for neonates with hemolytic disease of the newborn (HDN) who require either exchange or simple transfusion need to be compatible with the infant's blood type. (See 'Hemolytic disease of the newborn' above.)
- Leukoreduced PRBCs should be used in all neonatal transfusions because it reduces febrile non-hemolytic transfusion reactions, prevents alloimmunization, and reduces the transmission of certain infections (notably cytomegalovirus [CMV]). Most neonatal intensive care units also use irradiated RBCs, which do not provide a CMV-safe product but prevent transfusion-associated-graft-versus-host disease.
- CMV-seronegative PRBCs are reserved for immunodeficient neonates, those who are awaiting transplantation, and preterm infants of seronegative mothers. (See 'Packed red cells' above.)
- In the neonate, small volumes, which may be as low as 7 mL of blood for a single transfusion in extremely low birth weight infants (birth weight <1000 g), require the use of special equipment that allows several aliquots to be administered from a single unit. (See 'Administration' above.)

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Use of home cardiorespiratory monitors in infants

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INTRODUCTION — Home cardiorespiratory (CR) monitors have been available for approximately 30 years, and were originally intended to prevent sudden infant death syndrome (SIDS) in at-risk infants. Since then, it has become clear that the CR monitor is not an effective tool to prevent SIDS.

Nonetheless, there is some justification for the use of CR monitors in selected infants with other underlying disorders. Selection of infants for monitoring depends upon the infant's underlying problem and the capabilities of the monitor. In many cases, the primary utility of the monitor is diagnostic (ie, to distinguish genuine from false CR events and document the nature and frequency of CR events) rather than therapeutic (ie, to provide an alarm that allows intervention to terminate events).

The appropriate use of CR monitors for specific disorders, the capabilities and limitations of the devices, and the management of infants with CR monitors will be reviewed here. The pathophysiology, evaluation, and other approaches to managing the disorders for which CR monitoring is sometimes considered are discussed separately. (See "Sudden infant death syndrome" and "Apparent life-threatening event in infants" and "Management of apnea of prematurity".)

CONTROVERSY — The use of home CR monitors has become increasingly controversial. In a 1987 NIH Consensus Statement on Infantile Apnea and Home Monitoring, home CR monitoring was recommended for infants thought to be at-risk for sudden infant death syndrome (SIDS). At that time, at-risk infants were thought to include premature infants with episodic apnea or bradycardia, infants who had experienced one or more severe apparent life threatening events (ALTE), and siblings of two or more SIDS victims. However, the authors of the statement were also careful to point out that "the effectiveness of home monitoring in reducing infant mortality and morbidity is not yet established."

Since the publication of this document, advances in the understanding of the pathophysiology of these disorders, outcomes of clinical trials, and clinical experience have substantially narrowed the indications for CR monitor use [1]. One must also consider the high costs of continuous monitoring, which include the device, training and respite of caretakers, and analysis of recorded events. In addition, concerns have been raised that the use of CR monitors might distract from other established preventive measures (eg, safe sleeping environment for prevention of SIDS), have adverse effects on the parents' quality of life, and present difficulties in determining an end point for monitoring.

A major problem in assessing the role of CR monitors to prevent infant death is that clinical efficacy cannot be established. Randomized controlled trials are impractical because death is a rare event in these infants, and because families are unlikely to consent to randomization.

The rationale for or against the use of CR monitoring for specific disorders is discussed below. (See 'Monitoring decisions' below.)

DEVICES AND CAPABILITIES — Standard home cardiorespiratory (CR) devices detect when the heart rate falls below or above a preset range or when there is no chest wall movement for a preset length of time. Most currently used monitors also record waveforms during events (documented monitoring), which can facilitate

diagnosis and decisions about when to stop monitoring. Oxygen saturation measurements can be included on some monitors if specifically requested.

These devices directly measure central apnea by the lack of respiratory effort. They do NOT detect obstructive apnea in the absence of bradycardia.

Thus, the clinical utility of the monitor depends upon the pathophysiology of the underlying disorder. It will be more useful for infants at risk for central apnea or bradycardia (eg, apnea of prematurity) than for disorders in which apnea or bradycardia are late consequences of hypoxemia. If oxygen saturation measurements are included, the device may provide somewhat earlier recognition of events in infants with primary respiratory disease (eg, those with a tracheostomy or neuromuscular disease), provided that caretakers can respond in time to reverse the problem [2].

MONITORING DECISIONS — The decision as to whether or not CR monitoring should be considered in an individual infant varies with the underlying disorder.

Asymptomatic infants with risk factors for sudden infant death syndrome — Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under one year of age that remains unexplained despite a thorough case investigation, including autopsy, examination of the death scene, and review of the clinical history [3]. Although prematurity is one of several risk factors for SIDS, the mechanism and timing of SIDS are distinct from those of apnea of prematurity. (See "Sudden infant death syndrome".)

In the 1970s, it was proposed that prolonged central apnea was an early and, perhaps, primary event in the pathogenesis of SIDS [4]. This "apnea hypothesis" was based on observations of recurrent brief apneic episodes during sleep in several infants, which resolved as the infants matured. Infants with these features were thought to be at risk for SIDS, and CR monitoring was proposed in an effort to prevent death.

Since then, several important advances have indicated that apnea is not an initial event in the pathogenesis of SIDS:

- Several infants have died with home CR monitoring devices in place, and a body of literature has emerged presenting the data from so-called "death tracings" [5-7]. The data obtained from death tracings suggests that bradycardia occurs first and is followed by terminal apnea. It is hypothesized that hypoxia precedes the recorded bradycardia [8,9].
- The American Academy of Pediatrics launched the "Back to Sleep" campaign advocating supine sleeping in 1992 [10]. Since that time, the SIDS rates in the United States have decreased by over 40 percent [11-13].
- Increasing attention has been focused on the issue of child abuse and infanticide masquerading as recurrent apparent life-threatening events (ALTE) or SIDS [14-17]. A widely publicized case of five successive deaths in a family in New York resulted in greater recognition of this entity, especially in families with more than one occurrence among siblings [18].
- Epidemiologic studies and two decades of clinical experience have failed to show an effect of CR monitors in reducing the incidence of SIDS in infants presumed to be at risk [1,19,20].
- Studies using plethysmographic monitors capable of detecting both central and obstructive apnea in infants presumed at risk for SIDS displayed a high frequency of obstructed breathing, which would not be detected by conventional monitoring [21].

Thus, there are currently no data to support the therapeutic use of cardiorespiratory monitoring as a means of reducing the risk for SIDS in asymptomatic infants, regardless of SIDS risk factors that may be present (e.g. prior sibling SIDS death, or prematurity). However, the physiologic parameters recorded by current monitors may have some diagnostic value, by defining the types of physiologic abnormalities occurring in some subgroups of infants, including symptomatic preterm infants, infants with apparent life threatening events, and infants with other underlying disorders, as discussed below.

Preterm infants with persistent symptoms related to apnea of prematurity — Apnea of prematurity is defined as the sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or oxygen

saturation in an infant younger than 37 weeks postmenstrual age [22]. (See "Management of apnea of prematurity".)

Most apneic events are central (ie, cessation of respiratory effort), and the disorder is thought to be caused by immaturity of respiratory control mechanisms. The breathing pattern matures with increasing postmenstrual age. Nonetheless, preterm infants continue to have more episodes of prolonged apnea than infants born at term until about 43 weeks postmenstrual age [21].

Premature infants with persistent apnea of prematurity but who are otherwise ready for hospital discharge are candidates for home cardiorespiratory monitoring [1]. Implementation of monitoring requires counseling and training of the caretakers, follow-up and review of events by a professional, and determination of an end point for monitoring. (See 'Implementation' below.)

Infants with apparent life-threatening events — An apparent life-threatening event (ALTE) is an acute, unexpected change in an infant's breathing behavior that was frightening to the caretaker, and is characterized by some combination of apnea, color change, change in muscle tone, choking, or gagging. Infants experiencing ALTEs represent a heterogeneous group of patients of varying ages with diverse pathophysiology. Although a relationship between ALTEs and SIDS was initially suggested, studies during the past two decades have failed to confirm a causal relationship. (See "Apparent life-threatening event in infants", section on 'Lack of causal relationship between ALTE and SIDS'.)

A specific cause for the ALTE can be identified in over one-half of patients after a careful history, physical examination, and appropriate laboratory evaluation. In most of these cases, the cause will be identified during the hospital evaluation, and home CR monitoring does not have additional diagnostic value. (See "Apparent life-threatening event in infants".)

The decision for home monitor observation should be made on a case-by-case basis, depending upon the presumed cause of the ALTE after a careful investigation, the estimated risk of recurrence, and after considering with the family the potential benefits, uncertainties, and stresses involved. In general, CR monitors would be less helpful for infants with presumed obstructive pathophysiology than for those with central apnea. In some cases, the potential value of the monitor lies in its ability to record physiologic data that may provide reassurance that clinically important events are not occurring.

Other indications — In infants with underlying diseases predisposing to respiratory failure, home CR monitoring may facilitate rapid recognition of central apnea, airway obstruction, respiratory failure, interruption of supplemental oxygen supply, or failure of mechanical respiratory support [1]. Thus, infants with the following conditions are candidates for monitoring:

- Tracheostomy or airway abnormalities (see "Congenital anomalies of the intrathoracic airways and tracheoesophageal fistula")
- Neurologic or metabolic disorders affecting respiratory control
- Chronic lung disease (eg, bronchopulmonary dysplasia), especially those requiring supplemental oxygen, positive airway pressure, or mechanical ventilatory support (see "Management of bronchopulmonary dysplasia")

In some infants, oxygen saturation monitoring alone, or in conjunction with a CR device may provide more useful diagnostic information than a CR monitor alone. None of the currently available home CR monitors reliably detect obstructive apnea [21].

IMPLEMENTATION

Counseling of parents

- Families must be informed of the purpose of the monitor and what it can and cannot do. It is a tool to alert them to check the baby when an alarm is triggered either by the baby's heart rate falling below a preset limit or by the monitor's not detecting chest wall movement for a preset number of seconds.

Parents must know that the monitor cannot guarantee the safety of the infant and that infants have died while being monitored.

- Regardless of the indication for monitoring, caretakers should be counseled regarding SIDS risk reduction, especially with regard to infant sleep position, crib safety factors, avoidance of exposure to tobacco smoke, and the importance of regular medical check-ups.
- Families should be aware of the stresses of monitoring. As an example, some parents feel they cannot leave the infant, and child care can be difficult to find. False alarms can cause unnecessary sleep disruption.
- Families should be told how long to expect the baby to be monitored and what criteria will be used to discontinue monitoring. Factors to consider are:
 - The expected course of the disorder for which the infant is being monitored (eg, apnea of prematurity tends to resolve by 43 weeks postmenstrual age)
 - The risk of SIDS is very low after six months of age
 - The risk of becoming entangled in lead wires is increased after infants are able to roll over and sit up.

Professional support

- Caretakers must be taught how to perform cardiopulmonary resuscitation and other emergency responses to an alarm.
- Caretakers must have access at all times to technical support in case of problems with monitor function, and to professional support to answer questions which may arise regarding the infant's status.
- The recorded monitor data should be downloaded on a monthly basis. This should be reviewed by a professional with expertise in interpreting waveforms who can distinguish between true and false events. Clinical judgment must be used to determine whether recorded apneas or bradycardias are significant [23,24].

Monitor settings — Monitor settings should be appropriate for the infant's age. Incorrect settings can result in frequent false alarms and can fill up the monitor's memory by recording large numbers of "events."

Suggested settings:

- Apnea record — 15 sec
- Apnea alarm — 20 sec
- Tachycardia — 225 bpm
- Bradycardia limits vary by age and should be lowered as the infant grows:
 - Up to 44 weeks postmenstrual age — 80 bpm
 - 44 to 51 weeks postmenstrual age — 70 bpm
 - Over 52 weeks postmenstrual age — 60 bpm

False alarms are very common, and their frequency is determined by factors including the quality of transducer placement, the level of infant activity, and the appropriateness of the alarm threshold settings.

End point of monitoring — The end point of monitoring varies with the indication for monitoring. In general, six to eight weeks of normal downloads and no clinical events is considered sufficient. Parental readiness to discontinue monitoring is also a factor.

- For infants monitored because of apnea of prematurity, monitoring can be discontinued if no true events have been detected on downloads and no important clinical events have occurred in several weeks, and if the infant is older than 43 weeks postmenstrual age [1,21]. Apnea of prematurity may persist longer in infants born very prematurely [25].
- For infants monitored because of underlying respiratory disease or anatomic airway abnormalities, the decision to continue monitoring depends primarily upon the frequency and severity of the events that trigger alarms.

SUMMARY AND RECOMMENDATIONS

- The indications for CR monitor use have changed substantially during the past decade because of advances in the understanding of the pathophysiology of disorders associated with CR events during infancy, outcomes of clinical trials, and clinical experience. (See 'Controversy' above.)
- Standard home CR monitors detect heart rate and chest wall movement; oxygen saturation measurements can be included if specifically requested. The devices directly measure central apnea by the lack of respiratory effort. They do NOT detect obstructive apnea in the absence of bradycardia. (See 'Devices and capabilities' above.)
- Premature infants with persistent apnea of prematurity but who are otherwise ready for hospital discharge are candidates for home CR monitoring. The decision of whether to use a monitor depends on assessment of risks and benefits for the individual infant. Monitoring can generally be discontinued by 43 weeks postmenstrual age. (See 'Preterm infants with persistent symptoms related to apnea of prematurity' above and 'End point of monitoring' above.)
- Central apnea is not usually an initial event in the pathogenesis of sudden infant death syndrome (SIDS). There is no evidence that SIDS can be prevented by CR monitoring of asymptomatic infants, whether or not SIDS risk factors are present (e.g. prior sibling SIDS death, or prematurity). (See 'Asymptomatic infants with risk factors for sudden infant death syndrome' above.)
- Home CR monitoring may facilitate rapid recognition of an acute respiratory problem in infants with underlying diseases including tracheostomy or airway abnormalities, neurologic or metabolic disorders affecting respiratory control, or chronic lung disease. For many of these infants, inclusion of oxygen saturation measurements with the CR device may allow for earlier recognition of events. (See 'Other indications' above.)
- If CR monitoring is recommended, implementation requires counseling and training of the caretakers, professional oversight to analyze recordings and clinical events and determine an appropriate end point for monitoring. (See 'Implementation' above.)

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Apparent life-threatening event in infants

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INTRODUCTION — An apparent life-threatening event (ALTE) is not a specific diagnosis but a description of an acute, unexpected change in an infant's breathing behavior that is frightening to the caretaker and that includes some combination of the following features [1]:

- Apnea — usually no respiratory effort (central) or sometimes effort with difficulty (obstructive)
- Color change — usually cyanotic or pallid but occasionally erythematous or plethoric
- Marked change in muscle tone (usually limpness or rarely rigidity)
- Choking or gagging

In some cases, the observer fears that the infant has died. Recovery occurs only after stimulation or resuscitation. However, episodes are often mislabeled as "ALTEs" even when a parent reports that the child resumed normal breathing after simply being picked up and patted.

After early anecdotal reports of deaths from sudden infant death syndrome (SIDS) in infants with recurrent apnea [2], enormous amounts of attention, research, and clinical resources were focused on the problem of ALTE in infants. Although various cardiorespiratory, autonomic, and neurophysiologic differences have been demonstrated in ALTE infants as a group, these findings have NOT distinguished individual ALTE infants from normal controls nor provided premortem markers for the risk of SIDS [3]. ALTE infants represent a heterogeneous group of patients of varying ages with diverse pathophysiology. As a result, appropriate evaluation and management should be individualized. (See "Sudden infant death syndrome".)

DEFINITION AND EPIDEMIOLOGY — It is important to recognize that ALTE is not a specific diagnosis; rather, it describes a "chief complaint" that brings an infant to medical attention. The term ALTE was coined by the 1986 National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring. ALTE replaced misleading terms, such as "near-miss SIDS" or "aborted crib deaths", that implied a direct association between these symptoms and SIDS [1]. The potential for over-diagnosis is substantial, since the case definition depends upon the observations of frightened, medically untrained caretakers [4]. The incidence of ALTEs is estimated to be 0.05 to 1 percent in population-based studies [5-8].

Lack of causal relationship between ALTE and SIDS — An association between SIDS and ALTE had been suggested because of prior ALTE events in 5 percent of SIDS victims [9] and early anecdotal reports of SIDS in infants with recurrent apnea [2]. However, the vast majority of SIDS victims do not experience apnea prior to death. Furthermore, studies over the past two decades have failed to confirm a causal relationship between preexisting apnea and SIDS. Several other factors argue against a relationship between SIDS and ALTE:

- ALTE refers to a heterogeneous group of problems ranging from benign to near-fatal, whereas SIDS denotes a fatal problem.
- The case definition in ALTE depends upon parental observations, which have been shown to be unreliable in several studies [4,10-14].
- Over 80 percent of SIDS deaths occur between midnight and 6 AM [15], whereas 82 percent of ALTE episodes occur between 8 AM and 8 PM [16].
- Interventions to prevent SIDS (eg, supine sleeping) have not resulted in a decreased incidence of ALTE [17]
- The risk factors for SIDS and ALTE differ [18,19]. In one prospective population-based study, prone sleeping, lack of breast feeding, and maternal smoking were risks for SIDS, whereas behavioral

characteristics (eg, repeated apnea, pallor, history of cyanosis, and feeding difficulties) were risk factors for ALTE [17].

ETIOLOGY — A specific cause for the ALTE can be identified in over one-half of patients after a careful history, physical examination, and appropriate laboratory evaluation (table 1) [20]. Gastroesophageal reflux, neurologic problems (such as seizures or breath-holding spells), and infection account for the greatest number of ALTE-type episodes [21].

- Gastroesophageal reflux is frequently invoked to describe feeding-associated events, and is diagnosed in approximately 30 percent of infants presenting with an ALTE. However, there is little evidence that this represents pathologic reflux or that the events can be prevented by treatment for reflux, as discussed below. (See 'ALTE and gastroesophageal reflux' below.)
- A central nervous system disorder (most presenting as seizures, but ventricular hemorrhage or hydrocephalus were found in some) was ultimately diagnosed in 15 to 20 percent of infants with an ALTE presentation (data from two case series) [22,23].
- Less frequent causes are cardiac disease, upper airway obstruction, metabolic disorders, anaphylaxis, and other miscellaneous conditions.
- Accidental or intentional poisoning may be responsible for a small number of ALTE in some populations. In one institution, toxicology screens were performed in nearly half of the infants evaluated for ALTE. Of 274 results, 8 percent revealed clinically significant ingestions. Five percent of the infants screened positive for over-the-counter cold medications, although none of the parents admitted to administering these [24]. However, the extent to which the ingestion may have contributed to the ALTE is uncertain.
- The remaining cases are considered idiopathic if no cause can be identified after a thorough assessment.

ALTE and gastroesophageal reflux — Recurrent vomiting or regurgitation occurs commonly in patients with apparent life-threatening events (ALTE), but also in healthy infants. An association between reflux and apnea or bradycardia has not been demonstrated convincingly [25-27]. As a result, the role of reflux in infants with ALTEs is uncertain. Even when an episode of gastroesophageal reflux appears to have immediately preceded the ALTE, the direct cause of the respiratory event is probably laryngospasm. The reflux may have triggered the laryngospasm, but this does not mean that it is pathologic or that treatment of reflux will prevent future ALTEs [28,29]. Laryngospasm also may occur during feeding in the absence of gastroesophageal reflux.

Esophageal pH monitoring may be useful in the evaluation but only if an apparent event occurs while monitoring and can be temporally associated with a preceding episode of reflux by using simultaneous polysomnography or continuous oxygen saturation monitoring. Barium esophagrams are neither sensitive nor specific for detecting pathologic gastroesophageal reflux in infants. (See "Gastroesophageal reflux in infants", section on 'Diagnostic tests'.)

ALTE is more likely to be related to reflux, and the infant is therefore more likely to respond to antireflux therapy when:

- Gross emesis or oral regurgitation occurs at the time of the ALTE.
- Episodes occur while the infant is awake and supine.
- ALTE is characterized by obstructive apnea.

In infants with these characteristics, low-risk medical interventions (eg, thickening of feeds, trial of a milk-free diet, acid suppression, and possibly prokinetic agents) may be used, but these interventions should not replace or delay an evaluation for other causes of ALTE [29]. Because a causal association between reflux and ALTE rarely is established with certainty, and because the overall risk for death in these infants is low, invasive approaches such as antireflux surgery are rarely appropriate for this type of patient. (See "Gastroesophageal reflux in infants", section on 'Treatment options'.)

Feeding difficulties may be associated with ALTE even in the absence of gastroesophageal reflux. In a study of infants evaluated for ALTE in Austria, feeding difficulties were associated with a more than two-fold increase in ALTE events (multivariate relative risk 2.5, 95% CI 1.3-4.6) [17].

ALTE and child abuse — When an infant suffers recurrent, severe ALTE events requiring cardiopulmonary resuscitation (CPR) that occur only in the presence of a single caretaker, and a thorough diagnostic evaluation reveals no reasonable explanation for these dramatic repetitive events, then the diagnosis of intentional suffocation (Munchausen syndrome by proxy, a form of child abuse) must be considered.

In these cases, the deceptive parent (usually the mother) appears to be a dedicated caretaker [30-34]. This parent often has a health care employment background and a personal history of unusual illnesses. Extraordinary illnesses or SIDS may have occurred in previous siblings. A large case series of patients diagnosed with covert video surveillance provides a shocking chronicle of historical markers and clinical observations in infants who suffer life-threatening child abuse from intentional suffocation [34]. (See "Munchausen syndrome by proxy (medical child abuse)".)

Abusive head injury is another form of child abuse that must be considered in infants with ALTE. In a prospective series of 243 infants (<12 months) admitted to a tertiary care medical center for evaluation of ALTE, six (2.5 percent) were diagnosed with abusive head injuries, two of whom died in the hospital [35].

The presence of physical findings such as facial injury or bruising or a bulging anterior fontanel should prompt a thorough evaluation for abusive head injury. In a series of infants evaluated at a single center for ALTE, other factors that suggest abusive head injury include recurrent episodes of ALTE, vomiting or unexplained irritability, and a call by the caretaker to Emergency Medical Services (911) [36]. If abusive head injury is suspected, further investigation should include neuroimaging and dilated funduscopic examination. (See "Epidemiology, mechanisms, and types of abusive head trauma in infants and children".)

Retinal hemorrhages are associated with ALTE from abusive head trauma, but not other causes of ALTE. For example, an observational study of 108 children two years of age and younger admitted for an ALTE found that none had retinal hemorrhages on indirect ophthalmoscopy performed by an ophthalmologist [37].

DIAGNOSTIC EVALUATION — The diagnostic evaluation of the infant who presents with ALTE includes a thorough history and examination with additional testing directed by the findings of the initial clinical assessment. In a series of infants admitted to a tertiary center with ALTE, the diagnosis was made on the basis of the history and physical examination alone in 21 percent of cases, and confirmed with testing prompted by the history and physical examination in an additional 49 percent [38]. Furthermore, 18 percent of the tests ordered were positive, and only 6 percent contributed to the diagnosis.

If the detailed description of the event suggests that the child was physiologically compromised, then in-hospital observation with cardiorespiratory monitoring is indicated.

History — The most important diagnostic tool is a detailed description of the event and intervention obtained from the caretaker who witnessed the episode and any emergency personnel involved in the case. The key elements in the history are summarized in the table (table 2). With this information, the physician can determine whether the episode was truly life-threatening or merely frightening, a key factor in subsequent management decisions.

In addition, the history should include information about the pregnancy and perinatal period, the infant's usual behavior, sleep and feeding habits, a family history (including a history of siblings with ALTE, early deaths, genetic, metabolic, cardiac, and neurologic problems), a social history (including the presence of smoking, alcohol or substance use in the home, and a list of medications in the home) [14]. The family should be asked specifically about the possibility of accidental or intentional administration of poisons or medications, including over-the-counter cold preparations [24]. Such information may help in defining an etiology for the event (eg, heritable metabolic disease, unintentional or intentional ingestion).

Specific characteristics of the history that might suggest an association with gastroesophageal reflux are discussed separately. (See 'Management' below and 'ALTE and gastroesophageal reflux' above.)

A history of previous episodes of ALTE should particularly prompt consideration of abusive head trauma. (See 'ALTE and child abuse' above.)

Examination — Infants presenting with an ALTE should undergo careful physical examination, with particular attention to abnormalities in the neurologic, respiratory, and cardiac systems [39]. The examination should include:

- Measurement of height, weight, and head circumference and comparison of these values to standards for age and sex
- Measurement of vital signs
- Examination for physical signs of trauma (bruising, bulging anterior fontanel)
- Developmental assessment
- Evaluation for upper airway obstruction, including assessment of facial dysmorphism [40,41]

A dilated funduscopic examination should be considered [35,42], particularly if abusive head trauma is suspected. (See 'ALTE and child abuse' above.)

Initial evaluation — If the history and physical examination suggest that the event was not life-threatening, or if a probable explanation for the event is identified (eg, transient laryngospasm after an episode of gastroesophageal reflux), then no laboratory evaluation may be required. In some cases, a limited evaluation is performed to confirm the suspected diagnosis.

When the event is judged to be truly life-threatening and an explanation for the ALTE is not apparent based on the history and physical examination, the initial laboratory evaluation usually (but not necessarily) includes a complete blood count, urinalysis, plasma concentrations of glucose, electrolytes, blood urea nitrogen (BUN), calcium, magnesium, chest radiograph, and electrocardiogram. In addition, particularly if the infant has a change in sensorium, a toxicology screen to detect accidental or intentional ingestions of poisons or medications, including over-the-counter cold preparations, may be of value [24].

Additional evaluation — Further specific diagnostic studies may be indicated in selected cases (table 3). The additional evaluation depends upon the presenting symptoms and findings in the history, examination, and initial evaluation [39,43,44].

In the consecutive series of 243 infants with ALTE described above [38], among 171 infants in whom a particular diagnosis was suggested by the history and examination, the following tests contributed to establishing the diagnosis:

- Blood counts, chemistries, and cultures
- CSF fluid analysis and cultures
- Metabolic screening
- Screening for respiratory pathogens
- Screening for gastroesophageal reflux
- Chest radiograph
- Brain neuroimaging
- Skeletal survey
- Electroencephalogram
- Echocardiogram
- Polysomnography

Among the 72 infants in whom the history and examination were noncontributory, only the following tests contributed to establishing the diagnosis [38]:

- White blood cell count
- Screening for gastroesophageal reflux
- Urine analysis and culture
- Brain neuroimaging
- Chest radiograph
- Polysomnography

Consultation with a specialist in infant apnea and developmental aspects of respiratory control can be useful. Polysomnography may be helpful in the evaluation of on-going respiratory, cardiac, and neurologic dysfunction during sleep. Some authors believe that it can contribute to the prediction of subsequent ALTE [45,46], but it cannot predict the risk for future ALTE episodes or SIDS [47].

Multi-channel polysomnography typically includes [39]:

- An EEG to evaluate the sleep-wake state of the infant
- Measurement of thoracic and abdominal wall movement to evaluate breathing patterns and apnea characteristics (if present)
- Electrocardiogram sensors to evaluate heart rate
- Oximetry to measure oxygen saturation during sleep and after apnea
- Airflow changes (using thermistors that sense alterations in heat exchange or an end-tidal CO₂ monitor)
- Esophageal pH monitoring can be added when a temporal relationship between gastroesophageal reflux and apnea is strongly suspected

Multichannel polysomnograms are to be distinguished from two-channel "pneumograms", which should not be used in the evaluation of ALTE. "Pneumograms" provide continuous 12 to 24 hour recordings of chest movement and heart rate but provide no data on oxygenation or airway obstruction.

For infants with a history of recurrent difficulties while feeding (eg, observations of choking or repeated ALTEs) a videofluoroscopic swallowing study may be useful to evaluate for swallowing dysfunction.

MANAGEMENT — The history of ALTE must be taken seriously, even if the infant appears entirely well by the time he or she is evaluated. The apparent well-being should not be considered evidence that a potentially life-threatening event with successful resuscitation did not occur if the clinical history indicates otherwise.

In-hospital observation with cardiorespiratory monitoring is indicated for infants whose initial evaluation (whether by history, examination, or other diagnostic studies) suggests physiologic compromise. A brief period of in-hospital observation and monitoring immediately after an ALTE may provide important clinical information:

- Additional episodes may be witnessed by medical personnel. In one case series, the occurrence of documented in-hospital events during the initial investigation period increased the likelihood of additional events at home, especially in the first month after the initial event [14].
- Serious, underlying medical conditions (eg, hypoventilation or hypoxemia) may become apparent [43,44,48]. Documentation of apnea or bradycardia in association with clinical findings of inadequate respiratory effort, color change, or loss of tone will confirm the need for more specialized diagnostic studies (eg, extended Holter monitoring, esophageal pH monitoring, epilepsy monitoring, polysomnography, computed tomography or magnetic resonance imaging of the central nervous system, metabolic studies, or more invasive studies such as bronchoscopy).

Medical or surgical treatment of an underlying disorder is possible in about 50 percent of ALTE cases if additional studies identify a specific cause of the ALTE [16,49]. Management of the remaining 50 percent of cases depends upon the clinical history and the identification of infants at potentially high risk for adverse events.

Risk factors for recurrence — Multiple studies have reported a high frequency of subsequent apnea in infants with idiopathic ALTE episodes. The clinical significance of these subsequent "alarm conditions" is questionable because of the high incidence (>90 percent) of false apnea alarms on home monitors and the unreliability of parental observations [4,10-14]. As an example, 90 percent of parents report repeated alarms, but only 10 percent of children with an ALTE history have additional events that are considered clinically significant [16].

Risk factors for clinically significant recurrences include immaturity, a history of multiple ALTE preceding the hospital admission, and a viral respiratory tract infection, as illustrated by the following studies:

- A study of 59 infants presenting to an emergency department with an ALTE sought to identify characteristics that predicted recurrence and, therefore, required hospital admission [50]. Eight of these infants subsequently had serious events that required inpatient management (including apnea, infection, or seizures). All eight infants were either younger than one month of age or had a history of multiple ALTE during the 24 hours prior to admission. Although this study is small and lacks external validation, it suggests these may be useful characteristics for identifying infants at high risk.
- In another study of 625 infants admitted because of an ALTE, 7.4 percent had recurrence with an extreme event (defined as central apnea lasting more than 30 seconds, or extreme bradycardia or oxygen desaturation <80 percent lasting more than 10 seconds) [51,52]. In most cases, the event occurred within 24 hours of the hospital admission. The main risk factors for recurrence with an extreme event were viral respiratory tract infection, postconceptional age under 43 weeks, or history of prematurity (even if postconceptional age >43 weeks).

General recommendations — The caregivers of infants who have had an ALTE should receive training in standard cardiopulmonary resuscitation (CPR) for infants [39]. They should also be instructed in safe infant care practices including supine sleep position with face free, safe sleeping environments (avoiding adult or loose bedding, excessive clothing, extreme room temperatures), and elimination of prenatal and postnatal exposure to tobacco smoke [39]

Home monitoring — The diverse characteristics of infants with a history of ALTE preclude universal policies regarding the use of home CR monitoring [53]. The decision should be made on a case-by-case basis after considering with the family the potential benefits, uncertainties, and stresses involved.

Studies of infants with a history of ALTE but who are otherwise asymptomatic have failed to demonstrate a therapeutic benefit of home CR monitoring. However, in selected cases, monitor recordings may provide some diagnostic value, or may provide reassurance that clinically important events are not occurring. Providers and families should recognize that currently available home monitors only detect chest wall movement and heart rate. For some infants, particularly those in whom obstructive apnea is suspected, monitoring oxygen saturation by pulse oximetry may be a more appropriate physiologic signal to monitor. These issues are discussed in more detail in a separate topic review. (See "Use of home cardiorespiratory monitors in infants".)

PROGNOSIS — ALTEs that occur in infants with a history of prematurity usually represent an immaturity of respiratory control and generally resolve with maturation. In a longitudinal cohort study of 1079 infants, cardiorespiratory events recorded on home monitors were compared in healthy term infants, term infants with idiopathic ALTE, preterm infants with idiopathic ALTE, term siblings of SIDS victims, preterm siblings of SIDS victims, symptomatic preterm infants, and asymptomatic preterm infants [52]. Conventional alarm events were common among all groups, but only preterm infants were at increased risk of extreme alarm events, and these events disappeared once those infants reached 43 weeks postconceptional age. (See 'Risk factors for recurrence' above.)

Death — The overall risk of subsequent death in ALTE infants is estimated to be less than 1 percent [3], but the heterogeneity of the underlying conditions that present as apparent life threatening events limits the clinical usefulness of this estimate. Certain patient groups within the ALTE population are believed to have a greater mortality risk. Infants with recurrent ALTE requiring CPR have a very high risk of subsequent SIDS, ranging from 10 to 30 percent [54,55]. Unusual diagnoses, including metabolic diseases, neurodegenerative problems, or intentional suffocation, should be considered.

Long-term follow-up — The overall long-term outcome for "uncomplicated" ALTE infants is excellent. Controlled follow-up studies have reported a slight increase in subtle neurologic abnormalities at one to three years and an increased frequency of breath-holding spells; however, no differences were observed at 10 years [16,56,57].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These

articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics: (See "Patient information: Sudden infant death syndrome (SIDS)".)

SUMMARY AND RECOMMENDATIONS

- An apparent life-threatening event (ALTE) is not a specific diagnosis, but a description of abrupt changes in an infant's breathing, color, and state that are frightening to the caregiver. (See 'Definition and epidemiology' above.)
- Medical efforts should be focused on diagnosis of specific medical conditions for which specific treatments can be identified (table 1). Single events may never be adequately categorized. (See 'Etiology' above.)
- When ALTEs are recurrent and not explained by maturational delay (as in persistent apnea of prematurity), then an aggressive diagnostic approach, as outlined above, is required. (See 'Diagnostic evaluation' above.)

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Pathogenesis, clinical presentation, and diagnosis of apnea of prematurity

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INTRODUCTION — Apnea of prematurity is a developmental disorder in premature infants, which occurs as a direct consequence of immature respiratory control. Apnea of prematurity is most widely defined as cessation of breathing for more than 20 seconds or shorter events accompanied by oxygen desaturation and/or bradycardia [1]. The frequency and severity of symptoms is inversely proportional to gestational age, and almost all extremely low birth weight infants (birth weight below 1000 g) are affected.

The pathogenesis, clinical presentation, and diagnosis of apnea of prematurity are reviewed here. The management of apnea of prematurity is discussed separately. (See "Management of apnea of prematurity".)

DEFINITION

Apnea — Apnea is defined as the cessation of respiratory airflow. Short breathing pauses (5 to 10 seconds) occur frequently in premature infants and are normal. Apnea of prematurity is most widely defined when the respiratory pause is prolonged (20 seconds or greater). However, clinically significant apnea also includes shorter periods of apnea that is associated with cyanosis, oxygen desaturation, and/or bradycardia [1].

Apnea is classified as central, obstructive, or mixed, depending upon the presence of continued inspiratory efforts and upper airway obstruction.

- Central apnea — Inspiratory efforts are absent.
- Obstructive apnea — Inspiratory efforts persist, and airway obstruction is present.
- Mixed apnea — Airway obstruction with inspiratory efforts precedes or follows central apnea.

Most apnea spells in premature infants are central or mixed. This was illustrated in a study of physiologic recordings of 2082 apneic episodes in 47 infants: 40 percent of episodes were central, 50 percent were mixed, and 11 percent were obstructive [2].

Periodic breathing — Periodic breathing episodes are characterized by a pattern of alternating breaths and brief respiratory pauses. Although descriptions of periodic breathing vary, one commonly used definition is the repeated occurrence of three or more respiratory pauses longer than three seconds duration with less than 20 seconds of breathing between pauses. Period breathing is more common in preterm infants, and most apnea episodes occur in association with periodic breathing.

Irregular breathing is commonly associated with rapid eye movement (REM) sleep but is not directly associated with either periodic breathing or apnea of prematurity.

INCIDENCE — The incidence of apnea increases with decreasing gestational age.

- In one study, the overall incidence of apnea was 1 percent of all live born infants over a six-year period at a single institution [3]. Apnea increased from less than 0.1 percent in term infants to 7, 14, and 50 percent in infants born at 34 to 35 weeks gestation, 32 to 33 weeks, and 30 to 31 weeks, respectively. In term infants, the cause of apnea was almost always pathologic and included infection, aspiration, severe birth asphyxia, intracranial hemorrhage, seizures, drug depression, and micrognathia with obstruction of the airway.
- In a multicenter study the diagnosis of apnea based on notation of an apneic and/or bradycardiac event was made in about 50 percent of infants born between 33 and 34 6/7 weeks [4]. There was a wide range in the rate of apnea among the neonatal intensive care units as the criteria for apnea varied. Persistent apnea was associated with longer hospitalization.
- Apnea occurs virtually in all infants born at less than 28 weeks gestation based on review of cardiorespiratory recordings from pneumography, and cardiac and pulse oximetry monitoring [5,6]. However, infants born at 24 to 28 weeks gestation continued to exhibit apnea beyond 38 weeks post conception, which prolonged their hospitalization [5].

PATHOGENESIS — Rhythmic control of breathing requires proper and coordinated functioning of three major components:

- Central respiratory drive, which initiates inspiratory effort
- Maintenance of airway patency
- Adequate function and coordination of the respiratory muscles

Respiratory control mechanisms respond to changes in arterial PCO₂, PO₂, and pH via input from neural and chemical receptors. The respiratory center in the brain integrates input from these receptors and transmits neuronal signals via afferent pathways to the respiratory muscles, which maintain airway patency and drive the thoracic bellows to determine the level of ventilation. Although the exact mechanisms underlying apnea of prematurity are unknown, it is thought to be caused by impaired respiratory effort due to immaturity of one or more of the above components of respiratory control. (See "Control of ventilation".)

Central respiratory drive — Central control of breathing responds to input from the neural and chemical receptors that reflect arterial PCO₂, PO₂, and pH levels by changes in neuronal drive to the respiratory muscles. An intact system results in rhythmic breathing, but, in the preterm infant, immaturity appears to cause a faulty or incomplete central response to hypoxia and hypercapnia leading to apnea or periodic breathing [7,8].

Gestational age — Immaturity is the most important factor that influences rhythmic respiratory control in newborns. The irregular respiratory pattern of premature infants becomes more regular as gestational age

increases. Irregularity of breathing, which is commonly associated with REM sleep, is distinct from periodic breathing. (See 'Periodic breathing' above.)

As noted above, apnea occurs in 7 percent of infants born at 34 to 35 weeks gestation, 14 percent at 32 to 33 weeks, 50 percent at 30 to 31 weeks, and in virtually all infants born at less than 28 weeks gestation [3,5,6]. Infants born between 24 and 26 weeks gestation continued to exhibit apnea beyond 38 weeks post conception, which prolongs their hospitalization [5].

Immaturity appears to impair both rhythmic central respiratory drive and ventilatory response to hypercapnia and hypoxia.

- **Hypercapnia** – Preterm infants have a blunted ventilatory response to inhaled carbon dioxide, which increases with decreasing gestational age [9,10]. In addition, the response to carbon dioxide is lower in preterm infants with apnea compared with controls matched by gestational age, birth weight, and postnatal age [11]. There appear to be no differences in pulmonary mechanics, which suggests that the observed difference is due to variations in central respiratory drive.
- **Hypoxia** – Premature infants have a biphasic response to hypoxia with an initial increase (hyperventilation) and subsequent decrease in inspiratory efforts (hypoventilation and sometimes apnea) [12]. This biphasic response to hypoxia can persist up to 38 weeks postmenstrual age and may contribute to the persistence of apnea in some infants [13]. Although adults may also exhibit a decrease in inspiratory effort after long periods of hypoxia, the degree of respiratory depression is not as severe.

Premature infants are more likely to have apnea when the environmental temperature fluctuates than when it is stable, especially during episodes of hyperthermia or rewarming. In one study, for example, approximately 90 percent of apneic episodes occurred during fluctuations in the thermal environment [14].

Upper airway dysfunction — Patency of the upper airway is essential to the flow of respiratory gases between the environment and the alveolar-capillary interface. The neuromuscular function and reflexes that protect the upper airway develop at different rates during gestation and may be depressed by illness (eg, RSV infection, sepsis) or drugs, such as sedatives or barbiturates [15]. Preterm infants are at-risk for obstructive apnea because they have poor pharyngeal muscle tone, which can lead to hypopharyngeal collapse, and nasal tracheal intubation and the use of nasal catheters and prongs may produce swelling and subsequent nasal obstruction. In addition, there may be poor coordination between the diaphragm and airway dilating muscles in preterm infants, which may predispose to upper airway obstruction [16].

Nasal obstruction — Newborn infants depend upon a patent nasal airway for adequate ventilation because the majority of neonates are obligate nose breathers [17]. Although approximately 30 percent of term infants breathe through both their nose and mouth during sleep, oronasal breathing is uncommon in preterm infants [18]. In addition, most preterm infants younger than 35 or 36 weeks postmenstrual age do not switch to oral breathing during nasal occlusion. In these infants, apnea may be precipitated by intermittent nasal obstruction from swelling that may occur in association with suctioning, following nasotracheal intubation or during nasal CPAP, or with prolonged use of nasogastric tubes.

Hypopharyngeal obstruction — Resting tone and active contraction of the hypopharyngeal muscles are needed to maintain airway patency during breathing (figure 1) [19]. The hypopharynx is a frequent site of upper airway obstruction in premature infants because pharyngeal muscle tone is poor, especially during REM sleep, and phasic activity may be reduced. The infant's airway is especially susceptible to collapse when the neck is flexed [20].

The larynx and trachea are less common sites of airway obstruction because these rigid structures are less likely to collapse than the hypopharynx. Nevertheless, mild obstruction caused by laryngeal edema, vocal cord dysfunction, tracheal stenosis or laryngeal and/or tracheal malacia can precipitate apnea in some cases.

Airway protective reflexes — Upper airway protective reflexes (also referred to as laryngeal chemoreflex) may contribute to the pathogenesis of apnea, although the mechanism is poorly understood. This reflex appears to be mediated through irritant receptors in the larynx, and its response changes from apnea to coughing and swallowing, with maturation. This is illustrated in newborn animal models, in which instillation into the airway

of water or milk from a different species results in decreased ventilation or apnea [21]. Viral infections with respiratory syncytial virus may enhance the apneic response.

In addition, the characteristics of spontaneous prolonged apnea spells in premature infants (ie, central apnea, swallowing and obstructed inspiratory efforts) are similar to those seen with upper airway protective reflexes, which suggest that endogenous secretory stimuli may be a contributor to apnea of prematurity [22]. Prolonged hypopharyngeal suctioning or aspiration of small volumes of milk also may induce these findings. However, no temporal relationship has been demonstrated between apnea of prematurity and gastroesophageal reflux. (See "Gastroesophageal reflux in premature infants".)

Respiratory muscles and chest wall — Immaturity is associated with impaired coordination of the inspiratory muscles (the diaphragm and intercostal muscles) that results in ineffective ventilation. Diaphragm function may be impaired in premature infants because of diminished muscle mass, contractile strength, or because of the mechanical disadvantage of the supine posture. The instability of the rib cage in REM sleep also reduces the efficiency of the diaphragm in expanding the lungs.

A highly compliant chest wall also may contribute to the development of apnea. Chest wall compliance is increased in premature infants because the ribs are thin and poorly mineralized. As a result, the resting lung volume determined by the opposing recoils of the lungs and chest wall is low, potentially leading to inadequate tidal volume, uneven distribution of ventilation during breathing, and diminished oxygen reserves.

Genetics — There may be a genetic component to apnea of prematurity as illustrated by a concordance rate of apnea of 87 percent among monozygotic twin pairs versus 62 percent for same gender dizygotic twins [23].

CLINICAL PRESENTATION — Apnea typically becomes evident in the first two to three days of life after birth in premature infants who are breathing spontaneously without respiratory support. In infants treated with continuous positive airway pressure (CPAP) or mechanical ventilation, apnea may not be apparent until assisted ventilation is no longer required. Breathing pauses usually are accompanied by bradycardia and hypoxemia noted by pulse oximetry or, less commonly, clinical cyanosis.

Apnea that begins after the first week in infants not previously on respiratory support or that recurs after one to two weeks without apnea spells often is associated with a serious underlying condition, such as sepsis [6]. When it occurs, infants require a thorough evaluation for precipitating causes. (See 'Evaluation' below and "Clinical features and diagnosis of necrotizing enterocolitis in newborns".)

Apnea typically resolves before 37 postmenstrual weeks in infants delivered after 28 weeks gestation. However, in infants born before 28 weeks, apnea frequently persists after term postmenstrual age [5,6,24]. In a large study of cardiorespiratory events recorded on home monitors, 443 preterm infants 34 weeks or less were monitored during the first six months of life following hospital discharge [25]. Beyond 43 weeks postmenstrual age, extreme events were rare and occurred no more frequently in the preterm group than in healthy term infants

DIAGNOSIS — Although apnea of prematurity is the most common cause of apnea in preterm infants, it is a diagnosis of exclusion. Other causes of apnea need to be considered and eliminated before the diagnosis of apnea of prematurity is made.

Monitoring — All infants less than 35 weeks gestation should be monitored for apnea for at least the first week after birth because of the high prevalence of this disorder. We usually rely on cardio-respiratory monitors and/or pulse oximeters to detect the associated bradycardia and hypoxemia. In most neonatal intensive care units, cardio-respiratory monitors also measure impedance, which assess respiratory effort by detecting thoracic movement.

Differential diagnosis — The following conditions are associated with the development of apnea in susceptible infants:

- Hypoxemia
- Infection

- Metabolic disorders
- Unstable thermal environment
- Antepartum administration of magnesium sulfate or opiates to the mother
- Administration of opiates or general anesthesia to the infant
- Neurologic disorders including intracranial hemorrhage and neonatal encephalopathy [26]
- Necrotizing enterocolitis
- Congenital anomalies of the upper airway

Evaluation — The goal of the diagnostic evaluation is to identify any of the above conditions that are amenable to treatment, which would result in both resolution of the underlying condition and associated apnea.

The diagnostic evaluation includes the following:

- Maternal and neonatal history
 - Maternal administration of magnesium sulfate or opioids
 - Neonatal administration of opioid therapy
 - Risk factors for neonatal sepsis
 - Traumatic delivery and/or perinatal asphyxia (See "Systemic effects of perinatal asphyxia", section on 'Risk factors' and "Clinical features, diagnosis, and treatment of neonatal encephalopathy", section on 'Diagnosis of neonatal asphyxia'.)
 - Infant of a diabetic mother (See "Infant of a diabetic mother".)
- Assessment of the infant
 - Thermal environment
 - Signs and symptoms of hypoglycemia (eg, jitteriness, hypotonia, and lethargy) (See "Neonatal hypoglycemia", section on 'Who should be evaluated' and "Neonatal hypoglycemia", section on 'Clinical manifestations'.)
 - Signs and symptoms of sepsis (eg, temperature instability, lethargy, and poor feeding) (See "Clinical features and diagnosis of sepsis in term and late preterm infants", section on 'Clinical manifestations' and "Clinical features and diagnosis of bacterial meningitis in the neonate", section on 'Clinical features'.)
 - Signs and symptoms of neurologic impairment due to intraventricular hemorrhage, posthemorrhagic hydrocephalus, or neonatal encephalopathy (See "Clinical manifestations and diagnosis of intraventricular hemorrhage in the newborn", section on 'Clinical presentation' and "Management and complications of intraventricular hemorrhage in the newborn", section on 'Posthemorrhagic hydrocephalus (PHH)' and "Systemic effects of perinatal asphyxia", section on 'Risk factors' and "Clinical features, diagnosis, and treatment of neonatal encephalopathy", section on 'Diagnosis of neonatal asphyxia'.)
 - Assessment of the airway to detect congenital anomalies of the upper airway
 - Signs and symptoms of necrotizing enterocolitis (eg, abdominal distension, feeding intolerance, and lethargy) (See "Clinical features and diagnosis of necrotizing enterocolitis in newborns", section on 'Clinical presentation'.)
- Apnea must be distinguished from hypoxemia, cyanosis, and bradycardia that are sometimes associated with the introduction of oral feedings in premature infants. These changes in color and heart rate occur commonly before 34 to 36 weeks postmenstrual age as a result of ineffective coordination of sucking and breathing which may cause impaired ventilation. These events may persist in some neonates to postmenstrual age of 38 weeks [27]. High rates of milk flow may also contribute to reduced ventilation [28]. (See "Sucking and swallowing disorders in the newborn", section on 'Feeding disorders'.) Laboratory evaluation includes complete blood count, blood culture, and measurements of blood glucose, calcium, and electrolytes.

Other laboratory studies may be indicated if a metabolic disorder is suspected. In addition, cranial imaging should be obtained in cases in which severe intracranial hemorrhage or increased intracranial

pressure caused by posthemorrhagic hydrocephalus is suspected. (See "Presenting features of inborn errors of metabolism", section on 'Clinical presentations' and "Clinical manifestations and diagnosis of intraventricular hemorrhage in the newborn", section on 'Ultrasound screening'.)

SUMMARY — Apnea of prematurity is a developmental disorder in premature infants, which occurs as a direct consequence of immature respiratory control.

- Apnea of prematurity is most widely defined as cessation of breathing for more than 20 seconds, and is typically accompanied by oxygen desaturation and bradycardia. (See 'Definition' above.)
- The frequency and severity of symptoms is inversely proportional to gestational age, and almost all extremely low birth weight infants (gestational age less than 28 weeks) are affected. (See 'Incidence' above.)
- Apnea is classified as central, obstructive, or mixed, depending upon the presence of continued inspiratory efforts and upper airway obstruction while respiratory airflow is absent. In premature infants, most apnea spells are classified as either being central or mixed. (See 'Apnea' above.)
- Although the exact mechanisms underlying apnea of prematurity are unknown, it is thought to be caused by impaired respiratory response due to immaturity of respiratory control mechanisms including central respiratory drive, maintenance of airway patency, and adequate function and coordination of respiratory muscles. (See 'Pathogenesis' above.)
- Apnea of prematurity typically becomes evident in the second or third day of life in premature infants who are breathing spontaneously without respiratory support. It usually resolves before 37 postmenstrual weeks in infants delivered after 28 weeks gestation, but, in infants born before 28 weeks, apnea frequently persists after term postmenstrual age (PMA). (See 'Clinical presentation' above.)
- Although apnea of prematurity is the most common cause of apnea in preterm infants, it is a diagnosis of exclusion. Other causes of apnea need to be considered and eliminated before the diagnosis of apnea of prematurity is made. (See 'Diagnosis' above.)
- All premature infants should be monitored for apnea because of the high prevalence of this disorder. Monitoring is performed using cardiac monitors and pulse oximeters that also detect the associated findings of bradycardia and hypoxemia. (See 'Monitoring' above.)
- The goal of the diagnostic evaluation is to identify any underlying cause (eg, hypoglycemia and sepsis) that is associated with apnea and is amenable to treatment. The evaluation is based on a comprehensive history and assessment of the infant, and laboratory testing. (See 'Evaluation' above.)

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Hypertension in infants between one month and one year of age

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INTRODUCTION — The diagnosis of hypertension is typically made by comparing blood pressure (BP) to normative value. However, it is challenging to make the diagnosis of hypertension in infants because of the lack of robust normative data and because BP is not routinely measured in healthy infants.

The definition of hypertension based on available data, risk factors, and etiology for hypertension in infants between one month and one year of age will be reviewed here. The etiology and risk factors of hypertension in neonates and older children, and the management of hypertension in infants are discussed separately. (See

[Oreste Battisti : prematurity, brain]

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"Etiology, clinical features, and diagnosis of neonatal hypertension" and "Epidemiology, risk factors, and etiology of hypertension in children and adolescents".)

DEFINITION — As in older children, the definition of hypertension in infants is based upon BP percentiles. The systolic and diastolic BPs are of equal importance in determining the following BP categories (see "Definition and diagnosis of hypertension in children and adolescents"):

- Normal BP — Both systolic and diastolic BP <90th percentile.
- Prehypertension — Systolic and/or diastolic BP ≥90th percentile but <95th percentile
- Hypertension — Hypertension is defined as either systolic and/or diastolic BP ≥95th percentile measured upon three or more separate occasions. In children greater than one year of age, the degree of hypertension is further delineated by the two following stages.
- Stage 1 hypertension — Systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile.
- Stage 2 hypertension — Systolic and/or diastolic BP ≥99th percentile plus 5 mmHg.

NORMAL BLOOD PRESSURE — The 2004 Task Force report by the National High Blood Pressure Education Program (NHBPEP) Working Group defined percentile BP for height and gender in children ≥1 year old [1]. Although it does not provide any normative data on children less than a year old, limited data suggest that BP is relatively unchanged after the neonatal period to one year of age.

- In a study that measured systolic BP by Doppler ultrasound and sphygmomanometer, the mean BPs in male infants at six months and at one year of age were 92±13 mmHg and 94±12, and in female infants, mean BPs at six months of age and at one year of age were 93±14 mmHg and 93±11 mmHg [2]. The mean systolic BP rose from 76 mmHg at age four days to 96 mmHg at age six weeks and showed little further variation at six months and one year. Blood pressure was nearly normally distributed at all ages, and the 95th percentile for BP was 95 mmHg at four days and 113 mmHg between six weeks and one year.
- In a prospective study of 406 healthy term infants, no change in oscillometric BP measurements was noted between 6 and 12 months of age [3]. The median systolic and diastolic BP at six months of age were 102 (range 72 to 131) and 62.5 (range 34 to 81), and median values at 12 months were 101 (range 75 to 130) and 64 (range 41 to 84), respectively. The mean BP at 6 and 12 months remained the same (75 mmHg [48 to 99] versus 75 mmHg [55 to 94]).

A reference table of normal BP values at or after two weeks of age based on postconceptual age was developed based on a review of the literature on normal neonatal BP (table 1). From these data, the 95th percentile values for systolic, diastolic, and mean BPs for infants postconceptual age of 44 weeks (ie, one month of age for term infants) are 105, 68, and 80 mmHg, respectively.

In comparison, the NHBPEP task force reported the following 95th percentile BP ranges at one year of age based on height percentile (5th and 95th percentile height):

- Systolic BP – 98 to 106
- Diastolic BP – 54 to 58

Of note, the results of the studies performed in infants are based on oscillometric measurements, whereas the data in the NHBPEP Fourth Task force for one year old children are based on auscultatory measurements [1]. This is an important distinction because BP measurements obtained with oscillometric devices typically are higher than those obtained by auscultation. (See "Definition and diagnosis of hypertension in children and adolescents", section on 'Oscillometric devices'.)

Similar to older children, BP varies with height and BMI in infants and young children. In the Avon Longitudinal Study of Pregnancy and Childhood that included 1860 three-year-old children, height and body mass index (BMI) strongly correlated with the BP [4]. For each 10 cm increase in height, systolic pressure

increased by 4.4 mmHg and diastolic pressure by 1.2 mmHg. For each 1 kg/m² increase in BMI, systolic pressure increased by 1.1 mmHg and diastolic pressure by 0.4 mmHg.

The effect of postnatal growth pattern and ethnic differences on the BP in young children was also reported in a prospective study in 560 South Asian infants who were followed from birth to 3 and 12 months of age. Weight gain during the first three months appeared to correlate with higher systolic BP at one year [5].

Given the limited amount of available information in infants below one year of age, the above results suggest that normative data for one-year-old children can be used to help determine whether infantile BP values are excessive and guide BP management in affected patients. Based on the currently available data, the definition of hypertension used in our practice is the 95th percentile based on height from the NHBPEP task force normative data as described above [1].

ETIOLOGY — The causes of hypertension in infants between one month of age and one year of age are similar to those seen in patients with neonatal hypertension. In addition, many of these patients develop hypertension because of neonatal complications. (See "Etiology, clinical features, and diagnosis of neonatal hypertension" and "Etiology, clinical features, and diagnosis of neonatal hypertension", section on 'Etiology'.)

Causes of hypertension in infants beyond the neonatal period include:

- Renovascular injury due to neonatal placement of umbilical arterial catheters
- Bronchopulmonary dysplasia
- Renal injury due to perinatal complications (eg, perinatal asphyxia) (see "Acute kidney injury (acute renal failure) in the newborn", section on 'Perinatal asphyxia')
- Renal vein thrombosis (see "Pathogenesis, clinical features, and diagnosis of thrombosis in the newborn", section on 'Renal vein thrombosis')
- Neurologic disorders such as intracranial hemorrhage, increased intracerebral pressure, or seizures
- Congenital renal and urologic disorders (eg, polycystic kidney disease and obstructive uropathy) (see "Overview of congenital anomalies of the kidney and urinary tract (CAKUT)")
- Endocrine disorders, such as hyperthyroidism or congenital adrenal hyperplasia, especially due to 11-hydroxylase (CYP11B1) and 17-hydroxylase (CYP17) deficiencies, which are associated with an increased production of deoxycorticosterone (see "Evaluation and management of neonatal Graves' disease" and "Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency" and "Uncommon causes of congenital adrenal hyperplasia", section on 'CYP17 deficiency')
- Coarctation of the aorta (see "Clinical manifestations and diagnosis of coarctation of the aorta", section on 'Neonates')
- Medications such as caffeine, theophylline, corticosteroids, and beta-adrenergic agents
- Other rare causes include:
 - Tumors including Wilms tumor, pheochromocytoma, neuroblastoma, and mesoblastic nephroma
 - Orthopedic procedures, particularly those requiring skeletal traction [6]. Hypertension occurs soon after the procedure, can be severe enough to cause symptoms, and resolves on discontinuation of the treatment. Hypertension may be associated with hypercalcemia, which probably plays no causative role in traction-related hypertension.
 - Hypercalcemia
 - Drug withdrawal in infants of mothers with substance abuse due to heroin or cocaine
 - Closure of abdominal wall defect

WHO SHOULD BE EVALUATED — Because the incidence of hypertension is low in children less than three years of age, routine BP monitoring is not recommended by the NHBPEP Task Force unless the patient is at risk for hypertension [1].

Risk factors include the following [1]:

- History of neonatal complications requiring neonatal intensive care
- Congenital heart disease

- Recurrent urinary tract infection, hematuria or proteinuria
- Known renal or urologic disease
- Family history of congenital renal disease
- Solid organ or bone marrow transplantation
- Malignancy
- Treatment with drugs known to raise BP
- Other systemic illnesses associated with hypertension, such as tuberous sclerosis or neurofibromatosis
- Evidence of increased intracranial pressure

In particular, events during pregnancy or the neonatal period are an important risk factor for hypertension in this age group. Children with low birth weight, premature birth, or those who need neonatal intensive care treatment are at increased risk of developing hypertension during infancy and early childhood [4,7]. This was illustrated in a retrospective study of 650 infants discharged from neonatal intensive care unit (NICU) [7]. In this cohort, 2.6 percent had hypertension defined by systolic BP of more than 113 mmHg on three consecutive visits over a six-week period. Hypertension was diagnosed at a mean age of approximately two months post-term with correction for prematurity.

Infants with bronchopulmonary dysplasia (BPD) compared with those without BPD are also at increased risk to develop hypertension following discharge from the NICU [8,9]. In one study of infants with birth weight less than 1250 g, the overall incidence of hypertension was 6.8 percent and was 12.0 percent in those with BPD [9]. The mean age of onset of hypertension was 105 days (range 90 to 133 days). The severity of hypertension correlated with the severity of the pulmonary disease.

BLOOD PRESSURE MEASUREMENT — When comparing BP measurements, it is important to verify the method used to obtain normative data as oscillometric BP measurements are generally higher than those obtained by manual or direct methods. The data from the NHBPEP Fourth Task Force Report are based on auscultatory measurements, whereas the data presented previously are obtained by oscillometric measurements. Because accurate measurement of BP by auscultation in young infants is often difficult, initial BP measurement in this age group is typically performed by oscillometric devices. If using the NHBPEP Fourth Task Force Report tables to determine the BP percentile, one needs to verify the BP by auscultation. (See "Definition and diagnosis of hypertension in children and adolescents", section on 'Oscillometric devices'.)

Using the appropriately sized arm cuff is vital for accurate BP measurement. The appropriate size is a cuff with an inflatable bladder width that is at least 40 percent of the arm circumference at a point midway between the olecranon and the acromion, and the bladder length should cover 80 to 100 percent of the circumference of the arm. The NHBPEP Task Force recommends an arm cuff bladder that is 6 cm wide and 12 cm long for an infant with a maximum arm circumference of 15 cm (table 2). If the choice is between a cuff that is too small or one that is too large, use of the larger cuff will result in less error. (See "Definition and diagnosis of hypertension in children and adolescents", section on 'Cuff size'.)

BP measured while the infant is sleeping may be lower than awake BP [2,10]. In a study in infants between the ages of five to nine weeks, the mean systolic BP was about 6 mmHg higher in awake infants compared to those who were asleep (96 ± 11 versus 89 ± 11 mmHg) [2]. Others have confirmed that BP is lower in infants who are asleep or awake and calm compared with those who are awake and fussy or crying [10].

Our approach — We use the following standard protocol to measure BP in infants who are at risk for hypertension:

- Blood pressure measured by oscillometric device
- Infant in a quiet awake state or sleeping, while lying in a prone or supine position
- Use of an appropriate sized BP cuff
- Measurement performed in the right upper arm
- In infants who get agitated with arm cuff placement, our approach is to leave the infant undisturbed after cuff placement and measure BP only after the infant has calmed down

Ambulatory BP monitoring — Very little data are available on the role of ambulatory blood pressure monitoring (ABPM) in infants and young children. The successful use of ABPM in this age group has been reported in several case series [11-14].

- In a study on 97 healthy children aged 2 to 30 months (mean 13+3 months), a satisfactory BP profile was obtained in 86.6 percent children with an average of 75 percent satisfactory BP recordings [12].
- In another study, satisfactory readings were obtained in 77 percent of 101 children three to six years old. This study also revealed that in contrast to the older children with expected night-time dipping, a second decrease during bed rest after lunch occurred in these children [13].

However, several limitations restrict the clinical usefulness of routine ABPM in infants and young children:

- One of the main purposes of ABPM is to diagnose white coat hypertension, which is believed to be clinically insignificant in this age group.
- There are no reliable normative data for children less than five years of age.
- Technical difficulties include patient intolerance of the inflating arm cuff and limited availability of the appropriate size cuff.

DIAGNOSIS — The diagnosis of childhood hypertension is made when repeat BP values on three separate occasions are greater than the 95th percentile for the age, gender, and height of the patient [1]. As noted above, in infants below one year of age, there are no normative data to determine the 95th percentile for BP. Currently available data suggest that normative data for one year old children can be used to help define infantile hypertension. (See 'Normal blood pressure' above.)

As discussed above, we define hypertension when repeat BP values exceed the 95th percentile based on height from the NHBPEP task force normative data as described above [1]. (See 'Normal blood pressure' above.)

In our practice, we use the following clinical threshold for evaluation and treatment:

- For infants with an oscillometric awake BP of >100/60, management consists of follow-up BP monitoring and evaluation for an underlying cause of hypertension.
- Treatment is generally initiated for BP persistently $\geq 110/65$, or sooner if left ventricular hypertrophy is present.

In the absence of a routine BP measurement in children <3 years old, blood pressure measurements should be obtained in patients in whom there is a high index of suspicion for hypertension. (See 'Who should be evaluated' above.)

EVALUATION — Once it has been determined that the infant is hypertensive, an evaluation is performed to identify the cause of hypertension, treat any curable cause, and determine the extent of target organ damage. Because the causes of hypertension in this age group are often due to perinatal events, the evaluation is similar to that performed for neonatal hypertension. (See 'Etiology' above and "Etiology, clinical features, and diagnosis of neonatal hypertension", section on 'Evaluation'.)

The assessment includes:

- A focused history that reviews perinatal exposures (eg, maternal use of prescribed and illicit drugs, history of perinatal asphyxia), neonatal course (eg, umbilical arterial catheterization), presence or family history of congenital kidney or urinary tract anomalies, or concurrent conditions associated with hypertension (eg, bronchopulmonary dysplasia).
- Physical examination must include four-limb BP measurement and palpation of femoral pulses to rule out the possibility of coarctation of the aorta. Other findings that may explain the cause of hypertension include presence of dysmorphic features (eg, Williams syndrome), birth marks (eg, café au lait spots), ambiguous genitalia (eg, congenital adrenal hyperplasia), bulging and tense anterior fontanel, palpable kidneys, or any other abdominal masses, cardiac murmurs, and abdominal bruit.

- Initial laboratory evaluation includes urinalysis, complete blood count, and measurement of serum blood urea nitrogen, creatinine, electrolytes, and calcium. Further testing is guided by the initial evaluation and individualized for patient. (See "Evaluation of hypertension in children and adolescents", section on 'Further evaluation'.)
- Echocardiography is performed to determine whether there is left ventricular hypertrophy as evidence of end-organ involvement and to diagnose coarctation of aorta, if present.

SUMMARY AND RECOMMENDATIONS — Hypertension is uncommon in infants, and blood pressure (BP) is not routinely measured in infants and young children beyond the neonatal period. As a result, a high index of suspicion is important to identify infants beyond the neonatal period who are at risk for hypertension, so that hypertension can be diagnosed and managed appropriately.

- As is true in older children, hypertension in infants is defined as either systolic or diastolic BP that is ≥ 95 th normative BP percentile measured upon three or more separate occasions. However, there is limited information on normal BP in infants less than one year of age. Currently available literature suggests that normative data from one-year-old children can be used to help guide BP management in younger infants. (See 'Normal blood pressure' above.)
- The causes of hypertension in infants between one month and one year of age are similar to those seen in patients with neonatal hypertension. In addition, many of these patients develop hypertension because of neonatal complications, such as bronchopulmonary dysplasia, renovascular injury due to umbilical artery catheterization, renal vein thrombosis, and neurologic sequelae (eg, intraventricular hemorrhage). Other causes of infantile hypertension include congenital anomalies of the kidney and urologic tract (CAKUT), endocrine disorders (eg, congenital adrenal hyperplasia and hyperthyroidism), medications, and coarctation of the aorta. (See 'Etiology' above.)
- Because the incidence of hypertension is low in children less than three years of age, routine BP monitoring is not recommended unless the patient is at risk for hypertension. Infants at risk for hypertension include those with complications that required admission to a neonatal intensive care unit, congenital heart disease, CAKUT, and other illnesses and conditions associated with hypertension. (See 'Who should be evaluated' above.)
- BP measurement in infants should be performed in a standardized approach that routinely measures BP in the same extremity and position, using an appropriate size BP cuff in a quietly awake or sleeping infant. (See 'Blood pressure measurement' above.)
- The diagnosis of hypertension is made when repeat BP values on three separate occasions are greater than the 95th percentile for age. Because there are no normative data that contain 95th percentile BP values for infants less than one year of age, we use the following threshold based on currently available data. (See 'Diagnosis' above.)
- For infants with an oscillometric awake BP of $>100/60$, management consists of follow-up BP monitoring and an evaluation for an underlying cause for elevated BP.
- Treatment is generally initiated for BP persistently $\geq 110/65$, or sooner if left ventricular hypertrophy is present.
- Once it has been determined that the infant is hypertensive, an evaluation is performed to identify the cause of hypertension, treat any curable cause, and determine the extent of target organ damage. Because the causes of hypertension in this age group are often due to perinatal events, the evaluation is similar to that performed for neonatal hypertension. (See 'Evaluation' above and 'Etiology' above and "Etiology, clinical features, and diagnosis of neonatal hypertension", section on 'Evaluation'.)

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Prematurity and lungs

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Pathogenesis and clinical features of bronchopulmonary dysplasia

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INTRODUCTION — Bronchopulmonary dysplasia (BPD), also known as neonatal chronic lung disease (CLD), is an important cause of respiratory illness in preterm newborns that results in significant morbidity and mortality.

The pathogenesis and clinical features of BPD are reviewed here. Management, prognosis, and potential strategies to prevent BPD are discussed separately. (See "Management of bronchopulmonary dysplasia" and "Outcome of infants with bronchopulmonary dysplasia" and "Prevention of bronchopulmonary dysplasia".)

TERMINOLOGY — Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birthweight (BW). Data on BPD is often based upon the following classification of preterm infants who are categorized by their birthweight as follows:

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

These terms are used throughout this discussion.

DEFINITION — The definition of BPD has continued to evolve since 1967 when Northway first described the disorder, which resulted from prolonged mechanical ventilation in premature infants with severe respiratory distress syndrome [1]. This is due to changes in neonatal management (ie, surfactant, antenatal glucocorticoid therapy, and less aggressive mechanical ventilation) that have altered the pathology and clinical course of BPD. (See 'Pathology' below.)

Earlier definitions based upon oxygen requirement either at 28 postnatal days [2,3] or 36 weeks postmenstrual age (PMA) do not account for extreme prematurity (ie, birth weight <1000 g or gestational age <30 weeks) and the severity of respiratory disease [4,5]. These definitions became less accurate in predicting outcome because of the increasing survival rate of ELBW infants, and the increased prevalence of milder forms of BPD due to improved treatment of RDS. As an example, oxygen supplementation at 28 days of life in ELBW infants may be due to lung immaturity and not BPD. Whereas, an ELBW infant with mild BPD disease who required oxygen within the first 28 days of life, but not at 36 weeks PMA, would not be diagnosed as having BPD using the latter definition. The failure to include gestational age at birth or disease severity led to concerns that these definitions are inadequate, especially when comparing the efficacy of different therapeutic interventions and/or long-term outcome of ELBW infants with BPD.

NICHD criteria — In 2001, a consensus conference of the United States National Institute of Child Health and Human Development (NICHD) modified the pre-existing definitions of oxygen requirement by adding criteria that included gestational age (GA) and severity of disease (table 1) [6]. The timing of assessment is based upon GA:

- Patients who are <32 weeks GA are assessed at 36 weeks PMA or when discharged home, whichever comes first.
- Patients who are ≥32 weeks GA are assessed between 29 to 55 days of life or when discharged home, whichever comes first.

Infants who require supplemental oxygen for at least 28 postnatal days are classified as having mild, moderate, or severe BPD, depending upon the extent of oxygen supplementation and other respiratory support. To standardize the use of supplemental oxygen, the NICHD criteria also proposed that the need for oxygen be confirmed by using a physiologic test, although a specific test was not defined.

A study from the NICHD Neonatal Research Network reported that the NICHD criteria more accurately predicted pulmonary and neurodevelopmental outcomes at 18 to 22 months corrected age in preterm infants <32 weeks GA with BPD than previous definitions [7]. In particular, the definition of supplemental oxygen at 36 weeks PMA would have missed a substantial number of patients with mild BPD who may be at risk for pulmonary and neurodevelopmental complications. NICHD criteria more accurately predicted which preterm survivors would require pulmonary medication and rehospitalization for pulmonary disease. The incidence of

neurodevelopmental impairment (ie, lower mental and psychomotor developmental index scores, cerebral palsy, blindness, hearing impairment) increased with the severity of disease based upon the NICHD criteria.

Physiologic testing — As mentioned above, the NICHD criteria also proposed that the requirement of supplemental oxygen be confirmed by using a physiologic test, although a specific test was not defined. Currently, the clinical criteria used for oxygen supplementation varies widely [8]. Adoption of a BPD definition based upon physiologic testing would reduce the effect of clinical practice differences when comparing outcome among centers caring for these patients.

One prospective multicenter study compared a physiologic test based upon oxygen administration and saturation to the standard clinical definition of oxygen supplementation at 36 weeks corrected age [9,10]. The physiologic definition lowered the rate of BPD from 35 percent based upon the clinical definition to 25 percent, and reduced the variation in incidence among centers. These results demonstrated that the use of a standardized physiologic definition of BPD is feasible.

EPIDEMIOLOGY — The rate of BPD varies among institutions, which may reflect neonatal risk factors, care practices (eg, target levels for acceptable oxygen saturation), and differences in the clinical definitions of BPD [8,11,12].

Infants with BW <1250 g account for 97 percent of the cases of BPD [13]. The incidence of BPD increases with decreasing birth weight (BW), as illustrated in a report from the NICHD Neonatal Research Network from 1997 to 2002 [11]. In this study of over 18,000 VLBW infants, the overall incidence of BPD (defined as requiring supplemental oxygen at 36 weeks PMA) was 25 percent.

- BW from 1251 to 1500: 6 percent
- BW from 1001 to 1240: 14 percent
- BW from 751 to 1000: 33 percent
- BW from 501 to 750: 46 percent

In an eight-year (1994 to 2002) retrospective cohort study of six neonatal intensive care centers, the overall incidence of BPD has remained constant at 12 percent for preterm infants born before 33 weeks gestation despite the increased survival of infants born at earlier gestational age [14]. In addition, a decrease in the rate of severe BPD was noted. The reduction in the risk and severity of BPD are due to changes in neonatal care (ie, antenatal glucocorticoid therapy, postnatal surfactant therapy, and less aggressive ventilation) that have resulted in a milder pattern of lung injury referred to as "new" BPD.

PATHOLOGY — In surfactant-treated ELBW infants, the characteristic pathologic finding of BPD is disruption of lung development, referred to as the "new" BPD [6,15,16]. In these patients, decreased septation and alveolar hypoplasia lead to fewer and larger alveoli with a reduction in the surface area available for gas exchange. There is also dysregulation of pulmonary vasculature development (eg, abnormal distribution of alveolar capillaries, and thickening of the muscle layer of the pulmonary arterioles that results in increase in pulmonary resistance). In comparison to "old" BPD, there is a reduction of airway injury and inflammation.

These findings are in contrast to "old" BPD seen in infants prior to the availability of surfactant replacement therapy before the 1980s. The prominent pathologic findings in "old" BPD were airway injury, inflammation, and parenchymal fibrosis due to mechanical ventilation and oxygen toxicity [6,16] (figure 1). Similar changes may be seen in surfactant-treated infants who develop severe BPD. In these severely affected infants, fibrosis, bronchial smooth muscle hypertrophy, and interstitial edema ("old" BP) may be superimposed on the characteristic reduced numbers of alveoli and capillaries ("new" BPD). Pulmonary vascular changes, such as abnormal arterial muscularization and obliteration of vessels, may also occur.

Lung injury also is associated with increased elastic tissue formation and thickening of the interstitium. These tissue deformations may, in turn, compromise septation and capillary development. In one autopsy study, the amount of elastic tissue, septal thickness, and alveolar and duct diameters increased with the severity of BPD [17].

PATHOGENESIS — The etiology of BPD is multifactorial and is due to exposure of antenatal and postnatal factors (eg, mechanical ventilation, oxygen toxicity, and infection), which disrupts pulmonary development, and may cause inflammation and damage to the highly vulnerable premature lung (figure 1).

The following studies illustrate the effect of these factors upon the risk of developing BPD.

- In a prospective report from the ELGANS (Extremely Low Gestational Age Newborns Study) study, predictive factors for BPD included lower gestational age in this already extreme prematurity cohort, FiO₂ requirement greater than 0.25 at 14 days of life, and mechanical ventilation at one week of life [18].
- In a study of 1244 VLBW infants in North Carolina, significant risk factors for BPD were the need for ventilation at 48 hours of age (odds ratio 1.64), nosocomial infection (OR 2.0), and increased fluid intake on day two (OR 1.06 per 10 mL increase) [5]. Among infants ventilated at 48 hours, patent ductus arteriosus (PDA) was associated with increased risk (OR 1.9).
- In a study of 119 ELBW with mild initial respiratory distress who required less than three days of supplemental oxygen concentration >25 percent during the first five postnatal days, 44 (37 percent) developed BPD [19]. Risk factors for BPD included low birth weight (OR 2.9 per 100 g decrement), PDA (OR 6.2), and sepsis (OR 4.4).

Individual risk factors are discussed in the following sections.

Prematurity — The lung appears to be most susceptible to damage during the saccular stage of development from 23 to 32 weeks gestation [15,20]. At this stage, the premature lung has poorly developed airway supporting structures, surfactant deficiency, decreased compliance, underdeveloped antioxidant mechanisms, and inadequate fluid clearance (figure 1) [15,21]. The premature lung's structural and functional immaturity increases the risk of injury and disruption of normal pulmonary microvascular and alveolar development from external antenatal and postnatal insults.

In addition, fetal growth restriction in premature infants (gestational age below 28 weeks) appears to be an independent risk factor for BPD [22]. Growth restriction may have a significant impact on the vulnerability of lung injury.

Mechanical ventilation — Injury caused by mechanical ventilation is due to large tidal volumes (volutrauma) that overdistend airways and airspaces rather than increased airway pressures [23,24]. Because of the evidence that aggressive mechanical ventilation played a major role in the pathogenesis of BPD, a more conservative approach towards neonatal ventilation (ie, avoidance of high tidal volume) has evolved. This approach is one of the factors that have resulted in a milder form of BPD ("new BPD"). As a result, significant airway injury characteristic of the old BPD is less common, and is only seen in infants with severe BPD. (See 'Pathology' above and "Mechanical ventilation in neonates" and "Pulmonary outcomes of bronchopulmonary dysplasia".)

Acute lung injury results from inflations that are close to the maximum lung volume of small immature lungs, and plays a role in the chronic changes resulting in BPD. The risk of BPD increases with decreasing arterial carbon dioxide tension (PCO₂) as a measure of more aggressive ventilation that includes large tidal volumes [2,25,26].

Positive pressure ventilation typically induces bronchiolar lesions [27]. Disruption of airways may occur early in the course of treatment and may be manifested by increased pulmonary resistance [28]. In one study of ventilated preterm infants in the first five days after birth, mean pulmonary resistance was significantly greater in those who subsequently developed BPD compared with those who did not [29].

An animal study has shown that even a small number of large inflations soon after birth can adversely affect surfactant-deficient lungs [30]. In this study of newborn lambs, one lamb of each of five pairs was randomly assigned to receive six large manual inflations ("bagging") after preterm delivery, and before starting mechanical ventilation and receiving artificial surfactant. At four hours, the bagged animals compared with controls had

lower inspiratory capacity and maximal deflation, were more difficult to ventilate, and had less well expanded alveoli and more widespread lung injury on histologic examination.

Differences in the use of mechanical ventilation may explain some of the variation among hospitals in BPD rates. This was illustrated in a case-cohort study of 452 VLBW infants at two centers (two Boston hospitals and Babies' and Children's Hospital in New York) from 1991 to 1993 that found BPD was more prevalent in Boston than in New York (22 versus 4 percent) [12]. The initial respiratory management in Boston was more likely to include mechanical ventilation (75 versus 29 percent) and surfactant administration (45 versus 10 percent) during the study period.

Oxygen toxicity — High concentrations of inspired oxygen can damage the lungs, although the exact level or duration of exposure that is unsafe is not known. Cellular damage is caused by the overproduction of cytotoxic reactive oxygen metabolites (ie, superoxide free radical, hydrogen peroxide, hydroxyl free radical, and singlet oxygen), which overwhelm the neonates immature antioxidant system.

Preterm infants have inadequate antioxidant defenses because of nutrient deficiencies (vitamins A and E, iron, copper, zinc, and selenium) or immature antioxidant enzyme systems (superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase) [31]. Activity of catalase, glutathione peroxidase, and copper/zinc (Cu/Zn) superoxide dismutase in cord blood are lower in preterm than in term newborns [32]. There is also evidence of genetic variation in antioxidant defenses. This was illustrated by a study that showed infants with the less efficient isoform of glutathione-S-transferase-P1 were more susceptible to oxygen toxicity predisposing them to BPD [33].

Although antioxidant mechanisms are immature, there is some upregulation of this defense system in preterm infants with BPD. In a study of 44 preterm infants (gestational age from 25 to 30 weeks), Cu/Zn superoxide dismutase levels, followed sequentially from birth to the first week of life, were greater in infants who developed BPD compared with those without BPD by day six of life [34].

Infection — Both postnatal and antenatal infections are associated with BPD.

Postnatal — Sepsis is associated with an increased risk of BPD. This was illustrated in an observational study from a single Australian tertiary center of 798 preterm infants (mean GA 27.4 weeks) born between 1992 and 2004 that reported neonatal sepsis increased the risk of BPD (OR 2.71 95% CI 1.64-4.51) [35]. Infants with candidemia had the highest risk of developing BPD (OR 8.68, 95% CI 1.65-45.63).

The rate of BPD increases when sepsis is present in conjunction with a symptomatic patent ductus arteriosus (PDA). In a series of 119 ELBW infants who had mild or no initial respiratory distress syndrome, the risk of developing BPD was significantly higher with both sepsis and PDA (OR 48.3) compared with PDA alone (odds ratio 6.2) or sepsis alone (OR 4.4) [19].

Chorioamnionitis — Antenatal infection may contribute to the development of BPD [36-38]. This is suggested by the increased concentration of proinflammatory cytokines (interleukin [IL]-6, IL-1 beta, and IL-8) in the amniotic fluid of infants who subsequently develop BPD compared with those who did not [39]. In particular, infection with *Ureaplasma urealyticum* appears to cause a sustained dysregulated inflammatory response that impairs lung development, resulting in BPD [40,41]. In addition, impaired response to surfactant has been reported in premature infants born to mothers with severe chorioamnionitis. This poor response appears to be associated with an increased risk of BPD compared to infants who receive surfactant, but whose mothers who do not have chorioamnionitis [42]. (See 'Inflammation' below.)

In contrast, the previously mentioned Australian study found chorioamnionitis was associated with a decreased risk of BPD [35]. The following findings were noted:

- BPD was diagnosed in 25 percent of patients.
- Of the 761 cases with placental examination, chorioamnionitis alone was present in 18 percent, and chorioamnionitis and umbilical vasculitis occurred in 27 percent.

- Step-wise logistic regression analysis demonstrated a decrease in the risk of BPD with chorioamnionitis with or without umbilical vasculitis (OR 0.58, 95% CI 0.51-0.67), increasing gestational age (OR 0.59, 95% CI 0.51-0.67), and increasing birth weight (OR 0.30, 95% CI 0.11-0.78).

Conflicting results may be attributed to differences in study design, including the gestational age of patients and the definition of BPD.

Inflammation — Proinflammatory and chemotactic factors are present in greater concentration in infants who subsequently develop BPD compared with those without BPD [6,39,43-46]. These include IL-1 beta, IL-6, IL-8, IL-10, and interferon gamma. The presence of these mediators is associated with complement activation, increased vascular permeability, protein leakage, and mobilization of neutrophils into the interstitial and alveolar compartments. Release of reactive oxygen radicals, elastase, and collagenase by activated neutrophils results in lung damage [47]. Interaction between macrophages and other cell types (eg, endothelial and epithelial cells) perpetuates the production of proinflammatory mediators, and sustains the cycle of lung injury. Persistence of factors (eg, macrophage inflammatory protein-1 and IL-8) and decreases of counterregulatory cytokines (eg, IL-10, IL-17) may lead to unregulated and persistent inflammation [6].

The development of BPD may begin before birth in some newborns through intrauterine exposure to proinflammatory cytokines, possibly due to chorioamnionitis. (See 'Chorioamnionitis' above.)

Genetics — Genetic predisposition may influence the development of BPD. This was illustrated in a study of monozygotic and dizygotic premature twins with GA ≤ 30 weeks that demonstrated the correlation of the developing BPD, defined by the NICHD criteria, was greater in monozygotic compared with zygotic pairs [48]. However, further studies are required to determine whether or not there is a genetic predisposition, and if so, what are the underlying genetic factors.

Late surfactant deficiency — Delayed recovery or late deficiency of postnatal surfactant may play a role in the pathogenesis of BPD. In a study of 68 ventilator-dependent premature infants (gestational ages between 23 and 30 weeks), 75 percent of tracheal aspirates exhibited abnormally low surface tension [49]. In these samples, surfactant proteins A, B, and C, were reduced by 50, 80, and 72 percent, respectively. In addition, there appear to be a temporal association between samples with low surface tension and episodes of infection and respiratory deterioration. These results suggest that premature infants who require continued respiratory support have transient surfactant dysfunction or deficiency, which may affect their clinical status.

In a pilot trial of 136 premature infants (birthweights between 600 and 900 g) who required mechanical ventilation between day three and ten of life, patients were randomly assigned to receive low dose synthetic surfactant, high dose synthetic surfactant, or placebo [50]. Although there was a trend to lower oxygen requirements in the surfactant groups compared with the control group, and a lower incidence of either death or BPD in the high dose surfactant group compared with either the low dose surfactant or placebo groups, these differences did not reach statistical significance. A larger trial is currently underway that is examining the effect of late or periodic surfactant replacement, and possible synergistic effects, if combined with inhaled nitric oxide therapy upon the risk of developing BPD.

Other potential factors — Other potential pathogenetic contributors include endostatin and bombesin-like peptides.

Impaired angiogenesis — There is increasing evidence that suggests the growth of lung blood vessels actively promotes alveolar growth. Disruption of angiogenesis has been proposed as a mechanism that impairs alveolarization, thereby contributing to the new form of BPD [51]. (See 'Pathology' above.)

Support for the potential role of impaired angiogenesis in the pathogenesis of BPD includes the following:

- In one study, elevated cord plasma endostatin levels, an antiangiogenic growth factor, were associated with an increased risk of BPD in very low birth weight infants (birth weight less than 1500 g) [52].
- In a prospective study of 107 preterm infants born between 23 and 32 weeks gestation, the risk of BPD was increased in infants born to mothers with preeclampsia compared to those born to mothers without

preeclampsia (44 versus 22 percent) [53]. These findings suggest factors that trigger maternal endothelial dysfunction (impaired angiogenesis), resulting in preeclampsia, are transferred to infants, which may contribute to the pathogenesis of BPD. (See "Pathogenesis of preeclampsia", section on 'Systemic endothelial dysfunction'.)

Bombesin-like peptides — Injury may be mediated in part by bombesin-like peptides (BLP), which are derived from pulmonary neuroendocrine cells and play an important role in normal lung growth and maturation. In one study, the number of BLP-positive cells was greater in infants who died with BPD than in controls [54]. In a baboon model, urine BLP levels were increased soon after birth in animals who developed BPD, and administration of anti-BLP antibody attenuated the disorder [55]. In infants ≤ 28 weeks gestational age, elevated urine BLP levels in the first four days after birth were associated with an increased risk of BPD [56].

CLINICAL FEATURES — As discussed above, BPD is associated with multiple risk factors, including prematurity, mechanical ventilation, oxygen toxicity, sepsis, and patent ductus arteriosus. It occurs infrequently in infants with GA ≥ 30 weeks or BW more than 1250 g [6,13].

The evolution to BPD typically is recognized at approximately two weeks of age based upon the need for supplemental oxygen. This was illustrated in the previously mentioned ELGANS study that enrolled 1340 preterm infants less than 28 weeks gestation in a multicenter prospective study between 2002 and 2004 [18]. During the first two weeks of postnatal life, three clinical pulmonary courses emerged with differing rates of BPD.

- About 40 percent had persistent lung dysfunction defined as a consistent requirement of FiO₂ above 0.25. About two-thirds of these patients developed BPD.
- About 40 percent had deterioration of lung dysfunction defined as an increase of FiO₂ above 0.25 at 14 days of age. About one-half of these patients developed BPD.
- About 20 percent had no or minimal lung dysfunction defined as no consistent need of FiO₂ above 0.25. Only 17 percent of this group developed BPD.

Physical examination — The physical examination is variable. Infants usually are tachypneic. Depending upon the extent of pulmonary edema and/or atelectasis, they may have mild to severe retractions, and scattered rales may be audible. Intermittent expiratory wheezing may be present in infants with airway narrowing from scar formation, constriction, mucus retention, collapse, and/or edema.

Chest radiograph — As BPD evolves, the chest radiograph becomes diffusely hazy, reflecting atelectasis, inflammation, and/or pulmonary edema. Lung volumes are normal or low. There may be areas of atelectasis that alternate with areas of gas trapping, related to airway obstruction from secretions or other debris.

The chest radiograph in infants who develop severe BPD shows hyperinflation. Streaky densities or cystic areas may be prominent, corresponding to fibrotic changes. During acute exacerbations, pulmonary edema may be apparent.

Cardiopulmonary function — In patients with severe BPD, abnormalities of pulmonary function include decreased tidal volume, increased airway resistance, and decreased dynamic lung compliance. Uneven airway obstruction leads to gas trapping and hyperinflation with abnormal distribution of ventilation [57]. Bronchomalacia can result in airway collapse during expiration. Severely affected infants have hypoxemia and hypercapnia.

In these patients, pulmonary vascular resistance is increased because of reduced cross sectional area of pulmonary vessels. In addition, alveolar hypoxia in underventilated areas of the lung induces local vasoconstriction. The high microvascular pressure promotes increased fluid filtration into the perivascular interstitium. Elevated right atrial pressure inhibits pulmonary lymphatic drainage, further promoting pulmonary edema.

CLINICAL COURSE — Most infants improve gradually during the next two to four months. As pulmonary function improves, they can be weaned to continuous positive airway pressure, then supplemental oxygen alone, until they can maintain adequate oxygenation when breathing room air.

Some infants develop severe BPD that leads to prolonged ventilator dependence. The clinical course during the first few weeks after birth includes marked instability with frequent changes in oxygenation and intermittent episodes of acute deterioration requiring increased ventilator support. The marked instability typically subsides after four to six weeks.

Severely affected infants may develop pulmonary hypertension and cor pulmonale [58]. Elevated pulmonary vascular resistance may impair pulmonary lymphatic drainage and exacerbate interstitial edema. In some cases, anastomoses develop between pulmonary and systemic vessels that may worsen the pulmonary hypertension [58]. (See "Pulmonary outcomes of bronchopulmonary dysplasia", section on 'Pulmonary artery hypertension'.)

SUMMARY — Bronchopulmonary dysplasia (BPD) remains a major complication of prematurity, resulting in significant mortality and morbidity. (See "Outcome of infants with bronchopulmonary dysplasia".)

- The current definition of BPD is based upon the need for oxygen supplementation, gestational age of the infant, and the severity of disease (table 1). (See 'Definition' above.)
- Infants with birth weights (BW) <1250 g account for 97 percent of the cases of BPD. The incidence of BPD in very low BW infants (BW below 1500 g) is about 25 percent, although rates of BPD vary among institutions. The risk of developing BPD increases with decreasing birth weight (BW). (See 'Epidemiology' above.)
- Changes in neonatal management (ie, use of surfactant, antenatal glucocorticoid therapy, and less aggressive mechanical ventilation) have resulted in a milder form of BPD, referred to as "new" BPD. The "new" BPD is characterized by disruption of lung development that results in large alveoli and dysregulation of vasculature development. In contrast, the "old" BPD was characterized by airway injury, inflammation, and parenchymal fibrosis, which were primarily due to injury from mechanical ventilation and oxygen. (See 'Pathology' above.)
- The etiology of BPD is multifactorial and is due to exposure of antenatal and postnatal factors that cause arrest of pulmonary development, and potentially, inflammation and damage to the highly vulnerable premature lung (figure 1). These factors include mechanical ventilation, oxygen toxicity, infection, inflammation, and possibly genetic predisposition and late surfactant deficiency. (See 'Pathogenesis' above.)
- Infants who require oxygen supplementation above a FiO₂ of 25 percent at two weeks of age are at risk for developing BPD. Although the physical findings of BPD vary, most affected infants are tachypneic. Other findings include retractions, rales, and wheezes. (See 'Physical examination' above.)
- The chest radiograph in infants with BPD may be diffusely hazy, reflecting atelectasis, inflammation, and pulmonary congestions/edema. (See 'Chest radiograph' above.)
- Patients with severe BPD are hypoxemic and hypercapnic because of significant cardiopulmonary abnormalities. These include decreased tidal volume, increased airway resistance, decreased dynamic lung compliance, uneven airway obstruction, resulting in trapping and hyperinflation with abnormal distribution of ventilation, and increased vascular resistance. (See 'Cardiopulmonary function' above.)
- Most infants with BPD improve gradually during the next two to four months. Those with severe disease may have a prolonged course of mechanical ventilation, and may develop pulmonary hypertension and cor pulmonale. (See 'Clinical course' above.)

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Incidence and mortality of the premature infant

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INTRODUCTION — Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. It is associated with approximately one-third of all infant deaths in the United States. Infants born at or before 25 weeks of gestation have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for severe impairment [1].

The incidence and mortality rate of preterm birth will be reviewed here. The risk and pathogenesis of preterm birth and complications of prematurity are discussed separately. (See "Risk factors for preterm labor and delivery" and "Pathogenesis of spontaneous preterm birth" and "Short-term complications of the premature infant".)

DEFINITIONS — Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birthweight (BW).

One classification based upon BW includes the following categories (table 1):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

This classification based upon BW is primarily used in this review.

BW percentiles have been established for the appropriate GA (table 2).

Prematurity is also defined by gestational age (GA) as follows:

- Late preterm infants — GA between 34 weeks and 36 weeks and 6 days
- Very premature infants (VPT) — GA at or below 32 weeks
- Extremely premature infants (EPT) — GA at or below 25 weeks

INCIDENCE — Approximately 550,000 premature infants are born each year in the United States. In 2008, about 12.3 percent of all live births were <37 weeks GA and 2 percent <32 weeks GA (figure 1) [2,3]. Low birth weight (LBW) infants accounted for 8.2 percent of live births in both 2007 and 2008 [2].

In the United States, there has been a 21 percent rise in the overall proportion of preterm births since 1990, which peaked in 2006 with 12.8 percent of all live births born at a GA <37 weeks. This increase over the last two decades is reflected in all stages of prematurity as follows [2]:

- The birth rate of late preterm infants has risen by 25 percent since 1990. The percentage of late term birth peaked at 9.1 percent in 2006, and has slightly declined to 8.8 percent in 2008.

- The percentage of low birth weight (LBW) infants has increased in the United States from 6.7 percent in 1984 to 8.3 percent in 2006, and slightly declined to 8.2 percent in 2007 and 2008.
- The percentage of very low birth weight (VLBW) has increased from 1.2 percent in 1980 to 1.5 percent in 2006, and was unchanged in 2007 and 2008 .

In Norway, a population-based report of all live births in 1999 and 2000 reported an incidence of 0.5 percent of ELBW infants born between 22 and 27 weeks GA [4].

Multiple gestation and ART — In the United States, a major reason for the increased incidence of premature birth is the higher rate of multiple gestations in part due to assisted reproductive technology (ART). Infants of multiple gestation are prone to delivery early; half of all twin births and >90 percent of triplets are born premature. In 2007, 57 percent of twins and nearly all triplets (96 percent) were LBW [2].

- **Twin births** — In the United States, the twin birth rate reached a record high of 32.2 twins per 1000 total births in 2004, which has remained stable from 2004 to 2007. There has been a 70 percent increase in the twin birth rate from 1980 to 2004 [2].
- **Higher-order multiple births** — In contrast, the triplet and higher-order multiple births rate has declined 21 percent from a peak of 193.5 per 100,000 births in 1998 to 148.9 per 100,000 births in 2007 [2]. This is partly due to the American Society of Reproductive Medicine recommendation to limit the number of embryos transferred. (See "Multiple births" and "Strategies to control the rate of high order multiple gestation".)

Ethnicity — The incidence of premature births varies among ethnic groups. In 2007, the percentages of live births in the United States that were preterm by ethnicity were 17.5, 12.1, and 11.1 in non-Hispanic blacks, Hispanics, and non-Hispanic whites, respectively [2]. A higher rate of low birth weight infants in minority populations also occurs in England, with reported percentages of low birth weight live births of 11.5, 9.4, and 5.4 percent in Asian, black, and white mothers [5].

PATHOGENESIS FOR PRETERM BIRTH — Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3).

The four primary causes that lead to preterm labor and delivery are as follow and are discussed in detail separately. (See "Pathogenesis of spontaneous preterm birth".)

- Activation of the maternal or fetal hypothalamic-pituitary-adrenal axis
- Infection
- Decidual hemorrhage
- Pathological uterine distention

Risk factors for preterm birth — Risk factors associated with preterm labor and delivery include the following sociodemographic and obstetric factors, which are reviewed separately (table 4). (See "Risk factors for preterm labor and delivery".)

- **Maternal reproductive factors** such as history of preterm birth and maternal age. A U-shaped relationship exists between maternal age and the frequency of preterm birth. Women under 16 and those above 35 have a 2 to 4 percent higher rate of preterm birth compared with those between 21 and 24 years of age [6]. Among non-Hispanic black women, the upper age with an increased risk of preterm delivery is lower with preterm birth rates increasing at 27 to 29 years of age compared to 33 to 35 years of age for non-Hispanic white women.
- **Maternal disorders** such as infection, anemia, hypertension, preeclampsia/eclampsia, cardiovascular and pulmonary disorders, and diabetes.
- **Maternal lifestyle issues** such as physical activity, history of substance abuse or smoking, diet, weight, and stress.
- **Cervical, uterine, and placental factors** such as short cervix, cervical surgery, uterine malformations, vaginal bleeding, and placenta previa or abruption.

- Multiple gestation
- Fetal factors such as presence of congenital anomalies, growth restriction, fetal infections, and fetal distress.

MORTALITY — Low birth weight and prematurity are major contributors to infant mortality. In the yearly analysis from the National Center for Health Statistics that links all birth and infant deaths (through the first year of age) in the United States, birth weight less than 2000 g was associated with 61 percent of infant deaths in 2005 [1].

Factors that cause variation in premature mortality rates include:

- Degree of prematurity — Mortality rises with increasing immaturity (ie, decreasing birthweight and gestational age)
- Maternal ethnicity
- Level of neonatal care
- Congenital anomalies

Gestational age and birth weight — Mortality rates amongst premature infants correlate with birthweight and gestational age with decreases in both associated with poorer survival [1,4]. Thus infants born with the lowest gestational age and birthweight have the largest impact on infant mortality because they have the greatest risk of death. As an example, although infants who weigh less than 1000 g account for only 0.8 percent of births in the United States, they accounted for 55 percent of all infants deaths in 2005 [1].

In 2004, infant mortality rates per 1000 live births based upon birth weight were as follows (figure 2) [7]:

- 2500 g — 2.3
- < 2500 g — 56
- < 1500 g — 245
- < 500 g — 850

A similar relationship with increasing mortality rates per 1000 live births and decreasing gestational age (GA) was also noted:

- 37 to 41 weeks GA — 2.43
- 34 to 36 weeks GA — 7.3
- 32 to 33 weeks GA — 17
- Less than 32 weeks — 183

Mortality data for infants born at or below 25 weeks gestation who are at the limit of viability are reviewed separately. (See "Limit of viability".) Overall, more than two-thirds of infant deaths occur during the neonatal period defined as less than 28 days of age. The risk of dying within this neonatal period increases with decreasing gestational age. In addition, lower birth weights due to fetal growth restriction increase mortality at a given gestational age in premature infants born at or below 31 weeks gestation [8]. (See "Small for gestational age infant", section on 'Mortality'.)

Extremely preterm infants — Although infants born at or before 25 weeks of gestation have the highest mortality rate, about 50 percent [9-11], it appears that the survival rate of infants between 24 and 26 weeks gestation has improved with advances in neonatal care [10,11]. (See 'Trends over time' below and "Limit of viability".)

Risk factors for death or severe neurosensory impairment in extremely low birth weight (ELBW) infants (birth weight less than 1000 g) include bronchopulmonary dysplasia, brain injury, severe retinopathy of prematurity, and infection (eg, meningitis, sepsis, and necrotizing enterocolitis) [12]. (See "Short-term complications of the premature infant" and "Long-term neurodevelopmental outcome of premature infants".)

Late preterm infants — Late preterm infants (born between 34 weeks, and 36 weeks and 6 days gestation) are an "at risk population" with a three to five-fold greater risk of mortality than term infants. The mortality of later preterm infants is discussed separately. (See "Late preterm infants", section on 'Mortality'.)

Ethnicity — Mortality rates of premature infants vary among ethnic groups as demonstrated by infant mortality data from the United States in 2004 (figure 3) [7]. The highest mortality rate is in black infants at any given gestational age or birthweight compared to other ethnic groups.

For example, the infant mortality rates per 1000 live births for premature infants with birth weights <1500 g (very low birth weight infants) based upon maternal ethnicity were as follows:

- Overall — 244.5
- White — 231.9
- Black — 274
- Asian or Pacific Islander — 222.7

Similar differences in infant mortality rate based upon gestational age were reported among ethnic groups. The infant mortality rates per 1000 live births for premature infants with gestational age <32 weeks based upon maternal ethnicity were as follows:

- Overall — 182.5
- White — 168.4
- Black — 216.2
- Asian or Pacific Islander — 173.2

Health care disparities may in part explain the higher mortality rate of black infants versus other ethnic groups [13].

Level of neonatal care — Variation in neonatal care impacts on mortality rate and include:

- Changes in care over time with the introduction of new therapeutic interventions and changes in management.
- Delivery of care based upon hospital resources and experiences.

Trends over time — Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality rates of preterm infants, except in those who are at the limit of viability [10,14-17]. (see "Antenatal use of corticosteroids in women at risk for preterm delivery", section on 'Evidence of clinical efficacy' and "Treatment and complications of respiratory distress syndrome in preterm infants" and "Limit of viability")

This was demonstrated by the improved survival rate for VLBW infants (birth weights between 500 and 1500 g) reported by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network over four time periods (74, 80, 84, and 85 percent in 1988, 1990 to 1991, 1995 to 1996, and 1997 to 2002) [14,15]. However, there was little change in the survival rate of infants with birth weights between 501 and 750 g (about 55 percent) from the time periods between 1995 to 1996, and 1997 to 2002 [15].

In a study of extremely premature infants defined as GA at or below 25 weeks born in the Trent region of Great Britain, survival rates were compared from 1994 to 1999 and 2000 to 2005 [10].

- Survival rates increased from 24 to 41 percent in infants with GA of 24 weeks and from 52 to 63 percent in those with GA of 25 weeks.
- There was no change in the survival rate of infants with GA of 23 weeks between the two study periods (18 versus 19 percent).
- None of the 261 infants at or below 22 weeks gestation survived to discharge from the hospital during the entire study period from 1994 to 2005.

A regional population-study of two birth cohorts separated by 20 years (1985 to 1986, and 2005 to 2006) also demonstrated increased survival without severe neurodevelopment impairment [16].

Standard of neonatal care — Survival rates for VLBW infants are higher in centers that deliver a high volume of VLBW infants and provide the highest level of neonatal care (ie, level 3 neonatal intensive care unit [NICU]), as illustrated by the following:

- In a study from California that linked birth and death certificate data from 48,237 VLBW infants born between 1991 and 2000 [18], the highest survival rates for VLBW were in hospitals that had a level 3 NICU and an annual delivery rate of VLBW infants greater than 100 deliveries. In comparison, the lowest survival rate occurred in hospitals with level 1 care (no NICU) and an annual delivery rate of VLBW infants less than 10 (OR 2.72, 95% CI 2.37-3.12).
- A meta-analysis of 41 articles including the above study demonstrated a risk-adjusted increased death rate for VLBW and VPT (gestational age ≤ 32 weeks) infants born at centers without a level 3 NICU compared with those born centers with a level 3 NICU [19]. Calculated risk-adjusted odds ratio based on data from studies determined to be of adequate or high quality demonstrated higher mortality rates for infants born in non-level 3 hospitals for VLBW (adjusted OR, 1.62, 95% CI, 1.44-1.83) and VPT infants (adjusted OR, 1.55; 95% CI, 1.21-1.98). Unadjusted pooled mortality rates comparing infants born at non-level 3 centers to those born at level 3 centers were 38 versus 23 percent in VLBW infants and 15 versus 17 in VPT infants. Subgroup analysis of ELBW infants demonstrated similar results with increased death rates for those born at a non-level 3 center for both unadjusted mortality (59 versus 32 percent) and calculated risk-adjusted odds ratio (adjusted OR 1.8; 95% 1.31-2.46).

These results support perinatal regionalization with maternal transport of women at-risk to deliver a VLBW infant to a center that delivers a high volume of VLBW infants and provides level 3 neonatal care.

In the United States, about three-quarter of VLBW infants are admitted to a NICU based on representative data from 19 states [20]. Data did not distinguish between infants admitted at the facility of birth and those who were transported to a NICU from another facility. Using multivariate analysis, preterm delivery, multiple births, and cesarean delivery were associated with a greater likelihood of NICU admission among VLBW infants.

Substandard neonatal care is associated with increased mortality. A case-control study of the Confidential Inquiry into Maternal and Child Health Program (CEMC) in Great Britain, which matched all neonatal deaths (excluding those due to lethal malformations) in infants born at 27 to 28 weeks gestation in the United Kingdom during a two year period (1998 to 2000) with randomly selected survivors, showed increased infant mortality was associated with substandard neonatal care and early neonatal factors including fetal compromise but not maternal characteristics [21]. Areas where poor neonatal care were associated with an increased risk of dying included:]

- Hypothermia — Infants who died were more likely to be hypothermic (temperature $\leq 36^{\circ}\text{C}$) on admission to the neonatal intensive care unit (NICU) (73 versus 59 percent).
- Substandard ventilatory and cardiovascular management — Infants who died compared to survivors received substandard ventilatory (20 versus 7 percent) and cardiovascular care (15 versus 7 percent). Substandard care was defined as a failure to monitor or properly document blood gases and/or blood pressure, and make therapeutic adjustment to maintain blood gases and/or blood pressure within standard limits.

Congenital anomalies — Premature infants with major congenital anomalies have higher mortality and morbidity rates. In a study from the NICHD Neonatal Research Network, ELBW infants with congenital anomalies (eg, cardiac, renal, central nervous system anomalies, and chromosomal abnormalities) who survived the first 12 hours of life compared to those without any congenital abnormality had a higher mortality rate in the first 18 to 22 months of corrected age [22]. Premature survivors with major congenital anomalies were twice as likely to have neurodevelopmental impairment, have poor growth, and were at three-time greater risk of rehospitalization when compared with ELBW infants without major anomalies.

Time of death — In VLBW infants, about 50 percent of deaths occur in the first three days after delivery. This was illustrated by a study based on information from the National Inpatient Sample Database from 1997 to 2004

that included 115,350 VLBW infants [23]. Patients with congenital anomalies were excluded from the analysis. In this cohort, the distribution of birth weights was 10.6, 18.4, 16.9, and 54.1 percent for infants weighing <500 g, 500 to 749 g, 750 to 999 g, and 1000 to 1499 g, respectively. The following findings were noted:

- The overall survival rate was 77.5 percent. On the first day, 35 percent of the deaths occurred. By the end of the first three days and the 28th day, 58 and 90 percent of the deaths occurred.
- Deaths were more frequent for ELBW infants during the first day of life. Morality increased with decreasing birth weights as follows:
- For infants with birth weights <500 g, only 8 percent survived. Most of the deaths (72 percent) occurred in the first day of life and by the end of the third day 86 percent of deaths had occurred.
- For infants born between 500 and 749 g, the overall mortality rate was 49.2 percent, with 19.6 and 31.4 percent mortality at the end of the first and third day of life.
- For infants born between 750 and 1000 g, the overall mortality was 14.9 percent, with 3.1 and 6.4 percent mortality at the end of the first and third day of life.

In a study from the NICHD of 9575 VLBW infants, the overall mortality rate was 28 percent, and the highest mortality rate occurred in the first 12 hours of life [24].

Long-term mortality — Survivors of prematurity beyond the first year of life still remain at risk for early death compared to those born at term. In a population-based study from Norway of over one million individuals born between 1967 and 1988 and followed through 2002, those born prematurely (5.2 percent of the overall group) had an increased risk of death throughout childhood compared to individuals born full-term [25]. Mortality rates were greater for those born extremely premature (gestational age 22 to 27 weeks) and were generally higher for boys compared to girls at the same gestational age.

SUMMARY AND RECOMMENDATIONS

- Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. Premature infants are classified by birth weight or gestational age (table 1 and table 2). (See 'Definitions' above.)
- In the United States, about 12 to 13 percent of live births are premature and about 2 percent are born at a gestational age less than 32 weeks (figure 1). There has been a 21 percent rise in the overall proportion of preterm births since 1990, which is reflected in all stages of prematurity. Part of this increase in premature births is due to the increase of infants with multiple gestations. (See 'Incidence' above.)
- Approximately 80 percent of preterm deliveries occur spontaneously as a result of preterm labor (50 percent) or preterm rupture of membranes (30 percent); intervention for maternal or fetal problems account for the remaining 20 percent (table 3). The four primary causes that lead to preterm labor and delivery are activation of the maternal or fetal hypothalamic-pituitary-adrenal axis, infection, decidual hemorrhage, and pathological uterine distention. (See "Pathogenesis of spontaneous preterm birth".)
- Risk factors associated with preterm birth include obstetric and sociodemographic factors (table 4).(See "Risk factors for preterm labor and delivery".)
- Low birth weight and prematurity are major contributors to infant mortality. In the United States, prematurity was associated with approximately 37 percent of infant deaths. (See 'Mortality' above.)
- Increased mortality rates in premature infants are associated with the following:
- Increasing immaturity (ie, decreasing birthweight and gestational age) (See 'Gestational age and birth weight' above.)
- Hospitals with lower levels of resource and experience in delivering neonatal intensive care (See 'Standard of neonatal care' above.)
- Congenital anomalies (See 'Congenital anomalies' above.)
- Improvements in newborn intensive care, including the use of surfactant treatment and antenatal steroid therapy to prevent and treat neonatal respiratory distress syndrome, have resulted in decreased mortality

rates of preterm infants, except in those who are at the limit of viability. (See 'Trends over time' above and "Limit of viability".)

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Sudden infant death syndrome

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DEFINITION — Sudden infant death syndrome (SIDS), also called crib or cot death, is the leading cause of infant mortality between 1 month and 1 year of age in the United States. It is defined as the sudden death of an infant younger than 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history [1,2]. The cause of SIDS cannot be identified in most cases. Since the 1990s, however, new studies in pathology and epidemiology have provided the basis for an important evolution in the understanding of SIDS.

In 1991, the definition of SIDS was revised by an expert panel convened by the National Institute of Child Health and Human Development [2]. The new definition differs from the previous description (from 1969) in several important ways:

- It omits the phrase that the death was "unexpected by history." This change reflects one of the most significant lessons of SIDS research in the 1990s: SIDS victims were not entirely normal before death.
- The new definition emphasizes the necessity of autopsy, death scene investigation, and review of the clinical history to provide accurate counseling to parents.

Development and implementation of death scene [3] and autopsy [4] protocols have led to standardized approaches to unexpected infant deaths with increasing diagnoses of accidental asphyxia. Specific steps (external examination, radiology, internal examination, histology, microbiology, toxicology, electric, metabolic, and genetic studies) in the evaluation of unexpected infant deaths have contributed to increased accuracy in the diagnosis of SIDS, a diagnosis of exclusion [5]. A known cause of death is identified by the postmortem examination in approximately 15 percent of suspected SIDS cases, even when the clinical history and circumstances of death are consistent with SIDS (table 1) [6]. It is impossible, for example, to detect some congenital abnormalities, injuries, infections, or metabolic defects without an autopsy. Similarly, the death scene investigation is essential to exclude accidental, environmental, and unnatural mechanisms of death [7-10].

The diagnosis of SIDS must be consistent with the child's medical and family history:

- A family history of a previous SIDS death, the presence of undiagnosed neurologic problems, or a past history of failure to thrive or hypotonia warrants further investigation to exclude inherited metabolic diseases.
- A prior history of multiple dramatic episodes of unexplained apnea, cyanosis, or seizure may suggest deliberate asphyxiation, so-called Munchausen syndrome by proxy, an insidious form of child abuse [11]. (See "Munchausen syndrome by proxy (medical child abuse)".)

Due in part to potential inconsistencies in the diagnosis of SIDS, the term "sudden unexpected death in infancy" (SUDI) is often used to describe all unexpected infant deaths. The SUDI designation can then be sub-divided into explained SUDI and unexplained SUDI. Unexplained SUDI generally includes those cases considered SIDS by the medical examiner, as well as some cases that are not considered SIDS, but lack a clear explanation due to

uncertain circumstances. Reports in the literature increasingly use the term "unexplained SUDI" instead of "SIDS" to avoid inconsistencies between medical examiners in reporting SIDS as a cause of death.

EPIDEMIOLOGY — SIDS is the leading cause of infant mortality between 1 month and 1 year of age in the United States. The risk of SIDS in the United States is <1 per 1000 live births [12-14]. Higher rates (two to three times the national average) are found in black and American Indian/Alaskan native children [15,16]. A disproportionately high rate (15 to 20 percent) of SIDS cases occur in child care settings [16-18]. The risk of SIDS is slightly increased in boys (multivariate OR 1.49 (95%CI 1.14-1.83) in one large European case-control study) [19].

The incidence of SIDS in the United States has declined by more than 50 percent since the mid-1980s. The greatest reduction has occurred since 1992, when the American Academy of Pediatrics (AAP) issued a recommendation to reduce the risk of SIDS by placing infants in a supine position for sleep [20-24]. Between 1992 and 2001, the SIDS rate in the United States fell from 1.2 to 0.56 per 1000 live births [25,26]. Similar declines have occurred in other countries following Back to Sleep campaigns [27,28].

Data from the National Institute of Child Health and Human Development (NICHD) Collaborative SIDS Study have helped to define the epidemiologic features of SIDS (table 2) [29]. This landmark study was a multicenter, population-based, case-controlled project that included 10 percent of the live births in the United States. The pathologic diagnoses were confirmed by an independent panel of forensic pathologists.

In the NICHD study, the median age for SIDS deaths was 11 weeks, the peak incidence was between 2 and 4 months, and 90 percent occurred before 6 months of age [29]. A few sudden unexpected deaths resembling SIDS have been described within the first 24 hours of life [30]. This unique distribution strongly suggests that critical stages of development or maturation affect the risk of SIDS. The most important conclusion from this study was that no strong predictive and/or diagnostic characteristics of mothers or infants can be identified in most SIDS victims that would permit clinically useful screening for high-risk infants.

RISK FACTORS — Numerous risk factors for SIDS have been identified in observational and case control studies. Those that are consistently identified as independent risk factors include [16]:

- Young maternal age
- Maternal smoking during pregnancy
- Late or no prenatal care
- Preterm birth and/or low birth weight
- Prone sleeping position
- Sleeping on a soft surface
- Overheating

More than 95 percent of SIDS cases are associated with one or more risk factor, and in most cases, the risk factors are modifiable (usually sleeping position or environment or parental smoking) [31]. Risk factors for SIDS are discussed below. Those that can be modified to decrease the risk of SIDS are also discussed in the section on Prevention. (See 'Prevention' below.)

Maternal risk factors — There are two major maternal risk factors for SIDS that are independent of birth weight [19,29]:

- Maternal smoking
- Age of the mother under 20 years

These factors increased the risk of SIDS two to four-fold in the NICHD Collaborative SIDS Study [29].

Maternal smoking usually occurs both prenatally and postnatally, and it is unclear whether smoking during a specific developmental period is particularly harmful [32]. SIDS rates increase with the amount smoked [33,34]. Smoking is one of the most important preventable risk factors for SIDS, and smoking prevention/intervention programs have the potential to substantially lower SIDS rates [33,35]. Several studies have shown abnormal

cardiovascular responses to stimuli (eg, head-up tilt, hypoxemia, or CO₂ exposure) and impaired arousal to stimuli in infants born to mothers who smoked during pregnancy, suggesting a possible mechanism for this association [36-40].

Drug abuse and all its associated phenomena are also associated with an excessive number of SIDS deaths. In one report, a five-fold increase in SIDS risk was reported for infants of substance-abusing mothers in the Los Angeles area [41]. It is not known if this association is related primarily to the biologic effect of drugs in utero, an increased risk of prematurity and low birth weight, and/or other postnatal conditions (socioeconomic, environmental, or parenting behavior).

Maternal alcohol use is an important risk factor for SIDS in some populations. In a population-based case-control study among Northern Plains American Indians, SIDS was significantly associated with periconceptional maternal alcohol use (adjusted odds ratio 6.2, 95% CI 1.6-23.3) and first trimester binge drinking (adjusted OR 8.2, 95% CI 1.9-35.3) [42].

Pregnancy complications associated with an increased risk of SIDS include placenta previa, abruptio placenta, premature rupture of membranes, and elevated maternal alpha-fetoprotein [14,43-45]. The increased risk associated with these complications appears to be independent of their relationship with preterm birth.

Prematurity — Preterm infants are at a higher risk for SIDS than term infants [46-49]. Among low and very low birth weight infants, the SIDS rate has consistently been three- to fourfold higher than in term infants [49]. The postmenstrual age of peak vulnerability for SIDS appears to occur four to six weeks earlier among preterm than term infants [46].

It is unclear whether the population of low birth weight infants is experiencing a decline in the rate of SIDS similar to that in the general population. A similar decline was noted in New Zealand [48], but not in Sweden [50]. Preterm infants are subject to the same risk factors for SIDS as term infants, as discussed in greater detail below [48,51,52].

Supine positioning for sleep substantially reduces the risk for SIDS among premature infants. Although there are some concerns that supine positioning may reduce oxygenation in premature infants, two small studies have suggested that this may not be the case, at least among infants no longer in the acute phase of a respiratory illness [53,54].

The importance of supine sleep position for premature infants was demonstrated in a population based case-control study in England, in which the parents of 325 SIDS cases and 1300 age-matched control infants were interviewed [51]. In multivariate analysis, infants who were small at birth (<37 weeks and/or <2500 g) were five times more likely to die of SIDS than infants who were born at term or >2500 g. However, when infants who were small at birth were placed to sleep on their side or prone, they were 15 and 24 times more likely, respectively, to die of SIDS than infants who were not small at birth who were placed on their backs to sleep.

Apnea — Apnea or otherwise impaired respiratory function likely falls within the final common pathway of many of the proposed mechanisms for SIDS. However, the observation of apnea, apparent life-threatening event (ALTE), or other abnormalities in breathing patterns are not clinically useful predictors of SIDS risk, and monitoring for apnea using standard cardiorespiratory monitors does not reduce SIDS risk.

This was illustrated by the following studies:

- In case-control studies, a history of apnea or cyanosis is not specifically increased in SIDS victims [29]. Approximately 5 percent of parents of SIDS victims recall cyanotic episodes during the months before death, but this not substantially different from parent recall of cyanotic episodes in control infants, and may be influenced by recall bias.
- Prospective studies have failed to identify respiratory abnormalities that correlate with known SIDS risk factors: in a large series of infants followed longitudinally with cardiorespiratory monitors, neither "conventional" (apnea 20 to 30 seconds) nor "extreme" events (apnea >30 seconds) correlated with the

primary epidemiologic risk factors for SIDS, including time of night of the apnea and the infant's age [55]. (See "Management of apnea of prematurity".)

Low birthweight — Infants born small for gestational age (SGA) have an increased risk for SIDS [14,51,56]. Low birthweight has a weak but significant association with SIDS risk even after adjustment for gestational age and several other factors known to be associated with low birthweight, including maternal tobacco use and hypertension.

Sleep position — The prone sleeping position has been found to be associated with an increased risk of SIDS in a number of observational and case-control studies [19,57-62]. Additional support for this association comes from the decreased rate of SIDS in various countries following recommendations to place infants on their back or side to sleep [21,25,26,63-65].

Increasing evidence also suggests that avoidance of side positioning is important, perhaps because the probability of rolling from the side to the prone position is greater than that of rolling from the supine to the prone position [66-68]. (See 'Epidemiology' above.) As the proportion of infants placed to sleep in the prone position has decreased, the relative contribution of side-sleeping to SIDS risk has increased [51,66,69-72], as suggested by the following studies:

- In a population-based case-control study, the risk of SIDS was increased for infants placed on the side and found in the prone position (adjusted odds ratio 8.7) [70]. In the same study, the risk of SIDS was also increased among infants who were usually placed supine but were placed on their sides or prone for the last sleep (OR 6.9 and 8.2, respectively) [70].
- Other case-control studies have demonstrated an increased risk of SIDS when infants unaccustomed to the prone position are placed in the prone position [73,74].
- A population-based study noted decreases in SIDS mortality associated with non-prone sleep positioning, and documented further decreases associated with specifically supine positioning of infants for sleep [75].
- Use of infant "sleep positioners" to position infants on their side has also been associated with several cases of infant deaths, as reported in a safety alert by the United States Food and Drug Administration (FDA) [76].

The increased risk among infants unaccustomed to the side or prone position highlights the importance of supine positioning for every sleep [16].

Sleep environment — Various aspects of the sleep environment, including the sleep surface, sleepwear, bedding, room temperature, and whether or not the bed or room are shared with parents also appear to affect the risk of SIDS, as illustrated below.

- In a case-control study, soft cot mattresses were associated with a twofold increased risk of SIDS that was independent of the prone position [77]. Other forms of soft bedding (eg, polystyrene beads, natural fiber mattresses) also have been associated with an increased risk of SIDS [78,79]. Sheepskin bedding has been associated with an increased risk for SIDS when infants are placed in the prone position [80,81]. The risk sheepskin bedding presents to infants sleeping in the supine or lateral positions is less clear. There are reports of deaths by "suffocation" attributed to crib bumper pads [82], prompting the Canadian Pediatric Society to caution against their use [83].
- In a population-based case-control study performed in California, fan use was associated with a 72 percent reduction in SIDS risk (adjusted odds ratio 0.28, 95% CI 0.10 - 0.77) [84]. The effect was greater for infants with other environmental SIDS risk factors, including prone or side sleeping, bed sharing, and warmer room temperature. The study was limited by low participation rates and recall bias, and needs confirmation by prospective studies.
- In a population-based case-control study among Northern Plains American Indians, SIDS was significantly associated with two or more layers of clothing on the infant (adjusted OR 6.2, 95% CI 1.4-26.5) [42]. Another study noted an increased risk with swaddling or in heated rooms [79].
- Whether swaddling infants increases or decreases the risk for SIDS is unclear, and may depend on sleeping position. Swaddling increases the risk for SIDS associated with prone sleeping position [79], whereas limited evidence suggests that swaddling in the supine position does not increase SIDS risk,

and might actually be protective [85]. This may be because swaddling keeps the infant in the unsafe or safe sleeping position, respectively. Swaddled infants are less likely to be aroused by external stimuli, but this effect is not seen in infants who are routinely swaddled and it is unclear if it is clinically relevant in infants who are in the supine position [86,87].

- A reported association between SIDS risk and infants sharing a bed with their parents has proven controversial [24,88-90]. However, there does appear to be an association at least for younger infants (eg, younger than 4 months of age) [19,91-95], or if the mother smokes [16,19,66,93]. There is a consistent association between increased risk of SIDS and sharing a couch or sofa with parents [16,27,91,92,96,97]. Based on these findings, the AAP suggests that bed-sharing be avoided, although room-sharing is encouraged [16].
- Room sharing, without bedsharing, between parents and infants appears to reduce the risk of SIDS [19,91,92,96,97]. In addition, the risk associated with sleeping in the prone position appears to be mitigated if the child is sharing a room with an adult. In a case-control study from New Zealand in which 393 infants who died from SIDS were compared to 1592 controls, the relative risk associated with sleeping in the prone position was reduced by approximately 80 percent if the infant slept in the same room as an adult [98]. A similar reduction in the risk of SIDS was not seen if the infant shared a room with another child.

Pacifier use — Use of a pacifier ("dummy", "soother") during sleep appears to reduce the risk of SIDS. This was shown in a meta-analysis of seven studies, in which the multivariate summary odds ratio was 0.71 [95% CI 0.59-0.85] for usual pacifier use, and 0.39 [95% CI 0.31-0.50] for pacifier use during last sleep [99]. The mechanism for this association is unclear; it may be related to the lowered arousal threshold during pacifier use [100,101]. (See 'Pathology and pathogenesis' below.) Because of this apparent reduction in risk, the AAP suggests offering a pacifier during sleep, provided that it does not interfere with establishment of breast feeding [16].

Breastfeeding — The association between breastfeeding and risk of SIDS is inconsistent [71,96,102-106] and is complicated by confounding factors (eg, maternal age, smoking) [107-111].

Immunizations — SIDS is not associated with diphtheria-tetanus-pertussis (DTP) vaccine or other vaccines [112-114]. In fact, immunization may lower the risk of SIDS [115-117].

Sibling of SIDS victim — Siblings of SIDS victims have a five- to six-fold increase in risk for SIDS [118-121]. However, assuming a SIDS rate of 0.56 per 1000 live births (0.06 percent) [25,26], the risk in subsequent siblings for most families remains less than 1 percent.

The small but increased risk of SIDS in siblings of SIDS victims is probably due to a combination of biologic and/or epidemiologic factors. However, it has not been possible to identify the relative importance of these factors because many of the risk factors for SIDS are the same as those for other causes of infant mortality [118]. In some cases, for example, deaths from inborn errors of metabolism may have been mistaken for SIDS. In other cases, the deaths may have resulted from child abuse or were in some way related to severe deprivation and poverty [122]. (See 'Differential diagnosis' below.)

Twins — In cohort studies, linking data from birth and death records, the crude risk of SIDS among twins is approximately twice that of singletons [12,13,123]. The increased risk is in part attributable to the higher proportion of twins that are preterm and/or of low birth weight [12,13]. However, in subset analyses of some studies, the risk of SIDS among twins born at ≥ 37 weeks gestation [123] or with birth weight ≥ 3000 gm [13], remained increased compared to singletons as described below:

- 37 to 38 weeks: Relative risk (RR) 1.31
- 39 to 40 weeks: RR 1.47
- ≥ 41 weeks: RR 2.09
- Birthweight ≥ 3000 g: RR 2.98

PATHOLOGY AND PATHOGENESIS — SIDS is characterized by several gross and microscopic autopsy features, even though none of these abnormalities is sufficiently grave to explain the infant's death (table 3) [5]. External findings include a well-developed, well-nourished child with frothy, blood-tinged fluid at the nares.

Internal findings include intrathoracic petechiae, pulmonary congestion and edema, upper respiratory tract inflammation, and hepatic hematopoiesis.

A triple-risk model has been proposed, suggesting that SIDS occurs in infants with underlying vulnerability (eg, genetic pattern, brainstem abnormality) who experience a trigger event (eg, maternal smoking, infection), at a vulnerable developmental stage of the central nervous or immune system [124-126].

Underlying vulnerability

Brain abnormalities — Emerging evidence suggests that underlying abnormalities in serotonin (5HT) signaling in the brain play a role in the pathogenesis of SIDS. These abnormalities could be either genetic in origin, or acquired from exposures in utero.

Several studies have shown subtle alterations or "delayed maturation" in the arcuate nucleus and other regions of the brain that participate in ventilatory and blood pressure responses to hypoxia and hypercarbia [127-130]. More recently, specific abnormalities of serotonin signaling have been shown, including decreased 5-HT(1A) receptor binding in the medullary areas of infants who succumbed to SIDS [131-133]. Male infants had particularly low binding, consistent with the clinical observation of a male predominance in SIDS cases [132]. Affected infants appear to have a deficiency in serotonin and its key biosynthetic enzyme, tryptophan hydroxylase, in the medulla [133]. Because serotonin signaling in the medulla is known to influence a broad range of autonomic processes, these findings are consistent with the hypothesis that SIDS is related to serotonin-mediated dysregulation of the autonomic nervous system.

In the study cited above [133], 95 percent of the infants dying of SIDS had one or more additional risk factors for SIDS (eg, prone position, intercurrent illness before death, male sex, or prematurity), and 88 percent had two or more risk factors. These observations underscore the notion that SIDS results from the simultaneous occurrence of multiple events.

All of the studies relying on brain tissue from autopsies are limited by small sample size and underrepresentation of some racial or ethnic groups in the sample. Similar studies in other populations will be necessary to confirm these findings and to determine if similar abnormalities are found in other populations with high risks for SIDS, such as African American infants.

Several other brain abnormalities have been reported in some SIDS victims. These include delayed maturation of the central nervous system, periventricular and subcortical leukomalacia, brainstem gliosis, increased brain weight, and alteration in the density of dendritic spines [134]. In autopsy studies, the density of kainate and muscarinic receptors in the arcuate nucleus (which mediate ventilatory responses in animal models) were decreased in more than one-half of SIDS victims studied versus controls [127,135].

Together, these findings support the concept that a brainstem abnormality or maturational delay related to neuroregulation or cardiorespiratory control is a critical contributor to the pathogenesis of SIDS. This hypothesis is supported by two additional findings:

- Maternal and antenatal risk factors indicating a less than optimal intrauterine environment have been described for infants who later died of SIDS [29,136,137]. These observations suggest that the presumed brain disorder may originate before birth (see 'Maternal risk factors' above).
- Subtle abnormalities in the regulation of cardiac, respiratory, and sleep arousal patterns have been observed in infants who subsequently succumbed to SIDS [138,139].

Genetic factors — The role that genetic factors play in susceptibility to SIDS is not clear. On the one hand, the overall low rate of SIDS in siblings, the lack of concordance in twins, and the finding that like-sex twins are at no greater risk than unlike-sex twins [12,13] suggest that SIDS is not a genetic disorder. On the other hand, the identification of gene polymorphisms in SIDS victims suggests that specific genetic polymorphisms may interact with specific environmental risk factors to increase the susceptibility to SIDS in critical situations [140,141]. Specific genetic polymorphisms in the following genes have been proposed to play a role in SIDS [140,141]:

- Genes encoding cardiac ion channels [142-145]
- Partial deletions of complement component C4 [146]
- Interleukin-10 promoter gene [147,148]
- Serotonin transporter gene [149-153]
- Testis-specific Y like gene [154], which is expressed in the fetal brain [155]
- Genes encoding heat shock proteins [151]
- Genes involved in the development of the autonomic nervous system [156,157]

Environmental triggers — Little is known about the mechanism of death in SIDS. One report described heart rate and respiratory effort wave form data recorded by memory monitors in three children who died while being monitored and whose autopsies reported SIDS as the cause of death [158]. Bradycardia, not apnea, was the predominant feature in these infants' deaths. One major caveat to interpreting this report is that the home monitors could not have detected obstructive apnea and did not record oxyhemoglobin saturation data.

Prone position — The mechanism for the apparent increase in risk with the prone position is not known. Some studies have suggested a role for suffocation associated with several factors, such as decreased arousal [159-161], hyperthermia, and the type of bedding [66,77-79,162,163].

- In one study of Belgian infants, prone sleep position was associated with longer duration of sleep, longer obstructive events, decreased behavioral arousal, longer interval between obstruction and arousal, and overall decreased reaction (arousal or sigh) to obstructive events [159]. In another study, arousal thresholds during both active and quiet sleep, were higher in infants younger than 5 to 6 months of age [160].
- In another study of 25 infant deaths that occurred during sleep in the prone position on cushions filled with polystyrene beads, accidental suffocation by rebreathing was found to be the most likely cause of death in most of the infants [78]. The cushion was thought to allow limited movement of the infant's head to obtain fresh air, and the estimated amount of subsequent rebreathing was lethal in a rabbit model.
- In a study of 393 cases of SIDS in New Zealand, infants who were found in the prone position with their face down were more likely to be younger, have a low birthweight, and to have used sheepskin bedding or pillows as compared to infants found other positions (prone with face to side, supine, or side) [164]. This finding suggests that infants dying of SIDS in the face down prone position represent a distinct subgroup, and that the mechanism of SIDS may differ depending on specific circumstances related to the infant's sleeping position.

Cardiac dysfunction — Some studies have suggested the control of cardiac function may be abnormal in infants at risk for SIDS, but results have been inconsistent. One large, prospective study found mildly increased heart rates in infants who subsequently died of SIDS [165]. Others have described prolonged QT intervals on electrocardiographic analysis [166] or sodium channel mutations associated with long QT syndrome in post-mortem tissues [167,168]. However, given the limitations of small sample sizes in cross-sectional studies of rare conditions, the incidence and role of cardiac abnormalities in SIDS remains controversial. Based on a study of the prevalence of functionally significant genetic variants associated with Long-QT syndrome, such abnormalities appear to be present in fewer than 10 percent of SIDS cases. (See "Clinical features of congenital long QT syndrome", section on 'Sudden infant death syndrome'.)

Susceptibility to SIDS is complex, and identifying high-risk infants who may be particularly vulnerable to cardiac disturbances is important. Further understanding of individual susceptibility across a broad spectrum of infants is needed to clarify pathogenesis and to develop responsible public health initiatives for SIDS prevention.

Infection — Infection is clearly the cause in a sub-group of explained sudden unexpected deaths in infancy [169]. There has not been convincing evidence of a role for infection as a cause of SIDS. However, similarities between the common autopsy findings and those of toxic shock have raised the possibility for a role for infectious triggers in cases of SIDS even in the absence of a recognizable tissue reaction, which may lead to a toxic shock-like event [170,171]. Implicated organisms include enteric bacteria (enterotoxigenic *S. aureus* and *E. coli*), and mild viral infections [170-172]. Variations in the innate immune system, including polymorphisms that result in an exaggerated pro-inflammatory response, have been found in a higher proportion of SIDS cases than in controls [147,170,173].

Distinguishing between autopsy findings that represent perimortem contamination and those that suggest infection as a trigger for SIDS is challenging and controversial. More than 70 percent of post-mortem bacteriological samples grow organisms when cultured, but this is not sufficient to attribute infection as a cause or trigger for death. However, one well-conducted study found that infants dying of SIDS were more likely to harbor organisms that are potentially pathogenic, as compared with infants dying from clearly non-infectious causes (eg, accidents or congenital heart disease) [174]. The bacterial colonization documented in this study could also be explained as an epiphenomenon, caused by another established epidemiological risk factor for SIDS such as prone sleeping, but not directly implicated as a cause of death.

Developmental timing — SIDS usually occurs between the second and fourth months of life, a period of remarkable developmental changes in cardiac, ventilatory, and sleep/wake patterns in otherwise normal infants. This coincidence of timing suggests that SIDS infants are vulnerable to sudden death during a critical period of autonomic maturation.

DIFFERENTIAL DIAGNOSIS — SIDS is a diagnosis of exclusion; other causes of sudden unexpected death in infancy (table 1) must be considered and excluded before a diagnosis of SIDS can be established. Among these, fatal child abuse and metabolic disease are particularly important, because they have implications for other children in the family.

Fatal child abuse — Fatal child abuse (filicide) is fortunately uncommon, but should be considered when a child dies suddenly and unexpectedly. Although precise figures are lacking, estimates of the frequency of infanticide among cases designated as SIDS range from 1 to 5 percent of such deaths [8,10,175-177].

Most deaths related to child abuse can be distinguished from SIDS by a complete autopsy, death scene investigation, and a review of the medical history [7,178]. However, the autopsy cannot distinguish between accidental or deliberate asphyxiation with a soft object and SIDS [6]. A report in 1990, for example, described 27 children who had been suffocated by their mothers [11]. Of the 33 children previously born into these families, 18 had died suddenly and unexpectedly between one and 36 months of age, including 13 who reportedly died from SIDS. In a chronicle of historical markers and clinical observations associated with life-threatening child abuse from intentional suffocation confirmed by covert video surveillance, one third of the abused infants had siblings whose deaths had been classified as SIDS [176].

Data from The Care of Next Infant programme (CONI), which supports parents who have had an unexpected and apparently unexplained infant death and is available in 90 percent of health districts in England, Wales, and Northern Ireland, were used to estimate the probability that a second episode of sudden unexpected and unexplained death is natural versus unnatural [121]. The following results were noted:

- Among 6373 infants who completed the program between 1988 and 1999, there were 57 deaths (8.9 per 1000); nine were inevitable, and 48 were unexpected; 44 families lost one child and 2 families lost two children.
- Excluding the second death in two families with two deaths, 40 deaths were considered to be natural (including SIDS), five were ultimately considered to be filicide, and one homicide (at the hands of a babysitter).
- Recurrent unexpected deaths among siblings were more often natural (including SIDS) than unnatural (odds ratio 6.7, 95% CI 2.8-19.4).
- The relative risk of recurrence of SIDS in siblings was 5.9, similar to that in other large epidemiologic studies [118-120]. (See 'Sibling of SIDS victim' above.)

Approach — Certain historical features, some of which overlap with inborn errors of metabolism, discussed below, should raise the suspicion of deliberate asphyxiation, but do not confirm it. These include [7]:

- Previous recurrent cyanosis, apnea, or apparent life-threatening event (ALTE) while in the care of the same person
- Age at death older than 6 months
- Previously unexpected or unexplained deaths of one or more siblings
- Previous death of infants under the care of the same unrelated person [11]

- Simultaneous or near-simultaneous death of twins [178]
- Evidence of previous pulmonary hemorrhage (such as marked siderophages in the lung)

Even when suspected, this form of child abuse is extraordinarily difficult to prove. The emphasis on full death scene investigations by appropriately trained individuals and careful review of the clinical and family history will minimize mistakes in ascertainment of the cause and manner of death [121].

Metabolic disease — Inborn errors of metabolism often present in early infancy with life-threatening episodes of metabolic decompensation. Metabolic disease has been shown to play a small (approximately 5 percent) but significant role in the cause of unexpected infant death [179]. In a report that included unexpected deaths in children up to 3 years old, previously undiagnosed metabolic diseases detected by postmortem screening were contributing factors in 1 percent [180].

The most common disorders that can cause sudden death are defects in the metabolism of fatty acids. Since the initial case report of medium chain acyl-CoA dehydrogenase deficiency in a SIDS victim in 1984 [181], more than 13 fatty acid oxidation disorders have been associated with sudden infant death. Some affected infants die during their first episode of fasting intolerance. Abnormal metabolites accumulate in the body tissues and can be identified in the liver, urine, or other body fluids. However, these deaths often meet the criteria for SIDS if appropriate investigations are not performed at the time of autopsy.

The autopsy finding of a fatty liver should raise the suspicion of a fatty acid oxidation disorder. (See "Presenting features of inborn errors of metabolism" and "Overview of the evaluation of inborn errors of metabolism in children", section on 'SIDS and ALTE'.)

Other metabolic diseases associated with sudden death include those related to the degradation of branched chain amino acids, urea cycle disorders, and propionic and methylmalonic acidemias. (See "Overview of maple syrup urine disease" and "Urea cycle disorders: Clinical features and diagnosis" and "Organic acidemias".)

Certain clinical features increase the probability of a metabolic disease as the cause of sudden infant death [182]:

- History of previous SIDS or unexpected death in a sibling (especially if the death occurred in the first weeks or after two years of life).
- Family history of a sibling or cousin with an apparent life-threatening event, Reye's syndrome, or myopathy.
- Symptoms or signs prior to death, such as neonatal hypoglycemia, an apparent life-threatening event, muscular hypotonia, vomiting, failure to thrive, hyperventilation, severe infections, or elevated aminotransferase levels.

Experts recommend that appropriate metabolic investigations be undertaken in all infants who die suddenly and unexpectedly, even if the diagnosis is initially considered to be SIDS [183]. The evaluation for metabolic disease in victims of SIDS is discussed separately. (See "Overview of the evaluation of inborn errors of metabolism in children" and "Presenting features of inborn errors of metabolism", section on 'SIDS or ALTE'.)

MANAGEMENT — The appropriate professional response to the death of any infant is compassionate, empathic, supportive, and nonaccusatory [7,184]. At the same time, it is essential to discover the cause of death, if possible.

Personnel in first response teams should be trained to make observations at the scene such as the position of the infant, marks on the body, body temperature and rigor, type of bed or crib and any defects, amount and position of clothing and bedding, room temperature, type of ventilation and heating, and reactions of the caretakers [7].

In the absence of evidence of injury or significant antecedent illness, the parents can be told that death appears to be due to SIDS. However, other causes can be excluded only after a thorough death scene investigation, postmortem examination, and review of the clinical history have been performed [7]. Parents should understand that these procedures will enable them and their physician to understand why their infant died and how other children in the family, including subsequent children, might be affected [7].

The family is entitled to see and hold the infant once death has been pronounced, if permitted by local protocols and statutes [7]. Many issues including religious support, grief counseling, and reactions of surviving siblings will require attention [185,186]. All parents should be provided with information about SIDS and the telephone number of the local SIDS support group (table 4). When appropriate, parents should be reassured that neither they nor a physician could have prevented their infant's death. It is important to maintain supportive contact with the parents during the time of the investigation. A family's anxiety can be further increased if there is a delay in notification of the autopsy results. In most cases, the parents can be informed promptly of the gross autopsy results without waiting for the microscopic examination [184].

PREVENTION — A number of epidemiologic and physiologic factors are associated with an increased risk for SIDS, but these factors cannot prospectively identify the infant at high risk for SIDS. There are, however, several interventions that can be effective in reducing the risk of SIDS [16,187-189]. Attention to these modifiable risks should begin in the newborn nursery, as sudden unexpected deaths in association with such risk factors have been reported as early as the first day of life [30], and appropriate role modeling by nursery staff has been shown to increase maternal adherence to recommendations [190].

Sleep position and environment — The following recommendations are made by the American Academy of Pediatrics [16], the Canadian Paediatric Society [189], and/or the United Kingdom Department of Health [188,191]:

- All infants, including infants with a history of prematurity, should be placed to sleep on their backs for every sleep, even if they are able to roll from their backs to the prone position [188]. Although earlier AAP policy statements suggested that side sleeping was an acceptable alternative to supine sleeping [23,24], side sleeping is no longer recommended. Prone positioning is encouraged when the infant is awake and observed. Prone positioning facilitates the development of shoulder girdle strength and avoidance of occipital plagiocephaly [24]. (See "Overview of craniosynostosis".)
- The safest place for an infant to sleep is in a crib (cradle, bassinet) in the parents' room for the first six months. Infants should not share a bed during sleep; they should not sleep on or share a sofa, recliner, armchair, or other type of cushioned chair.
- Infant "sleep positioners" should not be used, as described in an FDA Safety Alert [76].
- Maternal smoking during pregnancy and exposure of infants to tobacco smoke should be avoided.
- Infants should be placed to sleep on a firm surface; polystyrene filled cushions and sheepskin bedding should be avoided.
- Soft objects (eg, pillows, stuffed animals) and loose blankets should be kept out of the crib, bassinet, or cradle.
- The infant's head should remain uncovered. If blankets are used, the infant's feet should be placed at the bottom of the crib and the blankets tucked around the mattress to prevent the infant from moving into a position in which the head could be covered by the blanket.
- Overheating should be avoided; the infant should be lightly clothed for sleep; the bedroom temperature should be comfortable for a lightly clothed adult; if the infant is dressed in a sleeper, no more than a thin blanket should be necessary. Infants should not sleep next to a radiator or heater or in direct sunshine.
- The use of a pacifier during sleep may reduce the risk of SIDS. The AAP suggests that the pacifier should be used when placing the infant to sleep, but not reinserted once the infant is asleep [16]. The AAP suggests delaying the introduction of the pacifier until 1 month of age for breastfed infants to ensure that breastfeeding is firmly established [192]. There is some concern that pacifier use may increase the risk of acute otitis media (AOM) [193]. However, the incidence of AOM is relatively low during the first six months of life when the risk of SIDS is greatest. (See "Breastfeeding: Parental education and support" and "Acute otitis media in children: Epidemiology, microbiology, clinical manifestations, and complications" and "Acute otitis media in children: Prevention of recurrence".)
- Commercial devices, marketed to reduce the risk of SIDS, have not been sufficiently tested for efficacy or safety.

Home monitors — There is no evidence to support the role of home cardiorespiratory (CR) monitors in SIDS prevention, and the American Academy of Pediatrics recommends against prescribing home monitors for this purpose [194].

Hypotheses proposed during the 1970s suggested that infants with a history of apnea or an apparent life-threatening event (ALTE) are at risk for SIDS even if they are otherwise asymptomatic, and that death could be prevented by CR monitoring. However, studies done over the past decade have failed to confirm the relationship between SIDS and apnea. Moreover, studies of infants with a history of ALTE and others considered to be at risk for SIDS (such as siblings of SIDS victims) were unable to show any benefit of CR monitoring in preventing SIDS deaths. These issues are discussed in detail separately. (See "Apparent life-threatening event in infants", section on 'Lack of causal relationship between ALTE and SIDS' and "Use of home cardiorespiratory monitors in infants".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Sudden infant death syndrome (SIDS) (The Basics)")
- Beyond the Basics topics (see "Patient information: Sudden infant death syndrome (SIDS)")

SUMMARY AND RECOMMENDATIONS

- SIDS is defined as the sudden death of an infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history. It is the leading cause of infant mortality between 1 month and 1 year of age in the United States. (See 'Definition' above.)
- The mechanism of sudden death is unknown. The most compelling hypothesis involves a brainstem abnormality or maturational delay related to neuroregulation or cardiorespiratory control. The mechanism most likely involves abnormalities of serotonin (5-HT) signaling. (See 'Pathology and pathogenesis' above.)
- A number of risk factors for SIDS have been identified (table 2). These include exposure to cigarette smoke, maternal age <20 years, prematurity, prone sleeping position, soft bedding, and overheating. Apnea of prematurity, although a marker for prematurity, is not a risk factor for SIDS. (See 'Risk factors' above.)
- The appropriate professional response to the death of any infant is compassionate, empathic, supportive, and non-accusatory. At the same time, it is essential to discover the cause of death, if possible. (See 'Management' above.)
- The differential diagnosis of SIDS includes a number of disorders (table 1). Inborn errors of metabolism and child abuse are two important causes to remember, since early recognition may prevent morbidity/mortality in siblings of the index case. (See 'Differential diagnosis' above.)
- Prevention of SIDS entails education of caregivers regarding modifiable risks: supine sleep position for every sleep, elimination of prenatal and postnatal exposure to tobacco smoke, safe sleep environment. The safest place for an infant to sleep during the first six months is in a crib (cradle, bassinet) in the parents' room, and sleep positioners should not be used. The sleep surface should be firm and free of soft objects, loose bedding, excessive clothing, and extreme room temperatures should be avoided. The AAP suggests using a pacifier when placing the infant to sleep. Attention to these modifiable risks should begin in the newborn nursery. (See 'Prevention' above.)
- The use of home monitors has not been proven to reduce the incidence of SIDS and is not recommended for this purpose. (See 'Home monitors' above.)

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Pulmonary outcomes of bronchopulmonary dysplasia

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INTRODUCTION — Despite important advances in perinatal care and a steady decline in mortality rates among very low birth weight (VLBW) infants (<1500 grams) during the past two decades, bronchopulmonary dysplasia (BPD) remains a major complication of neonatal intensive care unit management and a significant cause of long term morbidity.

Knowledge of long-term effects of BPD has advanced significantly in recent years. These advances are supported by the development of standardized, physiology-based diagnostic criteria [1] and information about the outcomes of the growing adult populations of surviving premature infants.

Although the effects in adults are not yet fully known, it is clear that early lung injury in infancy can have life long consequences [2,3]. Many patients require multifaceted and multidisciplinary management well beyond the first year of life. Individuals born with very low birthweight have a substantially increased risk of hospitalization for respiratory disease as adults [3]; the risk and character of the respiratory disease may change as cohorts of infants treated with surfactant and other modern management techniques reach adulthood.

The long-term pulmonary outcomes of BPD are reviewed here. Long-term outcomes and management of nonpulmonary problems associated with BPD are addressed in a separate topic review. (see "Outcome of infants with bronchopulmonary dysplasia" and "Care of the neonatal intensive care unit graduate" and "Management of growth of preterm neonatal intensive care unit graduates").

The pathogenesis, clinical features, management, and potential strategies to prevent BPD are discussed separately. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia" and "Management of bronchopulmonary dysplasia" and "Prevention of bronchopulmonary dysplasia".)

EPIDEMIOLOGY — Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy (CLDI) [4]. Increasing rates of survival among the smallest infants due to changes in antenatal and postnatal respiratory management, including antenatal steroids and surfactant replacement, contribute to an overall increase in the incidence of BPD, even as other advances in the care of premature infants reduce the risk or severity of BPD in survivors and alter the underlying pathophysiology [4-7]. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia", section on 'Epidemiology'.)

PATHOPHYSIOLOGY — The pathophysiology of BPD is influenced by a combination of immaturity of the lung, exposures from therapeutic interventions, and heritable factors [8,9]. These factors result in one of two pathophysiologic processes, or a mixture of these: (see "Pathogenesis and clinical features of bronchopulmonary dysplasia", section on 'Pathology').

- Airway injury, inflammation, and alveolar septal fibrosis. These changes are usually associated with oxygen toxicity, barotrauma and infection, and are most prominent in infants with severe BPD who were born before the advent of modern management techniques. This type of pathophysiology is sometimes termed "classic" or "old" BPD, although occasionally infants in the post-surfactant era still acquire this form of the disease.
- Disruption of lung development, with decreased septation and alveolar hypoplasia leading to fewer and larger alveoli and dysmorphic pulmonary vasculature [10,11]. These changes are most prominent in

infants born after the advent of antepartum glucocorticoid use and surfactant treatment. As compared with infants with classic BPD, many of these infants were exposed to less traumatic ventilator support and lower levels of supplemental oxygen, but they are often of lower birthweight. Some of these infants have little or no respiratory distress after birth, but become chronically dependent on supplemental oxygen. Because of these distinctions from classic BPD, this type of pathophysiology is sometimes termed "new" BPD [12].

In late infancy and childhood, further changes may occur:

- Lung growth can improve pulmonary function, particularly in infants with mild BPD.
- Early injury can impair airway growth and so can cause deterioration of airway function and limitation of airflow, particularly in infants with very immature lungs [13-16].

PULMONARY FUNCTION

Pulmonary function testing — Pulmonary function testing during infancy is not routinely performed in most centers but can be helpful in tracking changes in pulmonary function, response to bronchodilators and diuretics, and overall severity of disease [17].

Pulmonary function testing in older children, adolescents, and adults is more widely available and is useful in following longitudinal changes in pulmonary function. Spirometry (measures of airflow) can be reliably performed in children as young as three years of age [18] and can be measured pre- and post administration of inhaled bronchodilators. Spirometric measures include the forced expiratory volume in one second (FEV1). Measurement of lung volumes include functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC) [17]. (See "Overview of pulmonary function testing in children".)

Late infancy — Older infants (6 to 12 months) who continue to have persistent respiratory symptoms often will have abnormal pulmonary function studies. However, the type of abnormality varies depending on the method of lung function testing used.

- One center made measurements of lung function every three months in a group of infants with BPD over the first year of life [19]. All infants were born between 24 and 31 weeks gestation, were supported with mechanical ventilation, and required supplemental oxygen at 28 days. Mean values of forced expiratory flows at each time point were less than 50 percent of the predicted values. Furthermore, the rate of increase in forced flows over the first year was also lower than predicted. This finding suggests that airway growth not only did not catch up to expected size over the first year, but it also did not even keep pace with the expected increase.
- A retrospective study examined infants with BPD who were born at 24 to 31 weeks gestation, were oxygen dependent for at least 28 days, and had persistent respiratory symptoms. At ages 10 to 20 months, pulmonary function studies demonstrated decreased flow rates and low FRC, indicating a component of restrictive lung disease [20].
- Another series described alterations in tidal mechanics and lung volumes in infants born before 29 weeks gestation [21]. 63 percent had a history of BPD (defined by a supplemental oxygen requirement at 36 weeks postmenstrual age), and half of whom had persistent wheezing [21]. Pulmonary function tests performed at one year of age demonstrated evidence of gas-trapping. These findings suggest small airway dysfunction. Since alveolar wall attachments tether small airways open, this finding could reflect either small airway damage, or the effect of reduced alveolar number, consistent with abnormal lung development, as is typical of "new" BPD.

Infants with BPD may require supplementary oxygen after hospital discharge [17]. In a series of infants with gestational ages 22 to 31 weeks treated in England in the late 1990s, 37 percent were discharged to home on oxygen. More than half of infants with BPD require hospital admission during the first two years of life, usually for acute respiratory infections [22]. (See "Management of bronchopulmonary dysplasia", section on 'Oxygen'.)

Childhood — Clinical symptoms often improve gradually with advancing age during childhood (ages 1 to 12 years) [4]. However, tests of pulmonary function may or may not improve, depending on the severity of the underlying disease:

Individuals with severe BPD have abnormal pulmonary function tests for many years. As an example, children with severe BPD studied during early childhood (<3 years of age) have decreased FEV1 as well as increased FRC, RV and RV/TLC as compared with healthy children [23]. These findings are consistent with persistent airflow obstruction and gas trapping. In a similar group of patients, sequential measurements during the first two to three years following hospital discharge demonstrated normalization of FRC (mL/kg) from initial low levels to more normal levels, and persistent limitations measured at FRC [24]. Approximately one third of these patients responded to bronchodilators. In another study, forced expiratory flow at two years of age was closely related to forced expiratory flow at eight years, suggesting little remodeling of the lung [15].

In many patients, especially those with mild disease, some pulmonary function tests gradually improve over time, possibly in conjunction with new alveolar development [14,25]. This was demonstrated in a study of 39 preterm infants (mean gestational age 29.8 weeks) with classic BPD who had serial measurements of tidal mechanics and lung volume from 1 to 36 months of age [25]. Although minute ventilation and respiratory effort remained increased throughout the study, FRC gradually decreased during the first six months, then became normal. Lung compliance improved from 50 percent of normal at one month of age to 80 percent of normal at 36 months. Specific pulmonary conductance (the reciprocal of resistance, normalized to FRC) was 50 percent of normal at one month, changed little until six months, and improved to 85 percent of normal at 36 months. Airway growth relative to lung volume remained slow during the first year of life but subsequently increased, leading to improved conductance.

In addition to the severity of the underlying BPD, birthweight and environmental factors, including tobacco smoke exposure and environmental allergens, affect the respiratory outcome [26,27].

Long-term changes — Long-term changes in pulmonary function have been described for individuals with the classic form of BPD, and may persist into adolescence and adulthood. Much less is known regarding the long-term outcome of infants managed with modern neonatal intensive care unit (NICU) strategies.

Classic BPD — Individuals with classic BPD may have abnormal pulmonary function tests throughout childhood and adolescence [28-31].

As an example, in a study of 147 adolescents born weighing less than 1500 g in the period 1977 to 1982, pulmonary function testing at a mean of 18.9 years demonstrated clinically significant reduction in airflow and deterioration in pulmonary function since the previous evaluation at eight years of age [32]. Similarly, long-term studies suggest that children ages 6 to 15 years with BPD demonstrate persistent airway obstruction, airway hyperreactivity, and hyperinflation of the lungs [28-31,33-51]. Both vital capacity and FEV1 are reduced as compared with control subjects [17]. These abnormalities may persist into adulthood [2]. The duration of oxygen dependence in the neonatal period may be a good predictor of respiratory morbidity during early childhood [52] and possibly of long-term pulmonary outcome [53,54].

Environmental factors may contribute to the pulmonary function abnormalities. Among individuals with extremely low birthweights (<1000 g), those who smoked during adolescence were more likely to experience a decline in pulmonary function during adolescence as compared with nonsmokers [55].

New BPD — The long-term outcomes discussed above describe changes in pulmonary function among individuals who developed BPD during the 1980s, before the advent of surfactant. Because of advances in NICU respiratory management, more recent cohorts of infants tend to have milder BPD. However, the recent cohorts are also more likely to have extremely low birthweight, and they may experience unique complications because of their immature lungs and/or because of different treatment exposures. Thus, the overall impact of newer interventions on long-term pulmonary function is unknown. (See 'Pathophysiology' above.)

Only a few studies have compared outcomes of early versus late cohorts. In one study, long-term pulmonary function was evaluated in two groups of subjects who were treated in a NICU in Norway [56]. The first group was born between 1982 and 1985, prior to the use of surfactant. The second group was born between 1991 and

1992, when surfactant was used as rescue therapy for respiratory distress syndrome. The mean FEV1 was similar between the two groups of children with BPD (81.9 and 80.8 percent predicted) and was lower than the control groups born during the two time periods (98.9 and 98.2 percent predicted). Pulmonary function might also be influenced by other differences between the groups, including the lower birthweight and younger age of follow up testing in the second group (10.6 versus 17.7 years).

ASTHMA-LIKE SYMPTOMS — Recurrent wheezing episodes are common in children and adolescents with a history of BPD [2,27,32,57,58]. Adolescents also experience reduced exercise tolerance, impaired ventilatory adaptation [30,49,59], and reduced gas transfer during physical activity [30,47,60]. Additionally, 40 to 50 percent of children with a history of BPD demonstrate significant airway hyperresponsiveness to exercise, histamine or methacholine, or a significant response to bronchodilator administration [61]. This prevalence of airway hyperreactivity, however, is not different from that of children born prematurely without BPD. Unlike children with asthma, those with BPD who have demonstrable airway hyperreactivity do not have elevated levels of exhaled nitric oxide (a marker for eosinophil-driven inflammation) [15,62] or an increased incidence of atopy [2].

Although children with BPD and children with asthma have similar symptoms, the underlying pathophysiology of these two diseases is different. The lung of the older child and adult recovered from BPD demonstrates airway wall thickening similar to individuals with asthma. However, in addition there are morphologic changes noted on CT scans of the chest, including linear and triangular opacities, mosaic perfusion, and air-trapping more akin to bronchiolitis obliterans [63], which are compatible with a diagnosis of fixed peripheral airway narrowing.

Children with asthma-like symptoms due to BPD may respond to inhaled corticosteroids, but the effect is less consistent than in children with asthma [17,64–66]. In some infants with central airway disease (tracheobronchomalacia), bronchodilators can exacerbate wheezing [17,67]. (See 'Acquired tracheobronchomalacia' below.)

PULMONARY ARTERY HYPERTENSION

Pathogenesis — Pulmonary artery hypertension (PAH) and the resultant right heart failure (cor pulmonale) associated with severe BPD is caused by both structural and functional changes within the lung. Gentler ventilatory practices and avoidance of oxygen toxicity may decrease the risk or severity of PAH [68,69].

- PAH in infants with BPD results from a combination of factors, including an absolute reduction in the size and complexity of the pulmonary vascular bed, increased resting tone of pulmonary artery smooth muscle, and increased reactivity of the arteries to a variety of stimuli. While current therapies can reduce pulmonary artery reactivity and promote remodeling that reduces resting pulmonary artery tone, the long-term effects of a reduced pulmonary capillary bed on the course of pulmonary hypertension in BPD patients are unclear.
- The effects of oxygen toxicity and ventilator-induced barotrauma and volutrauma on the immature lung can also interfere with alveolar development, reducing the number of alveoli and intraacinar arteries. The molecular mechanisms of these effects include impaired production of nitric oxide and vascular endothelial growth factor (VEGF), and increased expression of endoglin, which is involved in angiogenesis [70–72].
- Alternatively, chronic or intermittent alveolar hypoxia and acidosis cause acute vasoconstriction and produce further structural change within the affected pulmonary arteries, including endothelial cell injury, intimal proliferation, medial hypertrophy, and extension of muscle into the arterial wall.
- Left ventricular diastolic dysfunction (which may be caused by systemic hypertension and steroid use) can contribute to the PAH and pulmonary edema [73].

Natural history — The presence of PAH in infants with BPD is an important mortality risk factor. However, medial hypertrophy improves with age [74]. Therefore, infants surviving the initial stages of PAH often experience improvement.

As an example, in a study of patients with BPD and PAH treated during the surfactant era, 16 of 42 died within 6 months of diagnosis (median postnatal age at diagnosis and death: 4.8 and 10.9 months, respectively) [75].

Twenty-four of 26 survivors subsequently had improvement in their PAH (median follow up 9.8 months), but only five had normal right ventricular pressures.

Another study used serial Doppler echocardiography to investigate changes in pulmonary artery pressure (PAP) in preterm infants with BPD up to one year of age [76]. PAP was measured by the ratio of acceleration time to right ventricular ejection time (AT/RVET). PAP gradually fell with increasing age, but remained elevated as compared with a control group of healthy infants, as reflected by a lower median AT/RVET (0.31 versus 0.37).

Monitoring — Cardiac catheterization is the gold standard in detecting and determining the severity of PAH, but echocardiography is a reliable and safer modality to screen and monitor PAH in infants with BPD.

Doppler echocardiography — Doppler echocardiography is the most commonly performed procedure to assess pulmonary artery pressure in infants with BPD. It should be performed before hospital discharge in infants who continue to have a need for supplemental oxygen. If significant pulmonary hypertension is present, serial echocardiography every two to three months is recommended until resolution is assured [77].

Pulmonary artery pressure and the response to oxygen are estimated using tricuspid regurgitant jet velocity (TRJV) and/or pulmonary systolic time intervals [78]. Right ventricular structural or functional abnormalities are sometimes used as indirect indicators of PAH, including septal flattening, right atrial enlargement, and right ventricular hypertrophy, dilation, and function. In the previously mentioned case series of infants with PAH and BPD, severe PAH was defined as systemic or suprasystemic right ventricular pressure as estimated by echocardiography [75].

There are some limitations of doppler echocardiography in comparison to the more invasive cardiac catheterization. This was illustrated in a retrospective study of 25 children with PAH (including 17 patients with BPD) who underwent both echocardiography and cardiac catheterization [79]. TRJV could be measured in only 61 percent of infants. When this parameter could be measured, the presence or absence of PAH was correctly identified in 80 percent of studies, although echocardiography performed poorly in discriminating between mild and severe PAH. By contrast, echocardiographic evidence of abnormalities in right ventricular structure or function was a relatively poor predictor of PAH, particularly in studies in which TRJV could not be measured.

Cardiac catheterization — Cardiac catheterization is the gold standard for detecting PAH and for determining its severity. However, it is an invasive procedure with a significant complication rate. It can provide useful information in infants with severe PAH by evaluating cardiac anatomy, reactivity of the pulmonary vascular bed to oxygen or vasodilators, and assessing for development of large systemic-pulmonary collaterals which can contribute to the development of PAH by increasing pulmonary blood flow [17,80].

Electrocardiogram — Electrocardiograms (ECGs) have been used to assess PAH in infants with mild BPD who are improving. However, ECGs can be normal or have minimal abnormalities in some patients with PAH and severe right ventricular dysfunction [77]. We do not feel ECGs are adequate for monitoring cardiopulmonary status and assessing pulmonary artery pressure in infants with moderate or severe BPD.

CENTRAL AND UPPER AIRWAY DISEASE — The central airways span the glottis to the lobar or segmental bronchi. Acquired damage to the airways in infancy may persist into early childhood and beyond. Infants and young children with BPD are at risk of central airway collapse or obstruction, which can lead to "BPD spells" or cyanotic or life-threatening episodes, chronic wheezing unresponsive to bronchodilator therapy, recurrent atelectasis, lobar emphysema, or failure to wean from mechanical ventilation or to tolerate tracheal extubation [17].

Acquired tracheobronchomalacia — Tracheobronchomalacia is characterized by abnormally compliant, collapsible central airways. In infants with BPD, it is thought to result from barotrauma, chronic or recurrent infection, and endotracheal intubation. Tracheobronchomalacia tends to improve with age, as the tracheal cartilage matures and becomes less compliant [81-84]. Nonetheless, it has been noted in patients with BPD as old as 35 months [85-90]. (See "Congenital anomalies of the intrathoracic airways and tracheoesophageal fistula", section on "Tracheomalacia" and "Tracheomalacia and tracheobronchomalacia in adults".)

Symptoms of tracheobronchomalacia include "BPD spells" or reflex apnea (episodes of cyanosis that may be life-threatening) during infancy. Affected infants and children may also have chronic wheezing that does not improve or worsens with bronchodilator therapy or increased work of breathing [17]. The symptoms typically increase with crying or exertion.

In one study, tracheomalacia was found in 45 percent of infants with BPD undergoing bronchoscopy, and bronchomalacia in 34 percent [91]. However, this and other studies describe a population selected for symptoms, so the actual incidence of tracheobronchomalacia in infants or older children with BPD is unknown.

Prolonged pressure deformation in the immature airway can also increase the size of the airway, causing tracheomegaly. Tracheomegaly has been described in extremely low birth weight infants (<1000 g) after mechanical ventilatory support [92].

Glottic and subglottic damage — Injury to the glottis and surrounding structures has been reported after endotracheal intubation in newborns [93-102]. Epithelial damage after endotracheal intubation is a common occurrence [97,99], but most superficial lesions resolve without further sequelae [94,95,101]. Acquired subglottic stenosis and laryngeal injury is seen more often in infants who have been intubated for a week or longer and who required three or more intubations [93,94,101]. The use of inappropriately large endotracheal tubes has also been implicated [93,101,102].

Postextubation stridor is the most common sign of moderate to severe subglottic stenosis or laryngeal injury [93,101]. The child may have chronic symptoms or exhibit symptoms only during acute upper respiratory tract infections. Children with BPD and stridor should be evaluated endoscopically to determine the level and cause of airway obstruction. (See "Assessment of stridor in children".)

Tracheal and bronchial stenosis and granuloma formation — Acquired tracheal or bronchial stenosis or granuloma formation has been reported in a subset of infants with BPD as old as 17 months [85,86,91,103-107]. Stenosis and granulation formation is probably not the result of lung disease itself but rather the result of trauma from artificial airways and suctioning techniques [108-111]. These injuries can cause long-term pulmonary problems, including acquired lobar emphysema or persistent lobar atelectasis, depending on the degree of luminal obstruction. Acquired lobar atelectasis occurs when a partial obstruction allows air to enter the lung distal to the lesion on inspiration but prevents egress of air on exhalation; lobar atelectasis can develop if the obstruction is complete on both phases of respiration. These complications are seen much less frequently, since the practice of "deep suctioning" (passing a suction catheter until resistance is felt, then applying suction to the airway) has been abandoned by most neonatal units.

SLEEP HYPOXEMIA — Infants with a history of BPD are more likely to experience hypoxemic episodes during sleep [112-116], and these episodes may be clinically silent [113]. Episodes of desaturation are more common during REM sleep [113], when intercostal and upper airway muscle tone is reduced, leading to a reduction in both functional residual capacity and upper airway resistance. The former leads to further closure of diseased and narrowed airways as FRC falls below closing volume, thereby producing an increase in low V/Q regions. Arousal due to hypoxemia appears to be age-dependent but may lead to decreased sleep time during REM sleep in these infants [117,118]. Other contributing factors that may play a role include inadequate autonomic response mechanisms [119] and hypoxemia-induced airway narrowing [120].

Hypoxemic episodes during sleep can also affect older children. In one study of patients aged three to five years with severe BPD, multiple prolonged episodes of desaturation occurred during sleep, especially during REM sleep, despite adequate oxygen saturation when awake [121]. In another study of 17 children (mean age nine years), there were similar findings [122]. Increased thoraco-abdominal asynchrony during sleep has also been found in children with severe BPD (age range 19 to 46 months) [123]. Sleep related hypoxemia may also lead to decreased biventricular function [124] and impaired autonomic heart rate control in these children [125]. The incidence of sleep-disordered breathing is greater in school-age children with a history of prematurity, but not necessarily of BPD, compared with those born at term [126].

Sleep hypoxemia is associated with growth delay in infants with BPD [127]. The clinical consequences of sleep hypoxemia in older children with BPD are not established. Obstructive sleep apnea in children with or without BPD can cause sleep fragmentation with multiple nighttime arousals, and lead to neuropsychological morbidity,

including decreased school performance. Similarly, there is an increased risk of pulmonary hypertension in rats and adult patients with hypoxemia during sleep, but there are no data addressing chronic sleep hypoxemia and risk of pulmonary hypertension in the pediatric population at this time.

The management of infants with evidence of sleep hypoxemia is discussed separately. (See "Management of bronchopulmonary dysplasia", section on 'Oxygenation'.) A polysomnography study is indicated in infants or children with BPD and symptoms of upper airway obstruction during sleep (eg snoring). (See "Evaluation of suspected obstructive sleep apnea in children".)

RESPIRATORY INFECTION — Respiratory infections, including respiratory syncytial virus (RSV), are more severe in children with BPD and contribute to high rates of rehospitalization, especially within the first year. These infections may be life-threatening, and those with severe lung-function abnormalities are more susceptible [128]. This is especially true for those infants who still require supplemental oxygen at the time of infection [129]. Furthermore, children with BPD who had been hospitalized with an RSV infection within the first two years of life have increased health care costs and worse lung function at school age than those who did not experience an RSV-related hospitalization [130].

For these reasons, infants and children with BPD require additional immunizations, and prophylaxis for RSV is indicated for some infants. (See "Care of the neonatal intensive care unit graduate", section on 'Immunization'.)

IMPLICATIONS

Oxygen Therapy — Hypoxic episodes in infants and children can be linked to, and even worsen, already impaired lung mechanics, elevated airway resistance, and obstruction [113,119,120]. Oxygen supplementation is known to benefit these infants by decreasing airway resistance [131] and decreasing pulmonary vascular resistance, thus reversing some components of pulmonary artery hypertension [132-134]. It can also improve central respiratory drive [115], increase sleep duration by increasing REM sleep [117], and increase growth velocity [127,134,135].

Infants beyond term and with mature retinal development should receive oxygen supplementation as needed to maintain a target saturation of 93 percent or more, particularly in infants with pulmonary artery hypertension [17,77]. As the infant's respiratory status improves, the supplemental oxygen should be slowly weaned. Adjustments should be guided by monitoring with pulse oximetry in a variety of states, recognizing that oxygenation often decreases during or after feeding [113,136], sleep [113,115,116], and during intercurrent illnesses. Additionally, sustained growth and stamina for therapies or periods of play must be assured while supplemental oxygen is withdrawn. (See 'Sleep hypoxemia' above and "Management of bronchopulmonary dysplasia", section on 'Oxygenation'.)

Tracheostomy — Infants with obstructive central and upper airway disease may require a chronic tracheostomy for months or even years after hospital discharge. Such infants require coordinated care involving their primary physician, pediatric otolaryngologist, pulmonologist, and provider of home care services. A speech pathologist is often helpful in the evaluation and management of swallowing and speech development. (See 'Central and upper airway disease' above.)

Before these patients can transition to home care, the family must be trained in tracheostomy maintenance and emergency procedures. Two caregivers should be identified and trained in routine suctioning, cleaning and changing the tracheostomy, general respiratory assessment, and cardiopulmonary resuscitation of a patient with a tracheostomy. The caregivers must demonstrate proficiency in routine and emergency skills before the child is discharged from the health care facility to home. Families should have a back-up tracheostomy tube that is one size smaller than the one in use; this will be easier to insert in case of accidental decannulation.

For any child with a tracheostomy who is at high risk for airway complications and cannot call for help or self-correct a problem, some form of monitoring should be used when not under direct visual monitoring. Pulse oximetry is often chosen over a cardiorespiratory monitor since hypoxemia or tachycardia will occur before bradycardia from prolonged hypoxemia, and a child with a critically obstructed or displaced tracheostomy tube will make ineffective breathing efforts that will delay the cardiorespiratory monitor from alarming. (See 'Cardiorespiratory monitoring' below.)

Because all monitors have limitations, daily skilled nursing care is considered to be a standard of care for a child at home with a tracheostomy; minimum hours of nursing care are not evidence-based, but range between 8 hour/day for children with tracheostomies, and longer (up to 16 hours/day in some US states) for children requiring mechanical ventilation via the tracheostomy. This support allows the child to be visually monitored at least while the parents sleep. (See 'Cardiorespiratory monitoring' below.)

Guidelines on the care of the child with chronic tracheostomy have been published [137]. Children with tracheostomies should undergo periodic bronchoscopy every 6 to 12 months to monitor the airway, assess tracheostomy tube size, and evaluate readiness for decannulation. Granulomas often form near the tracheostomy site and require removal; other complications include recurrent tracheitis or bronchitis, and (rarely) hemorrhage.

Cardiorespiratory monitoring — Routine use of cardiorespiratory monitors is not indicated for children with BPD after hospital discharge. However, home monitors may be appropriate for selected infants who are at risk of acute obstructive events due to tracheobronchomalacia or stenosis, or those who require tracheostomies or supplemental oxygen. In this case, it is important to monitor oxygen saturation or a device that can detect obstructive apnea; standard cardiorespiratory monitors do not detect obstructive apnea in the absence of bradycardia. Providers and families should recognize that monitors provide only indirect evidence of airway compromise, and alarms are often delayed. There is no good substitute for close direct observation of the tracheotomized patient. (See "Use of home cardiorespiratory monitors in infants", section on 'Other indications'.)

Acute respiratory illness — To reduce risks for asthma and respiratory infections, all families should be counseled to take the following measures:

- Frequent handwashing and avoidance of exposing the infant and young child to respiratory infections; administration of standard and supplementary immunizations, and prophylaxis for RSV as indicated. (See "Care of the neonatal intensive care unit graduate", section on 'Immunization' and 'Respiratory infection' above.)
- Strict avoidance of tobacco smoke exposure. Eliminating all smoking within the home is an important goal; intermediate measures to limit a child's exposure are not very effective. (See "Control of secondhand smoke exposure" and 'Pulmonary function' above.)
- Anticipatory guidance to ensure that adolescents do not begin to smoke, and support for smoking cessation in those who do. (See 'Asthma-like symptoms' above.)

Care setting — Children, adolescents, and young adults with BPD may be followed-up in a number of outpatient clinic settings. These include a pediatrician's office or a hospital-based follow-up clinic. In either case, the patient should be referred to a pulmonologist familiar with the care of these often medically fragile patients. (See "Care of the neonatal intensive care unit graduate".)

SUMMARY AND RECOMMENDATIONS

- Early lung injury in infancy due to bronchopulmonary dysplasia can have life long consequences, manifested by altered pulmonary function, central and upper airway disease, and in some cases, pulmonary hypertension.
- In infants who were born before the advent of modern NICU management techniques, BPD is typically characterized by airway injury with inflammation and alveolar septal fibrosis. These changes are usually associated with oxygen toxicity, barotrauma, and infection. (See 'Pathophysiology' above.)
- Infants born after the advent of antepartum glucocorticoid use and surfactant treatment are more likely to display disruption of lung development, with decreased septation and alveolar hypoplasia leading to fewer and larger alveoli and dysmorphic pulmonary vasculature. (See 'Pathophysiology' above.)
- Recurrent wheezing episodes are common in children and adolescents with a history of BPD, but the underlying pathophysiology is somewhat different from asthma. Bronchodilators are effective on only about half of these patients. In infants or children with tracheobronchomalacia, bronchodilators may actually worsen symptoms. There are no data on the use of inhaled steroids to control asthma symptoms in children with a history of BPD. (See 'Asthma-like symptoms' above.)
- Infants with severe BPD may develop pulmonary artery hypertension (PAH). Infants who have a need for supplemental oxygen at the time of hospital discharge should be evaluated for PAH using doppler echocardiography, which should be performed before hospital discharge. If pulmonary hypertension is

present, these infants should be followed with serial assessment as outpatients. (See 'Pulmonary artery hypertension' above.)

- Infants and young children with BPD are at risk of central airway collapse due to tracheomalacia, which can aggravate underlying thoracic airway disease associated with BPD and produce "BPD spells" or cyanotic or life-threatening episodes, chronic wheezing unresponsive to bronchodilator therapy, a propensity for atelectasis, and failure to wean from mechanical ventilation or to tolerate tracheal extubation. (See 'Central and upper airway disease' above.)

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Treatment and complications of respiratory distress syndrome in preterm infants

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INTRODUCTION — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. The lungs of preterm infants lack adequate pulmonary surfactant, one of the constituents of the air-liquid interface that lines the alveolar surfaces and terminal airways. RDS is a result of surfactant deficiency, which increases the surface tension in the air-liquid interface of the terminal respiratory units. Surfactant deficiency leads to atelectasis, increases ventilation perfusion mismatch, and leads to lung injury, which is mediated by a marked pulmonary inflammatory response.

As RDS is due to lung immaturity, the best intervention would be to prevent premature birth. However, if premature birth cannot be avoided, RDS may be prevented with the use of antenatal steroid therapy and the prophylactic (early) administration of exogenous surfactant. (See "Prevention of spontaneous preterm birth" and "Prevention of respiratory distress syndrome in preterm infants".)

Despite the initiation of preventive care, RDS may still develop and is associated with both acute and chronic complications. Once the diagnosis of RDS has been established, management is directed toward specific measures to replace surfactant and ensure adequate oxygenation and ventilation, as well as general supportive measures. The treatment of established RDS and its complications of RDS are discussed in this topic review (algorithm 1).

The diagnosis of RDS is discussed elsewhere in the program. (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn", section on 'Diagnosis'.)

SURFACTANT THERAPY — Prior to the introduction of exogenous surfactant, RDS was associated with significant morbidity and mortality. Beginning with the first study of 10 infants in 1980, numerous clinical trials have shown that exogenous surfactant replacement therapy is highly effective in reducing mortality and morbidity in infants with RDS [1-4]. In a large multicenter blinded controlled trial, 789 infants (birth weight 600 to 1750 g) who developed RDS within six hours of birth were randomly assigned to either surfactant or placebo [3]. Surfactant was associated with significantly lower mortality rate (18 versus 27 percent) and a lower risk of developing pulmonary interstitial emphysema (19 versus 39 percent) and other pulmonary leak complications including pneumothorax (12 versus 26 percent) [3].

Such benefits of exogenous surfactant are due primarily to improved lung mechanics with a decrease in ventilation perfusion mismatching that results in improved oxygenation. In one study, for example, single dose surfactant improved the oxygenation in 77 percent of treated compared to 13 percent of control infants defined by an increase in the arterial to alveolar oxygenation ratio from 0.2 to >0.3 [5]. The improved arterial/alveolar ratio lasted the duration of the study (48 hours) in 66 percent of treated infants compared to 9 percent of controls.

Types of surfactant — A wide variety of surfactant preparations, which include natural and synthetic products, have been developed. At the present time, only natural animal derived surfactant preparations are available (table 1).

In a meta-analysis, animal-derived surfactant extract treatment in infants with established RDS decreased the risk of pneumothorax, pulmonary interstitial disease, mortality, and the combined outcome of BPD or death [6].

The different preparations of surfactant, including their relative efficacy, are more fully discussed elsewhere in the program. (See "Exogenous surfactant therapy in preterm infants".)

Indications

Rescue therapy — As recommended by the American Academy of Pediatrics and European consensus guidelines, rescue surfactant should be given when the diagnosis of RDS is established [7,8]. The diagnosis is based upon the infant's oxygen requirement, clinical examination, and chest radiograph (algorithm 1). (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn", section on 'Diagnosis'.)

In infants older than 30 weeks, the diagnosis of RDS is established when the arterial to alveolar oxygen ratio is less than 0.22 to 0.3 [9,10]. This corresponds to an arterial PaO₂ value of less than 80 mm Hg with oxygen administration of greater than 40 percent. These older infants typically have not received prophylactic or early surfactant as they have a lower risk of developing the disorder. Numerous trials have shown benefits of rescue surfactant therapy in this group of neonates [1-4].

The amount of surfactant for the initial rescue dose is based upon the specific surfactant preparation utilized (table 1):

- Poractant alfa — 2.5 mL/kg (200 mg phospholipid/kg)
- Calfactant — 3.0 mL/kg (105 mg phospholipid/kg)
- Beractant — 4.0 mL/kg (100 mg phospholipid/kg)

There are no current data to recommend a specific natural surfactant preparation over another. Choice of surfactant preparation is based upon the preference and availability at the site of clinical care. (See "Exogenous surfactant therapy in preterm infants".)

Post-prophylactic or early therapy — In infants less than 30 weeks gestation, the standard of therapy is to provide prophylactic or early surfactant. Additional doses of surfactant therapy is administered if the patient has an oxygen requirement >30 percent.

Subsequent surfactant administration decreases mortality and morbidity in infants less than 30 weeks gestation with RDS [1,4,11]. In a double-blind study, 826 infants (gestational age <30 weeks with birth weights 700 to 1100 g) who received a single prophylactic dose within the first 30 minutes of life and continued to require mechanical ventilation at 12 to 24 hours of life were randomly assigned to two air placebo treatments or to two additional doses of surfactant [11]. Compared with placebo, surfactant therapy resulted in significant lower mortality rates at 28 days of life (10 versus 17 percent), and a lower incidence of necrotizing enterocolitis (2 versus 6 percent). There was, however, no difference in the incidence of pneumothorax, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage in the surviving infants. (See "Prevention of respiratory distress syndrome in preterm infants".)

Continued therapy — After the initial dose of surfactant given for treatment of RDS, the patient's response is assessed based upon their continued oxygen requirements. If there is clinical evidence of persistent disease, we continue surfactant therapy [12,13]. Based upon clinical practice, we define persistent RDS as a continual or recurrent oxygen requirement of greater than 30 percent, independent of age.

Surfactant therapy is administered for a total of 3 to 4 doses based upon continued oxygen needs and the specific surfactant preparation given. Multiple dosing of natural surfactants compared to single dosing regimens leads to lower incidence of pneumothorax, and reduced mortality in patients receiving surfactant therapy [12-14]. In one study, for example, 357 preterm infants (birthweight 700 to 2000 g) with severe RDS were randomly assigned to either a single or multiple dose protocol of natural surfactant [13]. Infants who received multiple doses compared to a single dose of surfactant had a lower incidence of pneumothorax (9 versus 18 percent) and mortality rate (13 versus 21 percent).

Repeat dosing is dependent upon the preparation used as follows (table 1):

- Poractant alfa — Initial dose of 2.5 mL/kg (200 mg phospholipid/kg), followed by subsequent dose of 1.25 mL/kg every 12 h for up to a total of 3 doses
- Calfactant — Initial dose of 3.0 mL/kg (105 mg phospholipid/kg), and repeated every 12 h for up to a total of 3 doses.
- Beractant — Initial dose of 4.0 mL/kg (100 mg phospholipid/kg), and repeated every 6 h for up to a total of 4 doses.

MECHANICAL VENTILATION AND CPAP — Surfactant deficiency results in impaired lung expansion (atelectasis) due to decreased surface tension in the air liquid interface at the terminal respiratory units that results in RDS. As the disease progresses, it may lead to respiratory failure secondary to inequalities in ventilation perfusion matching and to increases in intra- and extra-pulmonary shunting.

In patients with RDS, intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) has been used to correct atelectasis and facilitate the repeated administration of exogenous surfactant. In addition, other supportive measures aimed at improving hypoxemia (ie, arterial oxygenation) include increasing the concentration of supplemental oxygen and increasing the mean airway pressure.

It is increasingly appreciated that mechanical ventilation is associated with volutrauma and barotrauma, and the use of high concentrations of supplemental oxygen is associated with oxygen toxicity; all of which contribute to the development of bronchopulmonary dysplasia (BPD) [15-17]. In premature baboons, a five day compared to one day intubation with subsequent stabilization on CPAP resulted in poorer lung mechanics and respiratory function (eg, lower arterial to alveolar oxygen ratio, higher PaCO₂, and poorer respiratory drive), increased histopathologic findings of cellular bronchiolitis and peribronchiolar alveolar wall thickening, and increased lavage levels of cytokines [18].

Continuous positive airway pressure (CPAP) has been used to prevent atelectasis and pulmonary shunting and avoid the pulmonary insults from mechanical ventilation in infants with RDS who have not developed respiratory failure. In addition, different modes of ventilation have been evaluated to reduce pulmonary injury in infants who require ventilation because of respiratory failure.

Continuous positive airway pressure (CPAP) — Among premature infants without respiratory failure, continuous positive airway pressure (CPAP) is an alternative to mechanical ventilation to prevent atelectasis because mechanical ventilation is associated with an increased risk of BPD [10,15,19,20]. Evidence clearly supports the role of CPAP in larger infants (birth weight ≥1500 g). However, data are more limited upon the benefit CPAP in very low birth weight infants (birth weight <1500 g).

Larger preterm infants — In larger babies with RDS, CPAP is the preferred modality based upon a meta-analysis that reported a lower mortality and morbidity rate in infants with birth weights greater than 1500 g who were placed on CPAP compared to those initially supported with mechanical ventilation [20]. Larger preterm infants can be extubated and stabilized on CPAP after rescue administration of exogenous surfactant [21].

In a study from Australia of infants greater than 30 weeks gestation with respiratory distress, nasal CPAP compared to oxygen administered by hood decreased the need for transfer to a regional tertiary center (23 versus 40 percent) [22]. However, there was a trend for an increased risk of a pneumothorax in infants treated with CPAP. Although these results suggest that possible treatment with CPAP alone in treating larger infants with mild RDS, further trials would be necessary before nasal CPAP therapy in lieu of treatment with exogenous surfactant could be considered in these patients.

Very low birthweight infants — The potential benefit of CPAP compared to intubation and mechanical ventilation is less clear in infants born before 30 weeks gestation or with birth weights below 1500 g with RDS. Data are limited to a single clinical trial and several observational studies.

In the single multicenter clinical trial, 610 infants born at 25 to 28 weeks gestation who required respiratory support were randomly assigned to either CPAP or intubation with mechanical ventilation at five minutes of age [23]. Surfactant therapy was not mandated and was used according to local protocol at each of the participating centers. The following findings were noted at 36 weeks gestational age:

- There was no difference in mortality rate between infants treated with CPAP versus those who were intubated and ventilated (OR 1.1, 95% CI 0.57 to 2.12).
- There was no difference in the need for oxygen therapy between the two groups (OR 0.76, 95% CI 0.54 to 1.09). In addition, the majority of survivors in both groups required little or no oxygen therapy. An oxygen concentration of 30 percent or more was administered to 9.4 percent of the CPAP and 8.8 percent of the intubated groups.
- There was no difference between the two groups in the combined primary outcome of death and the need for oxygen therapy at 36 weeks gestational age (OR 0.8, 95% CI 0.58 to 1.12).
- The intubation rate of infants initially assigned to CPAP was 46 percent. Reasons for intubation included administration of oxygen with a concentration greater than 60 percent, a PaCO₂ greater than 60 mm Hg, persistent apnea, or metabolic acidosis not responsive to medical therapy.
- The incidence of pneumothorax was greater in the CPAP group (9.1 versus 3 percent).
- Surfactant administration was lower in those who received CPAP compared to intubated infants (38 versus 77 percent).

One major limitation of this study was that randomized therapy was not blinded. In addition, this study did not answer whether after initial intubation and surfactant administration, outcome differs between infants who are extubated and stabilized on CPAP compared to those who continue to be intubated and ventilated. Nevertheless, these results suggest that starting respiratory support with CPAP does not adversely affect very low birth weight infants with the possible exception of the increased risk of pneumothorax, which may in part be due to the lack of surfactant administration in the CPAP group.

Other support for the routine use of CPAP in very low birth weight infants are based upon observational studies.

- One study demonstrated a lower risk of BPD with early and routine use of CPAP used at one center compared to routine use of mechanical ventilation at two other centers in infants with birth weights less than 1500 g [15].
- In a single center study of 261 preterm infants (birth weight \leq 1250 g), 76 percent of infants who did not receive surfactant therapy were maintained successfully on CPAP without the need for intubation and mechanical ventilation [24].
- One study demonstrated no difference in the neurodevelopment or growth of preterm infants placed upon early CPAP from 1998 to 1999 compared to historical controls not treated with CPAP from 1996 to 1997 at four years of age [25].

Our approach — Based upon the above observations, our current recommendation is that after intubation and administration of surfactant, preterm infants with RDS, regardless of birth weight, can be extubated and stabilized on CPAP if the infant is active, exhibits spontaneous respiratory effort, and is not in respiratory failure. In larger preterm infants, CPAP is the initial therapy for respiratory symptoms.

Nasal intermittent positive pressure ventilation — Nasal intermittent positive pressure ventilation (NIPPV) augments nasal CPAP by delivering ventilator breaths via the nasal prongs. Although NIPPV avoids the trauma of endotracheal placement tube, it still is a delivery mode of positive pressure ventilation.

Data are limited in comparing NIPPV to conventional ventilation. In a small trial of 64 infants who were $<$ 32 weeks gestation cared for at two different sites, patients with mild to moderately severe RDS were randomized sequentially to either NIPPV or conventional ventilation (CV) after the first administered dose of surfactant [26]. Infants who were treated with NIPPV compared to those treated with CV had a lower risk of the combined outcome of death and BPD (20 versus 52 percent). There were no differences in the total duration of supplemental oxygen or positive pressure ventilation, and the need for reintubation between the two groups.

Similarly, data are limited comparing the efficacy of NIPPV to CPAP in reducing the need for intubation and mechanical ventilation.

- In an open-label randomized trial of 76 preterm infants stratified by gestational age (28 to 30 weeks, and 31 to 34 weeks) and surfactant use, the need for intubation and mechanical ventilation was lower in the group that received NIPPV compared to those treated with CPAP [27].

- In a trial of 200 preterm infants (gestational age 26 to <34 weeks), there was no difference in the primary outcome of mechanical ventilation within the first 72 hours of life between the NIPPV and nasal CPAP (nCPAP) groups (25 versus 34 percent; relative risk 0.77, 95% CI 0.48-0.1.15). A post-hoc analysis demonstrated that infants in the NIPPV group were more likely to remain extubated than those who received nCPAP from 24 to 72 hours of life. In this study, exogenous surfactant was given only as rescue therapy.
- In another trial of 84 preterm infants born <35 weeks gestation, infants initially treated with NIPPV compared with those who received nasal CPAP were less likely to require endotracheal intubation and ventilation (25 versus 49 percent) and develop BPD (2 versus 17 percent) [28]. In this study, exogenous surfactant was given only as rescue therapy. One limitation of this study is the small number of patients, especially the VLBW and ELBW infants who are at highest risk for BPD.
- In a retrospective review of preterm infants with birth weights below 1250 g, patients treated with NIPPV compared to those who received CPAP had a higher incidence of BPD or death (39 versus 27 percent) [29]. However, NIPPV therapy was associated with a lower mean birth weight and gestational age, and more frequent administration of surfactant than those who were treated with CPAP, suggesting that NIPPV was administered to a more severely ill group. In a subgroup analysis of infants with the lowest birth weights (500 to 750 g), infants treated with NIPPV (n=84) compared to those treated with CPAP (n=27) had a lower rate of BPD (43 versus 67 percent) and a similar mortality rate (11 versus 12 percent).

These findings suggest an increased benefit with NIPPV versus CPAP in the preterm infants with RDS. However, additional trials are required to confirm the safety of the increased efficacy of NIPPV compared with CPAP in the treatment of RDS [30].

Mechanical ventilation — The best mode of ventilation remains unclear in patients in whom mechanical ventilation is necessary because of respiratory failure [31,32]. Mechanical ventilation modalities include pressure control ventilation, patient triggered ventilation, volume control, and high frequency positive pressure ventilation. (See "Mechanical ventilation in neonates".)

High frequency oscillatory ventilation (HFOV), a technique of rapid ventilation with very small tidal volumes, appeared to be a promising alternative as it reduced lung injury in animal models compared to conventional ventilation. However, nearly all trials comparing HFOV to conventional ventilation performed in preterm infants with RDS (since surfactant replacement therapy has been available) showed no increased benefit in regards to mortality and development of BPD [33-35]. In one randomized study of 400 infants between 23 and 28 weeks of age, no difference in the composite primary outcome (death or chronic lung disease, diagnosed at 36 weeks of postmenstrual age) was observed between conventional ventilation or high-frequency oscillatory ventilation [34].

There is, however, one large study that reported a survival benefit with HFOV, contrary to the previously cited studies. In this trial of 500 preterm infants (601 to 1200 g birth weight), the proportion of infants who survived without BPD was slightly greater with HFOV than with conventional ventilation (56 versus 47 percent) [36]. But, this study was performed in centers experienced in the use of HFOV and strict protocols were utilized in patient management. Similar results may not be achieved at centers with less experience or without such strict protocols. In addition, there may be increased complications of HFOV in the hands of inexperienced clinicians [33,37]. At present, there is no evidence that favors the routine use of high frequency ventilation over conventional ventilation [34,37].

Conventional ventilators also can be classified by the mechanism used to determine the amount of gas delivery for each inspiration. Most centers, including ours, use pressure control that delivers inspiration based upon the selected peak inspiratory pressure (PIP) at a synchronized mandatory rate (SMV). Other ventilators control their delivery by tidal volume (volume control). In addition, there are ventilators that are patient-triggered requiring delivery based upon the inspiratory effort of the patients measured by chest movement or breath (assist/control ventilation), air flow or airway pressure.

There appears to be no significant advantage of one type of conventional ventilator over another. With respect to SMV versus assist/control, for example, one study randomly assigned premature infants (BW between 500 to 1249 g) requiring mechanical ventilation to either mode of ventilation [32]. There was no difference between the

two groups in the length of time required for mechanical ventilation, the need for supplemental oxygen at 36 weeks postmenstrual age, or the proportion of infants alive and extubated at 14 days of age.

Summary — At the present time, there are no studies that suggest that any one mode of conventional ventilation is better than another regarding long-term outcomes [31]. Different modes may be beneficial in select clinical settings and is dependent upon the knowledge and experience of the clinician caring for the patient.

No matter which mode of ventilation is selected, it is crucial to minimize the time on mechanical ventilation and optimize management to facilitate weaning from ventilator support.

Criteria for mechanical ventilation — Assisted ventilation should be initiated when respiratory failure occurs. Respiratory failure is verified by one of the following:

- Respiratory acidosis, documented by an arterial pH <7.20 and a PaCO₂ >60 mm Hg
- Hypoxia, documented by an arterial PaO₂ <60 mm Hg despite oxygen supplementation of 70 percent on nasal CPAP
- Severe apnea

These are general guidelines for respiratory failure and the measurements need to be taken into the context of other assessments of the patient's cardiopulmonary function. If the patient meets the general criteria for respiratory failure in neonates, we initiate mechanical ventilation using these initial settings:

- Rate of 60 breaths per minute
- Inspiratory time of 0.2 seconds
- End expiratory pressure of 5
- Peak inspiratory pressure that adequately expands the chest wall that is titrated to the lowest level that will ensure adequate ventilation.

These initial settings meet the criteria for rapid rate low tidal volume ventilation that has been associated with lower rates of pneumothoraces and perhaps mortality compared to lower rate strategies [38,39].

Weaning the ventilator is a gradual process and is started when the patient is able to maintain acceptable oxygenation and ventilation on low peak inflation pressures of less than or equal to 20 cm H₂O.

INHALED NITRIC OXIDE — It is well established that inhaled nitric oxide (iNO) provides benefit in the treatment of term or late preterm infants with persistent pulmonary hypertension. In addition, animal studies demonstrated that iNO reduced lung inflammation, improved surfactant function, attenuated hyperoxic lung injury, and promoted lung growth [40-44]. (See "Persistent pulmonary hypertension of the newborn", section on 'Inhaled nitric oxide'.)

A number of randomized masked controlled clinical trials have been conducted to evaluate the safety and efficacy of iNO in preterm infants with respiratory distress [45-50]. These trials have significant differences in study design (eg, dose, duration, early versus late administration of iNO, and severity of illness).

Despite these variations in study design, a systematic review, which included 14 trials with 7 follow-up studies and one observational study, was performed to assess the efficacy and safety of iNO. The following findings were noted:

- There was no difference in mortality between the iNO and control groups (RR 0.97, 95% CI 0.82-1.15). Subgroup analysis based on dosing of iNO (5 ppm, 10 ppm, 20 ppm, or titrated to response) and birth weight also demonstrated no difference in mortality between the iNO and control groups.
- There was no difference in the incidence of BPD (despite variation in the definition of BPD used) between the iNO and control groups (RR 0.93, 95% CI 0.86-1.003).

- Subgroup analyses based on dosing showed no difference between the two groups when the iNO dose was 5 ppm, 20 ppm, or titrated to response. There was a decrease risk of BPD in the group that was treated with 10 ppm iNO compared with controls (RR 0.75, 95% CI 0.61-0.91).
- In one study, a lower risk of BPD was observed in infants with birth weights between 1000 and 1250 treated with iNO compared with controls (30 versus 60 percent, RR 0.5, 95% CI 0.32-0.79) [47]. However, there was no difference between the groups in infants with birth weights below 1000 g.
- There was a small difference of improved composite outcome of death or BPD in the iNO group compared with controls (RR 0.93, 95% CI 0.87-0.99). However, there was heterogeneity among the studies as eight reported no difference between the groups, whereas three showed a significant benefit of iNO over placebo. Two studies also demonstrated a reduction in the composite outcome of death or BPD in infants with birth weights above 1000 g [46,47].
- There was no evidence of increased adverse effects (patent ductus arteriosus, sepsis, necrotizing enterocolitis, severe retinopathy of prematurity, pulmonary hemorrhage, or air leaks) with the use of iNO compared with placebo.
- There were no differences in neurodevelopment outcome as follows:
 - There was no difference in the composite outcome of brain injury defined as intraventricular hemorrhage with ventriculomegaly, intraparenchymal hemorrhage, or periventricular leukomalacia between the two groups.
 - There was no difference in the incidence of cerebral palsy in follow-up assessments at 18 months, and 4 to 5 years of age.
 - There was no difference in cognitive ability between the two groups.
 - There was no difference in the incidence of neurodevelopmental impairment, which included assessment of cognitive, neuromotor and sensory function, between the two groups.

Cost-effectiveness — In the United State, iNo is an expensive intervention. Conflicting results were reported from two studies that evaluated the cost-effectiveness of this intervention in two of the previously discussed trials.

- In the first study, retrospective economic evaluation showed the cost of treating infants treated with iNO was similar to those in the placebo for the birth hospitalization (\$194,702 versus 193,125) [48,51]. The cost of the drug (estimated as \$12,000 for a course extending to 30 days) was offset by a decrease in days of ventilation and hospital admissions. In this analysis, daily costs were determined based upon respiratory support from a database of all daily charges for a similar group of infants cared for in a tertiary NICU. In a sub-group analysis, cost of iNO treated infants was lower than those in the placebo group. The authors concluded that iNO appears not to increase costs and is cost-effective if started between 7 and 14 days of life.
- In the second study, retrospective economic evaluation showed the cost of caring for infants treated with iNO was not statistically different than those in the placebo group during birth hospitalization and first-year of life (\$235,800 versus 198,300) [47,52]. The cost of the drug was set at \$125/hr to a cap of \$12,000 for a course extending to 30 days. In this analysis, costs were calculated by review of detail hospital bills from the NICU course for 80 percent of patients and by assigning costs for rehospitalization for days on the in-patient ward or intensive care unit. In a sub-group analysis, costs were significantly higher for iNO treated infants among infants in the lowest birth weight group of 500 to 749 g. The authors concluded that iNO, which was started within 48 hours of life until 21 days or extubation, did not lower costs and had a poor cost-effectiveness profile.

These two studies differed by the dose of iNO and the timing of iNO [47,48].

Our approach — Based upon the currently available data, we do not recommend the routine administration of iNO to preterm infants with RDS. Until an effective regimen is determined that demonstrates a substantial benefit of iNO justifying the cost, iNO administration should be limited to clinical trials [53]. This approach is consistent with the conclusions of an expert panel convened by the National Institute of Health that found the available evidence based on the above systematic review did not support the use of iNO in the treatment of preterm infants below 34 weeks gestation who require respiratory support [54].

POSTNATAL GLUCOCORTICOID — Postnatal glucocorticoid therapy, when given to premature infants in the first day of life, improves pulmonary and circulatory function and decreases the incidence of BPD. However, short-term complications, such as intestinal perforation, and metabolic instability; and more importantly, long-term abnormal neurodevelopmental outcomes in treated infants have led to strict restriction in the use of postnatal corticosteroid therapy. As a result, we do NOT recommend the routine use of postnatal glucocorticoid steroids to prevent or treat BPD.

A more in-depth discussion on the use and risk of postnatal corticosteroid therapy is found elsewhere in the program. (See "Postnatal use of glucocorticoids in bronchopulmonary dysplasia".)

SUPPORTIVE CARE — Additional supportive care for the preterm infants is needed to optimize the previously discussed specific measures for treating RDS.

Thermoregulation — Infants should be maintained in a thermal neutral environment to limit energy expenditure to maintain core body temperature. Proper thermoregulation reduces oxygen consumption and caloric needs.

Rectal temperatures should not be obtained in infants with RDS because of the greater risk of trauma or perforation associated with their use. As a result, abdominal temperatures should be used to set the servo-controlling temperatures in incubators and in radiant warmers. The ambient temperature should be selected to maintain an anterior abdominal skin temperature of 36.9°C in small premature infants (less than 1000 grams) and 36.5°C in larger infants, which correlates to a rectal temperature of 37°C.

Fluid status — Fluid status must be carefully monitored as excessive fluid increases the risk of patent ductus arteriosus, necrotizing enterocolitis (NEC), and BPD [55].

Fluid balance is complex as immature kidneys have limited concentrating abilities and insensible losses vary with gestational age, use of radiant heaters and phototherapy, and the water content of inspired air. Fluids should be adjusted to maintain a slightly negative water balance, and positive water balance should be avoided. In addition, as shown in a systematic analysis, there is no evidence to support the routine use of diuretics in preterm infants with RDS [56]. In addition, the administration of early nutrition is important in the overall care of these premature infants. (See "Prevention of bronchopulmonary dysplasia", section on 'Fluid restriction' and "Fluid and electrolyte therapy in newborns" and "Parenteral nutrition in premature infants".)

Cardiovascular management — Systemic hypotension and failure of closure of the patent ductus arteriosus increase the risk of developing NEC and BPD.

- Systemic hypotension occurs commonly in the early stages of RDS. In patients with moderate to severe RDS, continuous arterial pressure is monitored through the umbilical artery catheter. Hypotension is treated with vasopressor support and cautious use of crystalloid solutions for intravascular expansion. In patients with persistent hypotension unresponsive to vasopressor and volume therapy, assessing serum cortisol levels should be considered and treatment with stress doses of hydrocortisone may be necessary [57]. (See "Short-term complications of the premature infant", section on 'Systemic hypotension'.)
- Patent ductus arteriosus (PDA) is common in preterm infants with RDS. It may contribute to difficulties in weaning from mechanical ventilation and predispose the patient to BPD. The clinical features, diagnosis and management of PDA are discussed elsewhere in the program. (See "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants".)

COMPLICATIONS — Therapy with exogenous surfactant and antenatal corticosteroids have lowered the mortality and morbidity associated with RDS. Nevertheless, complications and deaths still persist. Complications are most often due to the therapeutic interventions, including placement of arterial catheters, supplemental oxygen, positive pressure ventilation, and the use of endotracheal tubes.

Endotracheal tube complications — Displacement or misplacement of the endotracheal tubes occurs commonly. Endotracheal tube placement into a main stem bronchus leads to hyperinflation of the ventilated lung and atelectasis of the contralateral lung. The hyperinflation may contribute to air leaks and the air-block syndrome. (See "Pulmonary air leak in the newborn" and 'Pulmonary air leak' below.)

Other complications from intubation include subglottic stenosis and atelectasis postextubation [58]. Esophageal and pharyngeal perforations rarely occur and may be confined to the mediastinum or extend into the pleural cavity [59].

Pulmonary air leak — Pulmonary air leaks, also known as air block syndrome, is the most common acute complication of RDS. Air leaks are due to the rupture of an overdistended alveolus usually from positive pressure due to mechanical ventilation. The air from the ruptured alveoli dissects along the perivascular connective tissue sheath. This dissection can move toward the hilum, resulting in a pneumomediastinum, or into the pleural space, producing a pneumothorax. Less commonly, air may dissect into the pericardial space, subcutaneous tissue, or peritoneal space, causing pneumopericardium, subcutaneous emphysema, and pneumoperitoneum, respectively. In the preterm infant, the perivascular connective tissue is more abundant and more compliant allowing air trapping in the perivascular space, resulting in pulmonary interstitial emphysema (PIE).

The clinical features, diagnosis and management of each of these pulmonary air leak disorders are discussed elsewhere in the program. (See "Pulmonary air leak in the newborn".)

Bronchopulmonary dysplasia — Bronchopulmonary dysplasia (BPD), also referred to as chronic lung disease of the neonate (CLD), is the main chronic complication of RDS. Despite improvements in the management of RDS, the incidence of BPD is still substantial.

The etiology of BPD is multifactorial. Inflammation, caused by volutrauma, barotrauma, oxygen toxicity, or infection, plays an important role in its development.

The lung appears to be most vulnerable before the alveolar stage of development (which occurs at approximately 31 to 34 weeks gestation), when alveolar formation is initiated. This is due to the premature lung's structural and functional immaturity, including poorly developed airway support structures, surfactant deficiency, decreased compliance, underdeveloped antioxidant mechanisms, and inadequate fluid clearance.

The pathogenesis, clinical features, prevention and management of bronchopulmonary dysplasia are discussed elsewhere in the program. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia" and "Prevention of bronchopulmonary dysplasia" and "Management of bronchopulmonary dysplasia".)

SUMMARY AND RECOMMENDATIONS — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. Recommendations for prevention of RDS are discussed elsewhere (see "Prevention of respiratory distress syndrome in preterm infants").

- We recommend administration of surfactant therapy in infants with RDS (Grade 1A). The initial dose of surfactant is dependent on the surfactant product selected (table 1). (See 'Indications' above.)
- We recommend retreatment with subsequent doses of surfactant if there are persistent clinical findings of RDS (Grade 1B). In our clinical practice, persistent clinical disease is defined as a continual or recurrent oxygen requirement of greater than 30 percent. (See 'Continued therapy' above.)
- We recommend that infants with RDS be treated with CPAP rather than mechanical ventilation if the baby is active and breathing spontaneously (Grade 1B). CPAP promotes lung expansion and prevents atelectasis. (See 'Continuous positive airway pressure (CPAP)' above.)
- If respiratory failure occurs, intubation and mechanical ventilation is initiated. The use of mechanical ventilation should be minimized as it increases the risk of developing pulmonary air leaks and bronchopulmonary dysplasia. (See 'Criteria for mechanical ventilation' above.)
- Until an effective regimen is determined that demonstrates a substantial benefit of iNO justifying the cost, we recommend NOT administering iNO to preterm infants with RDS (Grade 1B). If utilized, iNO should be limited to clinical trials. (See 'Inhaled nitric oxide' above.)
- We recommend NOT administering postnatal glucocorticoid steroids due to the increased risk of long-term abnormal neurodevelopmental outcomes (Grade 1B). (See "Prevention of bronchopulmonary dysplasia", section on 'Glucocorticoids' and "Postnatal use of glucocorticoids in bronchopulmonary dysplasia".)

- Supportive general care includes providing optimal thermoregulation, close monitoring of fluid balance and avoiding fluid overload, maintaining adequate blood pressure and perfusion, and detecting and treating persistent patent ductus arteriosus. (See 'Supportive care' above.)
- Complications are most often due to the therapeutic interventions, including placement of arterial catheters, supplemental oxygen, positive pressure ventilation, and the use of endotracheal tubes. (See 'Complications' above.)

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Prevention of respiratory distress syndrome in preterm infants

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INTRODUCTION — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. The lungs of preterm infants lack adequate pulmonary surfactant that normally lines the alveolar surfaces. RDS is a result of surfactant deficiency, which increases surface tension at the air-liquid interface in the alveoli and terminal airways; this leads to atelectasis, impaired gas exchange, and secondary lung injury.

As surfactant deficiency is due to lung immaturity, the best intervention for RDS is to prevent premature birth. Potential effective therapies have included cervical cerclage, use of tocolytic agents, prevention and treatment of infections, and smoke and alcohol cessation. (See "Prevention of spontaneous preterm birth".)

If premature birth cannot be prevented, a more directed therapeutic approach toward the neonate to prevent RDS includes:

- The use of antenatal steroid treatment to women in preterm labor, accelerating fetal lung maturation and surfactant production.

- The use of exogenous surfactant in the premature infant, providing adequate levels of surfactant and improving lung function.

The therapeutic approach to prevent of RDS will be presented here. The pathophysiology and clinical manifestations are discussed separately. (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn".)

Despite the initiation of preventive care as outlined in this topic review, RDS may still develop and is associated with both acute and chronic complications. The treatment and complications of RDS are discussed separately. (See "Treatment and complications of respiratory distress syndrome in preterm infants".)

ANTENATAL CORTICOSTEROID THERAPY — Antenatal corticosteroid (ACS) therapy is used in pregnant women at risk for preterm labor, as it enhances maturational changes in lung architecture and biochemistry, resulting in improved neonatal lung function. These changes increase the synthesis and release of surfactant and other components necessary for surfactant function, decreasing the incidence of RDS.

We recommend antenatal corticosteroid (ACS) treatment for women at risk for preterm delivery prior to 34 weeks of gestation to prevent RDS as outlined by National Institutes of Health (table 1). The efficacy and use of antenatal corticosteroid therapy are discussed in greater detail elsewhere in the program. (See "Antenatal use of corticosteroids in women at risk for preterm delivery".)

SURFACTANT THERAPY — Exogenous surfactant replacement therapy is widely used and is effective in reducing mortality and morbidity in infants with RDS [1,2]. Therapy provides surfactant into the lungs of preterm infants, preventing the development of RDS or (in some cases) diminishing its severity. Surfactant therapy varies in the types of preparation and the timing of administration.

Types of surfactant — A wide variety of surfactant preparations, which include natural and synthetic products, have been developed. At the present time, only natural surfactant preparations are available (table 2). The different preparations of surfactant including their relative efficacy are more fully discussed elsewhere in the program. (See "Exogenous surfactant therapy in preterm infants".)

Timing of surfactant administration — Surfactant is administered in preterm infants using three different timing strategies.

- Prophylactic surfactant therapy, which is administered at the time of delivery to infants at risk of RDS
- Early therapy, which is administered by two hours of age frequently before the diagnosis of RDS is made
- Rescue surfactant therapy, which is given once the diagnosis of RDS is established

In all three strategies, surfactant therapy improves mortality and morbidity in preterm infants when compared to untreated patients [3,4]. However, clinical trials suggest that prophylactic or early therapy is superior to rescue therapy alone in infants at high-risk for RDS (below 30 weeks gestation) [5-7].

Prophylactic or early versus rescue therapy alone — The decision to administer prophylactic or early surfactant therapy versus rescue therapy is based upon the identification of the infant at risk for RDS who may benefit from preventive therapy.

The principal risk factor is gestational age, with infants less than 30 weeks gestational age being at the highest risk for the development of RDS, as well as having the highest risk of mortality and morbidity associated with RDS.

In at-risk infants, prophylactic or early treatment is associated with a decrease in morbidity and mortality compared to rescue treatment for established RDS. This was best illustrated in two separate meta-analyses [6,7].

The first meta-analysis compared early to rescue therapy in four randomized controlled studies with 3459 patients [6]. Early treated patients received surfactant preparation within the first two hours of life and qualified

because they required intubation for early RDS, while rescue treated patients received surfactant after the diagnosis of RDS firmly was established. Two of the studies used natural surfactant and the other two synthetic preparations. The following results were reported:

- In all four studies, early treated patients had a significantly reduced mortality rate compared to rescue treated patients (19.5 versus 22.3 percent; RR 0.87, 95% CI 0.77 to 0.99).
- There was a significant decrease in complications in early treated patients compared to rescue treated patients including pneumothorax (11.9 versus 17.1 percent; RR 0.70, 95% CI 0.59 to 0.82), pulmonary interstitial emphysema (9.6 versus 14.8 percent; RR 0.63, 95% CI 0.59 to 0.82), and chronic lung disease (CLD) (8.7 versus 10.8 percent; RR 0.7, 95% CI 0.55 to 0.88).
- There were no differences in the incidences of patent ductus arteriosus, intraventricular hemorrhage (IVH), retinopathy of prematurity, bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC).

The second meta-analysis compared prophylactic to rescue therapy in eight randomized controlled studies with 2818 patients [7]. All patients were treated with natural surfactant preparations. Prophylactic treated infants were intubated in the delivery room and received surfactant therapy prior to the first breath or immediately after intubation and stabilization. Rescue treated patients received surfactant after the diagnosis of RDS was established. Studies selected infants at high risk for RDS using inclusion criteria of gestational age less than 32 weeks gestation. The results were as follows:

- In seven studies, prophylactic treated patients had a significantly reduced mortality rate compared to rescue treated patients (7.2 versus 11.7 percent; RR 0.61, 95% CI 0.48 to 0.77). In a secondary analysis of infants less than 30 weeks gestation, prophylactic therapy decreased mortality compared to rescue therapy (10.3 versus 16.3 percent; RR 0.62, 95% CI 0.49 to 0.78).
- There were decreases in the incidence of pneumothoraces and the development of pulmonary interstitial emphysema in infants treated with the prophylactic strategy compared to those treated with rescue strategy (3.3 versus 5.4 percent; RR 0.62, 95% CI 0.42 to 0.89) and (12.2 versus 19.8 percent; RR 0.54, 95% CI 0.36 to 0.82), respectively.
- There were no differences in the incidences of patent ductus arteriosus, IVH, retinopathy of prematurity, BPD, and NEC between groups.

These data indicate that for every 100 babies at high risk for RDS, prophylactic surfactant versus rescue therapy alone would result in approximately five fewer deaths.

Prophylactic versus early therapy — Although there are no clinical trials that compare prophylactic to early therapy, there is some indirect evidence to suggest that prophylactic therapy is superior to early therapy:

- Even short delays of administration of surfactant may worsen outcomes. In a randomized study of early versus delayed surfactant in 2690 infants at high risk for RDS, for example, the combined outcome of death and BPD was reduced by 11 percent in patients who received surfactant before two hours of life compared to those treated at three hours of life [8]. Although this study suggests earlier administration of surfactant is beneficial, it did not directly compare prophylactic administration in the delivery room to administration in the neonatal intensive care setting.
- There is evidence suggesting that spontaneous breathing or mechanical ventilation in infants with surfactant deficiency injures the lung within the first hour of life. This was demonstrated in an autopsy study of infants who died before 12 hours of life [9]. Nine infants who lived from 1 to 10 hours had evidence of hyaline membrane disease by histology.

These data suggest that the optimal timing for surfactant administration to prevent RDS is at the time of delivery for preterm infants at risk for RDS.

Gestational age — We do not routinely administer prophylactic surfactant to infants who are greater than 30 weeks gestation. These larger infants (usually greater than 1250 grams) are at a lower risk for developing severe RDS and clinical trials have not found a benefit of prophylactic over rescue treatment [10].

Our approach — Our clinical approach is to administer a natural surfactant preparation in the delivery room to infants at high risk for RDS. This approach is in concordance with a clinical report from the American Academy of Pediatrics published in 2008, which summarized the available literature and includes the following [5]:

- Intubation of infants born at or before 30 weeks gestation in the delivery room.
- Prophylactic natural surfactant therapy is administered through the endotracheal tube as soon as the infant is stable after intubation. We do not obtain a chest X-ray, as this would delay the administration of surfactant. Skilled personnel are required to ensure proper placement without the benefit of chest X-ray confirmation.

The recommended dose of surfactant is dependent upon the surfactant used (table 2). The dosing is expressed in mL per kg of body weight, but optimal dosing for each preparation has not been studied extensively. Studies comparing doses are limited, and firm conclusions about optimal dosing cannot be reached at this time. At present, dosing is based on the manufacturers' recommendations and is as follows:

- Poractant alfa — 2.5 mL/kg (200 mg phospholipid/kg)
- Calfactant — 3.0 mL/kg (105 mg phospholipid/kg)
- Beractant — 4.0 mL/kg (100 mg phospholipid/kg).

There are no current data to recommend a specific natural surfactant preparation over another. (See "Exogenous surfactant therapy in preterm infants".)

- After surfactant administration, extubation and stabilization on nasal continuous positive airway pressure (CPAP) can be considered if the infant is active, and exhibits spontaneous respiratory effort. (See 'Mechanical ventilation and CPAP' below.)
- For infants who are less than 30 weeks gestation who are born outside a level three neonatal intensive care unit, intubation and surfactant administration should be considered if competent personnel are available prior to transport.

An alternate approach is the initial use of continuous positive airway pressure alone, and subsequent intubation and administration of surfactant only in infants who develop significant respiratory symptoms. (See 'Surfactant and CPAP' below.)

COMBINATION OF STEROIDS AND SURFACTANT — The combination of antenatal corticosteroid and surfactant therapy appears to improve mortality rates and clinical outcome in survivors [11-16]. Although there is no single trial that has compared the use of antenatal corticosteroids alone, surfactant alone, combination of the two, and placebo, the use of combination therapy is recommended based upon overall observations. Interpretation of many of the studies is difficult since a few infants were not exposed to antenatal corticosteroid therapy. Despite this, the effectiveness of combination therapy is illustrated by the following:

- In one study, 430 preterm infants (gestational age between 23 and 29 weeks) were randomly assigned to receive prophylactic natural surfactant (100 mg of phospholipids/kg of Survanta) or placebo after initial stratification by birthweight and antenatal steroid exposure [15]. Treated patients could be given repeated doses of surfactant. Compared with placebo, surfactant resulted in a significant decrease in mortality rate (11 versus 19 percent), incidence of RDS (28 versus 57 percent), and incidence of pulmonary interstitial emphysema (23 versus 37 percent).
- In a retrospective study of 226 infants (<31 weeks gestation) who were treated with prophylactic surfactant, outcomes were analyzed based upon the administration and timing of antenatal steroids: group 1, no steroids; group 2, steroids within 24 hours before delivery; and group 3, steroids 24 hours to 7 days before delivery [16]. Group 2 had the lowest mortality rate and incidence of severe IVH. Compared with group 1, groups 2 and 3 also had significantly lower mortality rates and incidence of severe IVH.

MECHANICAL VENTILATION AND CPAP — Infants at risk for RDS are initially intubated to deliver the administration of exogenous surfactant. Subsequently, continuous mechanical ventilation has traditionally been utilized to help prevent atelectasis, even in infants without respiratory failure. However, it is increasingly

appreciated that continued ventilation is associated with volutrauma, thereby contributing to the development of bronchopulmonary dysplasia (BPD) [17-19].

Among infants without respiratory failure, continuous positive airway pressure (CPAP) is an alternative to help prevent atelectasis and reduce the risk of BPD. Most of the data supporting the use of CPAP has been observational [17,20-22]. Results are less clear in the single trial comparing CPAP to intubation and ventilation.

In this multicenter trial of 610 infants who were born between 25 and 28 weeks gestation, patients were assigned to nasal CPAP (pressure of 8 cm H₂O) or intubation and ventilation if they required respiratory support at five minutes of age [23]. The administration of surfactant was not mandated and followed local clinical practice. The following findings were noted:

- At 36 weeks corrected gestational age, there was no difference in the primary outcome of death or BPD (defined as need for oxygen therapy) between infants with CPAP versus those who were intubated (34 versus 39 percent, OR 0.8, 95% CI 0.58-1.12.).
- About half (46 percent) of the CPAP group were intubated during the first five days of life.
- Surfactant use was halved in the CPAP compared to the intubated group and days of ventilation were fewer. There was, however, no difference in the fraction of inspired oxygen (FiO₂) or maximum PaCO₂ during the two groups during the first five days of life.
- The risk of pneumothorax was greater in the CPAP compared to the intubated group (9 versus 3 percent).

This study was limited in that treatment was not masked and there were variations in other interventions including administration of surfactant and methylxanthine treatment (which is associated with a lower incidence of BPD). Nevertheless, these results suggest that it may be possible to initiate CPAP in preterm infants born ≤ 28 weeks and treat them with surfactant only if they require intubation. (See "Management of apnea of prematurity", section on 'Methylxanthine therapy'.)

Surfactant and CPAP — CPAP alone, versus CPAP in conjunction with surfactant without mandatory ventilation, may decrease the need and duration for mechanical ventilation and air-leak syndrome including BPD [24-26]

This was best illustrated in the SUPPORT (Surfactant, positive pressure, and pulse oximetry randomized) trial that randomly assigned 1316 extremely preterm infants (gestational age between 24 weeks and 27 weeks 6 days) to intubation and surfactant therapy or nasal CPAP alone within the first hour of life [25]. Patients who were in the surfactant group remained intubated and ventilated until they met predefined criteria demonstrating the ability to maintain adequate spontaneous ventilation and oxygenation. Patients who were assigned to the CPAP group were intubated and received surfactant within the first 48 hours of life if they met predefined criteria that included a requirement of supplemental oxygen with a FiO₂ greater than 50 percent or showed evidence of hemodynamic. In this study, infants were also randomly assigned to one of two target ranges of oxygen saturation. The following findings were noted:

- Eighty-three percent of the infants in the CPAP group were intubated and about two-thirds received surfactant.
- After adjusting for confounding variables (ie, gestational age, center, and family clustering), there was no difference between the CPAP and surfactant groups at 36 weeks postmenstrual age (PMA) in the primary outcomes of mortality (14.2 versus 17.5 percent, relative risk [RR] 0.81, 95% CI 0.63-1.03) and the rate of bronchopulmonary dysplasia defined as the use of supplemental oxygen at 36 weeks PMA (40.2 versus 44.3 percent, RR 0.94, 95% CI 0.82-1.06).
- Secondary analyses demonstrated the CPAP alone was associated with a lower rate of postnatal corticosteroid use and a shorter duration of ventilation. There were no differences in other secondary outcome measures between the two groups, including the risk of necrotizing enterocolitis, air leaks, severe intraventricular hemorrhage, severe retinopathy of prematurity and patent ductus arteriosus.

Although these results suggest that outcome using CPAP alone is as good as intervention with intubation and surfactant, an accompanying editorial expressed the following concerns regarding the study design of this trial [27]:

- The criteria used for extubation in the intubated/surfactant group appeared to be more stringent than those used in prior clinical trials, and resulted in a longer median duration of ventilation compared to previous studies [23].
- Randomization was performed before delivery, and as a result, some of the infants in the CPAP group who exhibited respiratory distress immediately after delivery, were intubated after birth and did not receive CPAP.
- The surfactant and ventilator group required more resuscitation in the delivery room (intubation, chest compressions, and epinephrine) and may have been a sicker group to begin with based upon the support they required in the delivery room. The outcome analysis did not appear to be adjusted for this finding.

Finally, it remains uncertain whether CPAP alone is a better alternative to intubation and prophylactic administration of surfactant as over 80 percent of the CPAP alone group eventually were intubated and the majority received surfactant. It is unknown whether there was an impact in the delay of intubation and surfactant in any of these patients. Further studies including long-term developmental outcome studies are needed to determine whether CPAP alone is a better alternative to intubation and prophylactic administration of surfactant in premature infants less than 30 weeks gestation.

Our approach — Our current recommendation is that, after intubation and administration of surfactant, the infant should be extubated and placed on CPAP if the infant is active, exhibits spontaneous respiratory effort, and does not seem to require mechanical ventilation [28]. However, others have suggested initial use of CPAP and administration of surfactant only if the patient requires intubation, based upon the concern that intubation can be difficult and may destabilize an infant's condition [23].

Historical cohort studies have demonstrated a decline in the incidence of BPD when changes in delivery care using these approaches were implemented.

- In the first study, delivery room practice changes included intubation with the administration of surfactant and extubation followed by continuous positive airway pressure treatment at delivery. This delivery room practice change away from mechanical ventilation was combined with targeting lowered oxygen saturation, and administering early amino acid supplementation on the admission to the NICU [29]. These changes were associated with a decrease rate of moderate and severe BPD in infants with birth weights below 1000 g from 43 to 24 percent.
- In the second study, practice changes included lower oxygen saturation goals and selective intubation policy for infants born at or below 29 weeks gestation [30]. Before the changes in practice, infants were intubated, given surfactant in the delivery room, and were managed subsequently on mechanical ventilation. After delivery room practice changes were implemented, infants that were spontaneously breathing with a good heart were stabilized without mechanical ventilation, and nearly two-thirds received nasal CPAP. These changes resulted in a decrease rate of BPD from 47 to 21.5 percent.

An alternative approach is initial CPAP for all preterm infants below 30 weeks gestation in the delivery room and, the use of early rescue surfactant in infants who develop a FiO₂ requirement greater than 0.5 or 0.6 [25,31].

SUMMARY AND RECOMMENDATIONS — The administration of antenatal corticosteroid, and prophylactic or early surfactant therapy to high-risk preterm infants reduces the incidence and severity of RDS.

- We recommend that ACS should be given to any pregnant woman at 24 to 34 weeks of gestation with intact membranes at high risk for preterm delivery (table 1) (Grade 1A). (See "Antenatal use of corticosteroids in women at risk for preterm delivery".)
- We suggest that infants born at or before 30 weeks gestation be intubated and receive a prophylactic natural surfactant preparation (Grade 2B). The dose is dependent upon the surfactant product selected. In preterm infants without respiratory failure, an alternative option is the administration of continuous

positive airway pressure alone. (See 'Surfactant therapy' above and 'Mechanical ventilation and CPAP' above.)

- After administration of surfactant and if the infant is active and exhibits spontaneous respiratory effort, we recommend extubation and stabilization on CPAP rather than continued intubation and mechanical ventilation (Grade 1B). (See 'Mechanical ventilation and CPAP' above.)
- We recommend not administering prophylactic surfactant therapy for infants greater than 30 weeks gestation (Grade 1B). (See 'Gestational age' above.)

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Mechanical ventilation in neonates

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INTRODUCTION — The introduction of mechanical ventilation in the 1960s was one of the major new interventions in neonatology, which provided life-saving support for infants with respiratory failure. Over the past forty years, along with other technologic advancements such as the administration of antepartum corticosteroids and replacement surfactant therapy, mechanical ventilation has led to improved neonatal survival, especially for premature infants born less than 30 weeks gestation with immature lung function. (See "Incidence and mortality of the premature infant".)

Although mechanical ventilation can be life saving, it may cause chronic lung injury that results in bronchopulmonary dysplasia (BPD), a major complication of prematurity. As a result, continued efforts have been focused upon development of new technology and strategies for neonatal ventilator care to maintain

adequate gas exchange but minimize lung damage. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia".)

Neonatal ventilator care, including the different types of mechanical ventilation and their advantages and disadvantages will be reviewed here.

BACKGROUND — The principal benefits of neonatal mechanical ventilation during respiratory failure are as follows:

- Improve gas exchange, primarily by lung recruitment to improve ventilation/perfusion (V/Q) matching (see "Physiologic and pathophysiologic consequences of mechanical ventilation", section on 'Physiologic shunt')
- Decrease work of breathing
- Provide ventilation in infants with respiratory depression or apnea

Approximately two-thirds of all infants admitted to the neonatal intensive care unit (NICU) require positive pressure ventilation [1]. Ventilation is commonly required for the following reasons:

- Respiratory distress syndrome (RDS) (see "Treatment and complications of respiratory distress syndrome in preterm infants", section on 'Mechanical ventilation and CPAP')
- Apnea due to prematurity or perinatal anoxia
- Infection: sepsis and/or pneumonia
- Post-operative recovery
- Persistent pulmonary hypertension (see "Persistent pulmonary hypertension of the newborn", section on 'Assisted ventilation')
- Meconium aspiration syndrome (see "Prevention and management of meconium aspiration syndrome", section on 'Assisted ventilation')
- Congenital anomalies, such as congenital diaphragmatic hernia (see "Congenital diaphragmatic hernia in the neonate", section on 'Ventilation')

With the improvement in survival rate of very low birth weight infants (birth weight less than 1500 g), research efforts have been devoted to developing new ventilation strategies to reduce lung damage from positive pressure ventilation, thereby reducing the incidence of BPD [2,3]. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia", section on 'Mechanical ventilation'.)

Indications for ventilation — Assisted ventilation should be initiated when respiratory failure occurs. Respiratory failure is verified by one of the following:

- Respiratory acidosis, documented by an arterial pH <7.20 and a PaCO₂ >60 mm Hg
- Hypoxia, documented by an arterial PaO₂ <60 mm Hg despite oxygen supplementation of 70 percent on nasal CPAP
- Severe apnea

Types of ventilation — Ventilators used in the neonatal intensive care unit (NICU) can be divided into two categories:

- Conventional ventilation or intermittent mandatory ventilation (IMV) is based upon setting a mandatory ventilator breath rate while continuous air flows through the ventilator circuit. The mode of mechanical ventilation refers to the method of setting the inspiratory support and time. As an example, during pressure-limited ventilation, inspiratory support ends after reaching the set inspiratory pressure, whereas in volume-targeted ventilation, inspiratory support ends after delivery of a set tidal volume. In some cases, support is terminated because a set time has elapsed.

Ventilatory breaths may be triggered by the patient's own inspiratory effort, referred to as patient-triggered or synchronized ventilation.

- High frequency ventilation is based upon the delivery of small volumes of air, which are equal to or smaller than the anatomic dead space, at an extremely rapid rate (300 to 1500 breaths per minute).

CONVENTIONAL VENTILATION — Conventional ventilation (CV) or intermittent mandatory ventilation (IMV) delivers a set number of breaths per minute while gas flows continuously through the ventilator circuit allowing spontaneous breathing by the patient. The mode of mechanical ventilation and the duration of the inspiration are determined by setting pressure, volume, flow, or time parameters. (See "Overview of mechanical ventilation", section on 'Types of breaths' and "Modes of mechanical ventilation".)

The most commonly used ventilator in neonates is the continuous flow, time-cycled pressure-limited (TCPL) ventilator that has been the standard ventilator in the NICU for more than three decades. Adaptions of the TCPL include synchronized and pressure support ventilation, which are increasingly used in the NICU setting.

Pressure-limited ventilation — The continuous flow, time-cycled pressure-limited (TCPL) ventilator provides a continuous flow of heated and humidified air and delivers a breath that is set by peak inspiratory pressure (PIP) and either the absolute inspiratory time or inspiratory:expiratory time ratio (I:E ratio). The delivered tidal volume is dependent upon the PIP, the lung compliance and resistance, and the tubing resistance. The tidal volume will be larger with an increase in PIP and lung compliance, and decreases with increased lung or tubing resistance. A background level of positive end expiratory pressure (PEEP) is adjusted independently. The clinician sets the PIP, I:E ratio, respiratory rate, PEEP, and inspired oxygen concentration (FiO₂).

Arterial oxygen tension (PaO₂) generally rises with increases in the FiO₂ and mean airway pressure (MAP) [4,5]. Mean airway pressure can be adjusted by changes in the I:E ratio, PIP, and PEEP, thereby affecting the PaO₂. The level of arterial carbon dioxide tension (PaCO₂) is determined by the minute ventilation, which is set by the respiratory rate and PIP.

The TCPL ventilator is relatively simple to use and less costly than other ventilators. Thus, it is the most commonly used ventilator in the NICU setting. Other advantages of this system include:

- Spontaneous respiration between ventilator breaths due to the continuous flow of air. Weaning from the ventilator by simply reducing the mandatory ventilator rate is an easy process and allows spontaneous patient breaths to contribute an increasing proportion of the minute ventilation.
- The ability to control the PIP and MAP. High airway pressure may be a contributor to chronic lung damage (ie, barotrauma).

However, the TCPL ventilator has the following shortcomings:

- Increased work of breathing during spontaneous breathing.
- Poor synchrony between spontaneous and mandatory breaths. Asynchrony has been associated with deterioration in oxygenation, increases in PCO₂, and reduction in tidal volume and minute ventilation [6]. In addition, wide fluctuations in arterial pulse pressure during asynchrony may increase the risk of intraventricular hemorrhage.
- Delivered tidal volume is poorly controlled with a wide range of breath-to-breath variability. This was illustrated in a study of preterm infants that demonstrated exhaled tidal volume was greater than the targeted volume for 25 percent of the breaths and less than the targeted volume for 36 percent of breaths [7]. Delivered tidal volume changes when there are alterations in lung compliance and resistance (which occurs with the administration of surfactant), circuit compressed gas volume, and endotracheal tube (ETT) leak.

Synchronized and patient-triggered ventilation — Synchronized and patient-triggered ventilators are adaptations of the TPLC ventilatory system that address the issue of asynchrony. They combine the features of the TPLC ventilator (ie, continuous flow, pressure limitation, and time cycle), with a flow sensor at the airway opening (ie, endotracheal tube adaptor) that detects changes in airway pressure, airflow, or respiratory movements as an indication of a spontaneous breath. The clinician sets the PIP, I:E ratio, respiratory rate, PEEP, and FIO₂.

- With synchronized ventilation, when the sensors detect the onset of a spontaneous breath, the ventilator delivers an intermittent positive pressure breath at a fixed rate in synchrony with the infant's inspiratory effort, referred to as synchronized intermittent mandatory ventilation (SIMV). SIMV prevents breathing out of phase with the ventilator ("fighting the ventilator"). In some ventilators, SIMV can be supplemented by pressure-support for the infant's spontaneous breaths. (See 'Pressure-support addition to SIMV' below.)
- With patient-triggered ventilation (also referred to as Assist/Control ventilation), a positive pressure breath is delivered with every inspiratory effort. As a result, if the infant has any spontaneous breaths, the ventilator delivers more positive pressure breaths than the set minimum rate, which usually results in a decrease in the PIP needed for adequate gas exchange.

In both types of ventilation, the ventilator delivers an operator selected minimal mandatory IMV rate to provide backup ventilation if the patient is apneic.

The theoretical benefits of synchronizing the infant's attempt to breathe with the mechanical breath from the ventilator include a lower peak inspiratory pressure (PIP), resulting in less air leak and chronic lung damage, and a reduction in the amount of sedatives administered, thereby shortening the weaning process from the ventilator.

Currently available data demonstrate some, but not substantial benefit of synchronized versus nonsynchronized ventilation including fewer periods of low oxygen saturation and less variability in breath-to-breath exhaled tidal volume [8-13]. However, synchronized ventilation does not appear to significantly reduce the mortality rate or the incidence of BPD. This was illustrated in a meta-analysis of five studies that included 1729 patients as follows [12]:

- Although there was a trend towards an increase in the death rate of infants using the SIMV or patient-triggered ventilator compared to those with conventional IMV, this was not statistically significant (RR: 1.19, 95% CI 0.95 to 1.49).
- There were no differences in the rates of air leaks, severe intraventricular hemorrhage, bronchopulmonary dysplasia, or extubation failure between the two groups.
- There was a shorter duration of ventilation in the infants who received synchronized or patient-triggered versus conventional ventilation (weighted mean difference of -35 hours, 95% CI -62 to 7 hours).

Although the overall outcome of mortality rate and the incidence of BPD did not differ between infants who received synchronized versus nonsynchronized ventilation, experts in the field suggest that synchronization may be useful in a subgroup of preterm infants below 28 weeks of age who are more susceptible to lung injury because of the shorter period of ventilation [14,15].

Pressure-support addition to SIMV — Pressure-support ventilation is a patient-triggered, pressure-limited, flow-cycled mode of ventilation. It delivers inspiratory support until the inspiratory flow decreases to a predetermined percentage of its peak value, usually 25 percent. When pressure-support is added to SIMV, the clinician sets the inspiratory pressure level, inspiratory flow rate, PEEP, FiO₂, and a mandatory respiratory rate.

In this mode of ventilation, flow cycling is used to assist every spontaneous inspiratory effort and terminates ventilator-derived breaths as spontaneous inspiration ends or inflation is completed. As a result, synchrony is improved because the patient modulates the duration of the inspiration. The tidal volume is dependent upon the ventilator settings and patient factors, such as lung compliance and level of consciousness.

The work of breathing is inversely proportional to the pressure support level because pressure support counteracts the resistance imposed by the endotracheal tube and ventilator circuit. The inspiratory pressure-support is usually set at 30 to 50 percent of the difference between the PIP and PEEP, but with some ventilators, a pressure support of 10 cm above PEEP level is necessary to reduce the work of breathing. In addition, a higher inspiratory flow rate shortens the time to reach maximal airway pressure, which decreases the work of breathing. A minimum mandatory ventilator rate is set by the user to provide backup ventilation in case of apnea.

There are limited data comparing SIMV with pressure-support to SIMV alone. Small observational studies suggested that the addition of pressure support resulted in an ability to reduce the mandatory ventilator

respiratory rate, which led to an overall reduction in mean airway pressure [16,17], an overall decrease in respiratory rate, and an increase in minute ventilation [18].

In the single randomized trial of 107 preterm infants (birth weight 500 to 1000 g) that compared SIMV with pressure-support to SIMV alone, infants assigned to SIMV with pressure-support during the first week of life were less likely to require mechanical ventilation at 28 days of life (47 versus 69 percent) [19]. However, the mean total days of mechanical ventilation and supplemental oxygen during the first 28 days of life did not differ between the two groups. There were also no differences in mortality rate, or the incidences of sepsis, patent duct arteriosus (PDA), grade III or IV intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), or stage III retinopathy of prematurity.

Volume-targeted ventilation — Several studies have demonstrated that volume distension of the lung, rather than peak airway pressure, induces microvascular lung injury [20,21]. As discussed previously, pressure-limited ventilation poorly controls the delivered tidal volume, resulting in a wide range of breath-to-breath tidal volumes. In particular, these large variations in delivered volume over time subject the immature lungs of preterm infants to risks of both overdistension and collapse of air spaces.

This is particularly problematic following the administration of surfactant, when lung compliance may rapidly change resulting in the delivery of excessive volume with the risk of progressive hypocarbia (risk factor for IVH) or pulmonary air leak due to pulmonary overdistension. As a result, beginning in the late 1990s, research efforts have been directed at controlling tidal volume during neonatal mechanical ventilation, especially in preterm infants [22].

In the neonate, two modes of volume-targeted ventilation have been generally used [1,23].

- **Volume-controlled (VC) ventilation** — The clinician presets the tidal volume (generally 4 to 6 mL/kg), the respiratory rate, and an inspiratory time limit. The duration of inflation is dependent upon the time to deliver the set tidal volume. However, the total volume may not be delivered if the preset inspiratory time limit is exceeded. The rate of flow, PIP, and inspiratory time may vary from breath-to-breath.
- **Volume-guarantee ventilation (VG)** — VG ventilation is a form of time-cycled, pressure-limited ventilation. The clinician selects an expiratory tidal volume, inspiratory time, and a maximum inspiratory pressure limit. A flow sensor is placed at the endotracheal tube, which measures the inspired and expired tidal volume. The PIP varies up to the preset maximum pressure as the ventilator delivers the preset tidal volume. PIP decreases with improvement in lung compliance and increased spontaneous respiratory effort by the infant.

Several studies have shown that VG combined with either SIMV or patient-triggered pressure-limited ventilation compared to conventional pressure-limited ventilation was associated with the following additional benefits:

- Provided effective gas exchange while reducing the number of high volume mechanical breaths [24]
- Maintained tidal volume closer to the targeted goal and reduced the incidence of hypocapnia (an indicator of overventilation) [1]
- Decreased PIP of triggered ventilations while maintaining the targeted tidal volume [25]

A meta-analysis of four trials that included 178 preterm infants compared the clinical outcomes of patients treated with volume-targeted ventilation (two used VC ventilation and the other two VG ventilation) to those who received pressure-limited ventilation [1]. The following findings were noted:

- There was no difference in the primary outcome of mortality between the two groups.
- Most of the secondary outcomes were not reported in all four studies. Data for the secondary outcomes included the following:
 - In two studies, the duration of intermittent positive pressure ventilation (IPPV) was decreased in the volume-targeted ventilation group compared to controls (WMD -2.93, 95% CI -4.28 to -1.57).
 - In two studies of 103 infants, the mean duration of ventilation was decreased in the volume-targeted ventilation group (weighted mean difference -2.9 days, 95% CI -4.3 to -1.7 days).

- Pneumothorax was decreased in the volume-targeted ventilation group (RR 0.23, 95% CI 0.1 to 0.8).
- Based upon two studies of 110 infants, grade III or IV intraventricular hemorrhage was decreased in the volume-targeted ventilation group (RR 0.32, 95% CI 0.1 to 0.9).
- Based upon three studies of 160 infants, there was a trend towards a lower risk of BPD in the volume-targeted ventilation group (RR 0.34, 95% CI 0.1 to 1.1).
- There were no differences in the rates of air leak, pulmonary interstitial emphysema, periventricular leukomalacia, or patent ductus arteriosus.
- There were no data comparing the long-term neurodevelopmental outcome between the two groups or long-term respiratory outcome.
- Although sub-analyses were performed for infants with birth weights less than 1000 g, the number of subjects included in these analyses was only 20. As a result, no meaningful conclusion for this subgroup can be made based upon the paucity of data.

In a subsequent trial of 109 premature infants (birth weight between 600 and 1500 g and gestational age between 24 to 31 weeks), the mean time required to achieve either an alveolar-arterial oxygen gradient of less than 100 mmHg or a mean airway pressure less than 8 cm H₂O appeared to be shorter in patients who received volume-controlled ventilation compared to those treated with pressure-limited ventilation, although the difference was not statistically significant (23 versus 33 hours) [26]. The mortality rate was 9 versus 19 percent between the two groups, but this was also not statistically significant.

Although the above results are suggestive that volume-targeted ventilation reduces the rate of complication rates due to mechanical ventilation with improved short-term outcome, caution needs to be exercised before this ventilatory mode can be recommended for routine use in the NICU setting because of the following reasons [23,27].

- The number of patients that have been studied is small, especially patients with birth weights below 1000 g.
- Results have been modest and have looked at short-term outcomes primarily related to the lung. There are no data on long-term neurodevelopmental data, which is a primary outcome goal of current neonatal intensive care.
- Studies have been conducted by a small group of investigators with expertise in the use of volume-targeted ventilation. In general, these ventilators are more difficult to operate than the TCPL ventilators that have been the standard mode of ventilation for many years. As a result, it is unclear whether these results would be replicated in a wider application of this modality by less experienced clinicians.
- There are variations in the delivery of tidal volume, inflation time, and peak pressures amongst the volume-targeted ventilators used in the above studies [28].
- In addition, if volume-triggered ventilation is used, it remains uncertain what is the optimal tidal volume [29].
- Volume-controlled ventilators are more expensive than pressure-limited ventilators, thus to justify the added expense, a significant improved outcome must be unequivocally confirmed.

Large randomized clinical trials are needed to determine whether or not volume-triggered ventilation offers significant clinical benefits over the standard pressure-limited ventilation. However, such trials will be challenging to conduct as these trials will require large number of patients and centers that can competently perform both modes of ventilation. In addition to the short-term outcomes of mortality and respiratory status, long-term outcomes, such as neurodevelopmental outcome, need to be evaluated.

HIGH FREQUENCY VENTILATION — High frequency ventilation (HFV) delivers small volumes of air, which are equal to or smaller than anatomic dead space, at an extremely rapid rate (300 to 1500 breaths per minute). Although there are differences in their designs, currently available HF ventilators deliver similar ventilatory output. Each HF ventilator applies continuous distending pressure to maintain lung expansion and superimposes small tidal volumes at a rapid rate.

The following three types of HF ventilators are used in neonates:

- The high frequency oscillator ventilator (HFOV) delivers small tidal volumes by oscillating air movements produced by the ventilator diaphragm or piston at frequencies of 600 to 900 breaths per minute (10 to 15 Hz), which result in both positive and negative pressure fluctuations and gas mixing. The clinician sets the amplitude and frequency of the pressure wave generated by the ventilator piston or diaphragm, MAP, inspiratory time, and FiO₂. Unlike the other two modes of HFV, expiration is an active process with HFOV and "sigh breaths" are not utilized. HFOV has been the most extensively studied HFV mode in neonates.
- The high frequency jet ventilator (HFJV) uses time-cycled pressure-limited, constant gas flow interrupters that are used in parallel with a conventional ventilator, which provides PEEP and intermittent conventional breaths at 2 to 10 breaths/min (referred to as sigh breaths). Sigh breaths are thought to prevent atelectasis. High frequency jet breaths are delivered through a special endotracheal adapter. The clinician sets PIP for both the jet and conventional breaths, PEEP, frequency of jet breaths (usually 420 breaths per minute), the inspiratory jet valve on-time (usually 0.02 seconds), and FiO₂. Expiration is passive and is dependent on chest wall and lung recoil.
- The high frequency flow interrupter (HFFI) is an adaptation of conventional mechanical ventilators that operates similarly to the HFJV. Gas from a high-pressure source is delivered into the standard ventilator circuit and endotracheal tube. High frequency breaths are produced when the flow of gas is interrupted by a valve mechanism. The clinician sets PIP, PEEP, frequency of breaths (usually between 6 and 20 Hz), and FiO₂. HFFI has been the least studied HFV mode in neonates.

Although data from animal studies suggested that HFV appeared to reduce lung injury compared to conventional ventilation [30], no significant benefit has been seen with any form of HFV compared to conventional ventilation in reducing mortality rate or the incidence of BPD in preterm human infants with respiratory distress syndrome (RDS) as discussed in the following sections.

Elective HFOV versus conventional ventilation — A meta-analysis of 10 trials with 3229 patients using individual patient's data demonstrated no difference in the outcome between elective HFOV and conventional ventilation (CV) in the treatment of preterm infants with RDS [31]. The mean gestational age of the included infants was 27.3 ± 3.8 weeks and mean birthweight was 989 ± 315 g. About 13 percent of infants had a birth weight that was less than the 10th percentile for gestational age and 56 percent had received antenatal corticosteroids. The following findings were noted:

- In nine trials, there were no differences in the three primary outcomes between the two groups:
- Death or bronchopulmonary dysplasia at 36 weeks postmenstrual age (RR 1.0, 95% CI 0.88-1.13).
- Death or severe neurologic injury defined as grade III or IV intracranial hemorrhage and/or cystic periventricular leukomalacia (RR 1.0, 95% CI 0.88-1.13).
- Death, severe neurologic adverse event, or bronchopulmonary dysplasia at 36 weeks postmenstrual age (RR 0.98, 95% CI 0.91-1.05).
- No specific subpopulations based upon sex, gestational age, presence of chorioamnionitis, oxygenation index at trial entry, or antenatal treatment with corticosteroids were identified who benefited from the use of HFOV compared with conventional ventilation. The timing of the first surfactant dose also did not alter primary outcomes between the two groups.

A meta-analysis of 15 trials with 3585 patients based upon trial data also reported similar findings [32]:

- There were no significant differences between the HFOV and CV groups in mortality rate at 28 to 30 days of life in nine trials (RR 1.09, 95% CI 0.88 to 1.35), at 36 to 37 weeks postmenstrual age (PMA), and at discharge in 13 trials (RR 0.98, 95% CI 0.83 to 1.14).
- There was no difference in the incidence of chronic lung disease (CLD) defined as oxygen therapy at 28 to 30 days of life in six trials (RR 0.98, 95% CI 0.88 to 1.1). When CLD was defined as oxygen therapy at 36 to 37 weeks PMA, there was a reduction of CLD in the HFOV group of borderline significance in 14 trials (RR 0.89, 95% CI 0.81 to 0.99).
- There was no difference in the risk of the combined outcome of death or CLD at 28 to 30 days of life in five trials (RR 0.94, 95% CI 0.85 to 1.04). At 36 to 37 weeks PMA, there was a small reduction of the

combined outcome of death or CLD in the HFOV group of borderline significance in 13 trials (RR 0.93, 95% CI 0.86 to 1.00).

- There was variability in the incidence of severe IVH among the 15 trials. Two trials reported that severe IVH, defined as grades III and IV, was higher in the HFOV groups. [33,34]. However, overall there was no difference in the rate of severe IVH (RR 1.11, 95% CI 0.95 to 1.3) from pooled data from all 15 trials.
- Although the age and methods of assessment differ among the six studies that evaluated long-term neurodevelopment outcome, in five trials there was no difference in neurodevelopmental status between the two groups. In one trial, the rate of moderate to severe neurodevelopmental outcome (defined as a Bayley psychometric test score of more than one standard deviation below the mean or a neurologic abnormality detected by neurologic examination) was higher in the HFOV group [33]. This study had also reported a higher risk of severe IVH in the HFOV group, which was associated with a greater likelihood of abnormal neurodevelopmental outcome [33].

Follow-up reports of two trials not included in the second meta-analysis presented outcome data. In the first study, there were no differences in neurodevelopmental and pulmonary outcomes at two years of age between the infants who were assigned HFOV versus those who received CV [35,36]. In the second study, although there was a higher incidence of severe IVH in the HFOV group, the incidence of cerebral palsy was lower in the HFOV group at two years of corrected age (4 versus 17 percent) [34,37].

These results suggest there is no additional substantial benefit of elective HFOV that warrants its additional cost over CV.

Elective HFJV versus conventional ventilation — HFJV has been less rigorously studied in preterm infants compared to HFOV. Results from two small clinical trials that randomly assigned patients to either HFJV or CV varied as follows:

- In one study of 73 preterm infants (birth weights between 500 to 2000 g) with RDS, 95 percent of whom received surfactant therapy, there were no differences in the rates of pulmonary air leak, need for oxygenation or ventilation at 36 weeks PMA, total duration of days for supplemental oxygen, and length of stay between the two groups [38]. Infants who were assigned HFJV were more likely to have Grade 4 IVH, cystic periventricular leukomalacia or death (17 versus 7 percent).
- In a multicenter study of 130 preterm infants (birth weights 700 to 1500 g) who received surfactant therapy, there were no differences in the mortality rate, and the incidences of retinopathy of prematurity (ROP), pulmonary air leak, and severe IVH. Infants assigned to HFJV compared to those who received CV were less likely to need oxygen at 36 weeks PMA or at home after discharge.

These results suggest that elective HFJV does not offer additional benefits over CV in reducing mortality rate or the incidence of BPD and in fact, based upon the first study, HFJV may be associated with a poorer outcome.

Rescue HFV versus conventional ventilation — Limited data from two studies performed in the late 1980s, prior to the general availability of surfactant, demonstrated no added benefit from HFV compared to CV as rescue therapy in preterm infants.

- One multicenter trial randomly assigned patients 182 preterm infants (gestational age less than 35 weeks and birth weight greater than 500 g) with pulmonary interstitial emphysema (PIE) or at risk of developing PIE to either HFOV or CV [39]. There were no differences in the mortality rate, the need for intermittent positive pressure ventilation at 28 days of age, or the incidences of PIE or gross pulmonary leak (eg, pneumothorax or pneumomediastinum) between the two groups. In patients without PIE at study entry, infants assigned to HFOV compared to those who received CV had a lower risk of developing pulmonary air leak (RR 0.73, 95% CI 0.55 to 0.96). However, the rate of IVH of any grade was greater in the HFOV group (RR 1.77, 95% CI 1.06 to 2.96).
- In a second study of 144 preterm infants with PIE, patients were initially assigned to either HFJV or CV, but if the criteria for treatment failure were met, crossover to the alternate ventilation mode was permitted [40]. Although the overall mortality based upon intention to treat was not different between the two groups (RR 1.07, 95% CI 0.67 to 1.72), mortality up until the point of crossover was lower in

the HFJV group. There was also a trend to a reduction in the incidence of BPD in the HFJV group (RR 0.77, 95% CI 0.54 to 1.07).

These data are inconclusive regarding the use of rescue HFV, especially as they were conducted prior to the general availability of surfactant therapy. Nevertheless, when infants fail CV with persistent poor gas exchange when positive inspiratory pressure (PIP) is equal to or greater than 30 cm H₂O or mean air pressure exceeds 12 cm H₂O in infants, HFV offers an alternate mode of ventilation that may provide better ventilation and oxygenation in the neonate with severe respiratory disease.

NONINVASIVE MECHANICAL VENTILATION — Neonatal nasal intermittent positive pressure ventilation (NIPPV) provides noninvasive respiratory support to preterm infants who otherwise would require endotracheal intubation and ventilation. It is an augmentation of continuous positive airway pressure (CPAP), which superimposes inflations set to a peak pressure delivered through nasal prongs or mask [15]. Some devices attempt to synchronize inflations with the infant's spontaneous inspirations.

Data are limited in the use of NIPPV and generally are based upon observational or very small clinical trials. As a result, it is uncertain whether or not the use of NIPPV is beneficial in neonates who require respiratory support and in what settings.

NIPPV has been used for the following indications [15,41]:

- Apnea of prematurity (see "Management of apnea of prematurity", section on 'Nasal continuous positive airway pressure')
- Following extubation; NIPPV compared to nasal CPAP has been shown to reduce extubation failure in infants who required intubation and ventilation [41-44]
- Primary mode of ventilation in preterm infants with RDS (see "Treatment and complications of respiratory distress syndrome in preterm infants", section on 'Nasal intermittent positive pressure ventilation')

OUR APPROACH — Based upon the currently available data, we do not routinely use either volume-targeted or high frequency ventilators in treating neonates who require respiratory support because these modes of ventilation do not add any significant benefit over the less costly and easier to operate standard time-cycled pressure-limited (TCPL) ventilators.

There appears to be no difference in the mortality rate or risk of BPD between synchronized and nonsynchronized pressure-limited ventilation. However, synchronized ventilation may have additional short-term benefits compared to nonsynchronized ventilation, including enhanced oxygenation stability, decreased blood pressure fluctuation, improved patient comfort, and reduced duration of ventilator support. (See 'Synchronized and patient-triggered ventilation' above.)

In our institution, synchronized intermittent ventilation (SIMV) using a TCPL ventilator is the initial mode of ventilation in most neonates requiring respiratory support. We initiate SIMV using low tidal volumes (4 to 6 ml/kg) with permissive hypercarbia (PCO₂ up to 60 mmHg with pH \geq 7.25).

Other modes of ventilation are used in selected settings:

- Pressure support ventilation (PSV) is generally reserved for infants with BPD who require long-term ventilator support or are difficult to wean from SIMV. Limited data suggest that PSV alone or combined with SIMV can maintain adequate gas exchange and augment spontaneous breathing while reducing the work of breathing and need for mandatory ventilator breaths. (See 'Pressure-support addition to SIMV' above.)
- High frequency ventilation is used as rescue therapy when positive inspiratory pressure (PIP) is equal to or greater than 30 cm H₂O or mean air pressure exceeds 12 cm H₂O in infants treated by conventional ventilation.
- We do not currently employ nasal intermittent positive pressure ventilation (NIPPV) due to limited available data. We utilize nasal CPAP for management of apnea of prematurity and early, mild RDS.

- We do not currently use volume-targeted ventilation. However, this may change if new data emerge from ongoing and future trials that identify a role for this mode of ventilation in neonates. (See 'Volume-targeted ventilation' above.)

SUMMARY AND RECOMMENDATIONS

- The principal benefits of ventilation are improved gas exchange, decrease work of breathing, and ventilation for patients with apnea or respiratory depression. (See 'Background' above.)
- Approximately two-thirds of all infants admitted to the neonatal intensive care unit (NICU) require positive pressure ventilation because of apnea, or poor gas exchange with ventilation and perfusion mismatch due to immature lung function, infection, meconium, congenital anomalies, or persistent pulmonary hypertension. (See 'Background' above.)
- Although mechanical ventilation is life saving and has improved neonatal survival, it may cause chronic lung injury resulting in bronchopulmonary dysplasia (BPD). (See "Pathogenesis and clinical features of bronchopulmonary dysplasia".)
- Ventilators used in the NICU setting can be divided into conventional and high frequency ventilators. Conventional ventilators are based upon delivery of a mandatory breath while continuous air flows through the ventilator circuit. High frequency ventilation (HFV) is based upon delivery of small volume of air (generally equal or less than the anatomic dead space) at an extremely rapid rate (300 to 1500 breaths per minute).
- Strategies using volume-targeted ventilation or HFV ventilation have been developed to reduce neonatal lung damage due to positive pressure ventilation. However, these modes of ventilation do not add any significant benefit over the less costly and easier to operate time-cycled pressure-limited (TCPL) ventilators that are used routinely in most NICUs. (See 'Volume-targeted ventilation' above and 'High frequency ventilation' above and 'Pressure-limited ventilation' above.)
- There appears to be no difference in the mortality rate or risk of BPD between synchronized and nonsynchronized pressure-limited ventilation. However, synchronized ventilation may have additional short-term benefits including enhanced oxygenation stability, decreased blood pressure fluctuation, improved patient comfort, and reduced duration of ventilator support. (See 'Synchronized and patient-triggered ventilation' above.)
- In our institution, synchronized intermittent ventilation (SIMV) using a TCPL ventilator is the initial mode of ventilation in neonates requiring respiratory support. We initiate SIMV using low tidal volumes (4 to 6 ml/kg) with permissive hypercarbia (PCO₂ up to 60 mmHg with pH \geq 7.25). (See 'Our approach' above.)
- Other modes of ventilation are reserved for selected settings. These include pressure support ventilation for infants with BPD who require long-term ventilator support or are having difficulty weaning from SIMV pressure-limited ventilation, and high frequency ventilation as a rescue therapy when infants fail SIMV pressure-limited ventilation. (See 'Our approach' above and 'Pressure-support addition to SIMV' above and 'High frequency ventilation' above.)

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Treatment and complications of respiratory distress syndrome in preterm infants

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INTRODUCTION — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. The lungs of preterm infants lack adequate pulmonary surfactant, one of the constituents of the air-liquid interface that lines the alveolar surfaces and terminal airways. RDS is a result of surfactant deficiency, which increases the surface tension in the air-liquid interface of the terminal respiratory units. Surfactant deficiency leads to atelectasis, increases ventilation perfusion mismatch, and leads to lung injury, which is mediated by a marked pulmonary inflammatory response.

As RDS is due to lung immaturity, the best intervention would be to prevent premature birth. However, if premature birth cannot be avoided, RDS may be prevented with the use of antenatal steroid therapy and the

prophylactic (early) administration of exogenous surfactant. (See "Prevention of spontaneous preterm birth" and "Prevention of respiratory distress syndrome in preterm infants".)

Despite the initiation of preventive care, RDS may still develop and is associated with both acute and chronic complications. Once the diagnosis of RDS has been established, management is directed toward specific measures to replace surfactant and ensure adequate oxygenation and ventilation, as well as general supportive measures. The treatment of established RDS and its complications of RDS are discussed in this topic review (algorithm 1).

The diagnosis of RDS is discussed elsewhere in the program. (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn", section on 'Diagnosis'.)

SURFACTANT THERAPY — Prior to the introduction of exogenous surfactant, RDS was associated with significant morbidity and mortality. Beginning with the first study of 10 infants in 1980, numerous clinical trials have shown that exogenous surfactant replacement therapy is highly effective in reducing mortality and morbidity in infants with RDS [1-4]. In a large multicenter blinded controlled trial, 789 infants (birth weight 600 to 1750 g) who developed RDS within six hours of birth were randomly assigned to either surfactant or placebo [3]. Surfactant was associated with significantly lower mortality rate (18 versus 27 percent) and a lower risk of developing pulmonary interstitial emphysema (19 versus 39 percent) and other pulmonary leak complications including pneumothorax (12 versus 26 percent) [3].

Such benefits of exogenous surfactant are due primarily to improved lung mechanics with a decrease in ventilation perfusion mismatching that results in improved oxygenation. In one study, for example, single dose surfactant improved the oxygenation in 77 percent of treated compared to 13 percent of control infants defined by an increase in the arterial to alveolar oxygenation ratio from 0.2 to >0.3 [5]. The improved arterial/alveolar ratio lasted the duration of the study (48 hours) in 66 percent of treated infants compared to 9 percent of controls.

Types of surfactant — A wide variety of surfactant preparations, which include natural and synthetic products, have been developed. At the present time, only natural animal derived surfactant preparations are available (table 1).

In a meta-analysis, animal-derived surfactant extract treatment in infants with established RDS decreased the risk of pneumothorax, pulmonary interstitial disease, mortality, and the combined outcome of BPD or death [6].

The different preparations of surfactant, including their relative efficacy, are more fully discussed elsewhere in the program. (See "Exogenous surfactant therapy in preterm infants".)

Indications

Rescue therapy — As recommended by the American Academy of Pediatrics and European consensus guidelines, rescue surfactant should be given when the diagnosis of RDS is established [7,8]. The diagnosis is based upon the infant's oxygen requirement, clinical examination, and chest radiograph (algorithm 1). (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn", section on 'Diagnosis'.)

In infants older than 30 weeks, the diagnosis of RDS is established when the arterial to alveolar oxygen ratio is less than 0.22 to 0.3 [9,10]. This corresponds to an arterial PaO₂ value of less than 80 mm Hg with oxygen administration of greater than 40 percent. These older infants typically have not received prophylactic or early surfactant as they have a lower risk of developing the disorder. Numerous trials have shown benefits of rescue surfactant therapy in this group of neonates [1-4].

The amount of surfactant for the initial rescue dose is based upon the specific surfactant preparation utilized (table 1):

- Poractant alfa — 2.5 mL/kg (200 mg phospholipid/kg)
- Calfactant — 3.0 mL/kg (105 mg phospholipid/kg)

- Beractant — 4.0 mL/kg (100 mg phospholipid/kg)

There are no current data to recommend a specific natural surfactant preparation over another. Choice of surfactant preparation is based upon the preference and availability at the site of clinical care. (See "Exogenous surfactant therapy in preterm infants".)

Post-prophylactic or early therapy — In infants less than 30 weeks gestation, the standard of therapy is to provide prophylactic or early surfactant. Additional doses of surfactant therapy is administered if the patient has an oxygen requirement >30 percent.

Subsequent surfactant administration decreases mortality and morbidity in infants less than 30 weeks gestation with RDS [1,4,11]. In a double-blind study, 826 infants (gestational age <30 weeks with birth weights 700 to 1100 g) who received a single prophylactic dose within the first 30 minutes of life and continued to require mechanical ventilation at 12 to 24 hours of life were randomly assigned to two air placebo treatments or to two additional doses of surfactant [11]. Compared with placebo, surfactant therapy resulted in significant lower mortality rates at 28 days of life (10 versus 17 percent), and a lower incidence of necrotizing enterocolitis (2 versus 6 percent). There was, however, no difference in the incidence of pneumothorax, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage in the surviving infants. (See "Prevention of respiratory distress syndrome in preterm infants".)

Continued therapy — After the initial dose of surfactant given for treatment of RDS, the patient's response is assessed based upon their continued oxygen requirements. If there is clinical evidence of persistent disease, we continue surfactant therapy [12,13]. Based upon clinical practice, we define persistent RDS as a continual or recurrent oxygen requirement of greater than 30 percent, independent of age.

Surfactant therapy is administered for a total of 3 to 4 doses based upon continued oxygen needs and the specific surfactant preparation given. Multiple dosing of natural surfactants compared to single dosing regimens leads to lower incidence of pneumothorax, and reduced mortality in patients receiving surfactant therapy [12-14]. In one study, for example, 357 preterm infants (birthweight 700 to 2000 g) with severe RDS were randomly assigned to either a single or multiple dose protocol of natural surfactant [13]. Infants who received multiple doses compared to a single dose of surfactant had a lower incidence of pneumothorax (9 versus 18 percent) and mortality rate (13 versus 21 percent).

Repeat dosing is dependent upon the preparation used as follows (table 1):

- Poractant alfa — Initial dose of 2.5 mL/kg (200 mg phospholipid/kg), followed by subsequent dose of 1.25 mL/kg every 12 h for up to a total of 3 doses
- Calfactant — Initial dose of 3.0 mL/kg (105 mg phospholipid/kg), and repeated every 12 h for up to a total of 3 doses.
- Beractant — Initial dose of 4.0 mL/kg (100 mg phospholipid/kg), and repeated every 6 h for up to a total of 4 doses.

MECHANICAL VENTILATION AND CPAP — Surfactant deficiency results in impaired lung expansion (atelectasis) due to decreased surface tension in the air liquid interface at the terminal respiratory units that results in RDS. As the disease progresses, it may lead to respiratory failure secondary to inequalities in ventilation perfusion matching and to increases in intra- and extra-pulmonary shunting.

In patients with RDS, intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) has been used to correct atelectasis and facilitate the repeated administration of exogenous surfactant. In addition, other supportive measures aimed at improving hypoxemia (ie, arterial oxygenation) include increasing the concentration of supplemental oxygen and increasing the mean airway pressure.

It is increasingly appreciated that mechanical ventilation is associated with volutrauma and barotrauma, and the use of high concentrations of supplemental oxygen is associated with oxygen toxicity; all of which contribute to the development of bronchopulmonary dysplasia (BPD) [15-17]. In premature baboons, a five day compared to one day intubation with subsequent stabilization on CPAP resulted in poorer lung mechanics and respiratory

function (eg, lower arterial to alveolar oxygen ratio, higher PaCO₂, and poorer respiratory drive), increased histopathologic findings of cellular bronchiolitis and peribronchiolar alveolar wall thickening, and increased lavage levels of cytokines [18].

Continuous positive airway pressure (CPAP) has been used to prevent atelectasis and pulmonary shunting and avoid the pulmonary insults from mechanical ventilation in infants with RDS who have not developed respiratory failure. In addition, different modes of ventilation have been evaluated to reduce pulmonary injury in infants who require ventilation because of respiratory failure.

Continuous positive airway pressure (CPAP) — Among premature infants without respiratory failure, continuous positive airway pressure (CPAP) is an alternative to mechanical ventilation to prevent atelectasis because mechanical ventilation is associated with an increased risk of BPD [10,15,19,20]. Evidence clearly supports the role of CPAP in larger infants (birth weight ≥ 1500 g). However, data are more limited upon the benefit CPAP in very low birth weight infants (birth weight <1500 g).

Larger preterm infants — In larger babies with RDS, CPAP is the preferred modality based upon a meta-analysis that reported a lower mortality and morbidity rate in infants with birth weights greater than 1500 g who were placed on CPAP compared to those initially supported with mechanical ventilation [20]. Larger preterm infants can be extubated and stabilized on CPAP after rescue administration of exogenous surfactant [21].

In a study from Australia of infants greater than 30 weeks gestation with respiratory distress, nasal CPAP compared to oxygen administered by hood decreased the need for transfer to a regional tertiary center (23 versus 40 percent) [22]. However, there was a trend for an increased risk of a pneumothorax in infants treated with CPAP. Although these results suggest that possible treatment with CPAP alone in treating larger infants with mild RDS, further trials would be necessary before nasal CPAP therapy in lieu of treatment with exogenous surfactant could be considered in these patients.

Very low birthweight infants — The potential benefit of CPAP compared to intubation and mechanical ventilation is less clear in infants born before 30 weeks gestation or with birth weights below 1500 g with RDS. Data are limited to a single clinical trial and several observational studies.

In the single multicenter clinical trial, 610 infants born at 25 to 28 weeks gestation who required respiratory support were randomly assigned to either CPAP or intubation with mechanical ventilation at five minutes of age [23]. Surfactant therapy was not mandated and was used according to local protocol at each of the participating centers. The following findings were noted at 36 weeks gestational age:

- There was no difference in mortality rate between infants treated with CPAP versus those who were intubated and ventilated (OR 1.1, 95% CI 0.57 to 2.12).
- There was no difference in the need for oxygen therapy between the two groups (OR 0.76, 95% CI 0.54 to 1.09). In addition, the majority of survivors in both groups required little or no oxygen therapy. An oxygen concentration of 30 percent or more was administered to 9.4 percent of the CPAP and 8.8 percent of the intubated groups.
- There was no difference between the two groups in the combined primary outcome of death and the need for oxygen therapy at 36 weeks gestational age (OR 0.8, 95% CI 0.58 to 1.12).
- The intubation rate of infants initially assigned to CPAP was 46 percent. Reasons for intubation included administration of oxygen with a concentration greater than 60 percent, a PaCO₂ greater than 60 mm Hg, persistent apnea, or metabolic acidosis not responsive to medical therapy.
- The incidence of pneumothorax was greater in the CPAP group (9.1 versus 3 percent).
- Surfactant administration was lower in those who received CPAP compared to intubated infants (38 versus 77 percent).

One major limitation of this study was that randomized therapy was not blinded. In addition, this study did not answer whether after initial intubation and surfactant administration, outcome differs between infants who are extubated and stabilized on CPAP compared to those who continue to be intubated and ventilated. Nevertheless, these results suggest that starting respiratory support with CPAP does not adversely affect very low birth weight infants with the possible exception of the increased risk of pneumothorax, which may in part be due to the lack of surfactant administration in the CPAP group.

Other support for the routine use of CPAP in very low birth weight infants are based upon observational studies.

- One study demonstrated a lower risk of BPD with early and routine use of CPAP used at one center compared to routine use of mechanical ventilation at two other centers in infants with birth weights less than 1500 g [15].
- In a single center study of 261 preterm infants (birth weight ≤ 1250 g), 76 percent of infants who did not receive surfactant therapy were maintained successfully on CPAP without the need for intubation and mechanical ventilation [24].
- One study demonstrated no difference in the neurodevelopment or growth of preterm infants placed upon early CPAP from 1998 to 1999 compared to historical controls not treated with CPAP from 1996 to 1997 at four years of age [25].

Our approach — Based upon the above observations, our current recommendation is that after intubation and administration of surfactant, preterm infants with RDS, regardless of birth weight, can be extubated and stabilized on CPAP if the infant is active, exhibits spontaneous respiratory effort, and is not in respiratory failure. In larger preterm infants, CPAP is the initial therapy for respiratory symptoms.

Nasal intermittent positive pressure ventilation — Nasal intermittent positive pressure ventilation (NIPPV) augments nasal CPAP by delivering ventilator breaths via the nasal prongs. Although NIPPV avoids the trauma of endotracheal placement tube, it still is a delivery mode of positive pressure ventilation.

Data are limited in comparing NIPPV to conventional ventilation. In a small trial of 64 infants who were <32 weeks gestation cared for at two different sites, patients with mild to moderately severe RDS were randomized sequentially to either NIPPV or conventional ventilation (CV) after the first administered dose of surfactant [26]. Infants who were treated with NIPPV compared to those treated with CV had a lower risk of the combined outcome of death and BPD (20 versus 52 percent). There were no differences in the total duration of supplemental oxygen or positive pressure ventilation, and the need for reintubation between the two groups.

Similarly, data are limited comparing the efficacy of NIPPV to CPAP in reducing the need for intubation and mechanical ventilation.

- In an open-label randomized trial of 76 preterm infants stratified by gestational age (28 to 30 weeks, and 31 to 34 weeks) and surfactant use, the need for intubation and mechanical ventilation was lower in the group that received NIPPV compared to those treated with CPAP [27].
- In a trial of 200 preterm infants (gestational age 26 to <34 weeks), there was no difference in the primary outcome of mechanical ventilation within the first 72 hours of life between the NIPPV and nasal CPAP (nCPAP) groups (25 versus 34 percent; relative risk 0.77, 95% CI 0.48-0.1.15). A post-hoc analysis demonstrated that infants in the NIPPV group were more likely to remain extubated than those who received nCPAP from 24 to 72 hours of life. In this study, exogenous surfactant was given only as rescue therapy.
- In another trial of 84 preterm infants born <35 weeks gestation, infants initially treated with NIPPV compared with those who received nasal CPAP were less likely to require endotracheal intubation and ventilation (25 versus 49 percent) and develop BPD (2 versus 17 percent) [28]. In this study, exogenous surfactant was given only as rescue therapy. One limitation of this study is the small number of patients, especially the VLBW and ELBW infants who are at highest risk for BPD.
- In a retrospective review of preterm infants with birth weights below 1250 g, patients treated with NIPPV compared to those who received CPAP had a higher incidence of BPD or death (39 versus 27 percent) [29]. However, NIPPV therapy was associated with a lower mean birth weight and gestational age, and more frequent administration of surfactant than those who were treated with CPAP, suggesting that NIPPV was administered to a more severely ill group. In a subgroup analysis of infants with the lowest birth weights (500 to 750 g), infants treated with NIPPV (n=84) compared to those treated with CPAP (n=27) had a lower rate of BPD (43 versus 67 percent) and a similar mortality rate (11 versus 12 percent).

These findings suggest an increased benefit with NIPPV versus CPAP in the preterm infants with RDS. However, additional trials are required to confirm the safety of the increased efficacy of NIPPV compared with CPAP in the treatment of RDS [30].

Mechanical ventilation — The best mode of ventilation remains unclear in patients in whom mechanical ventilation is necessary because of respiratory failure [31,32]. Mechanical ventilation modalities include pressure control ventilation, patient triggered ventilation, volume control, and high frequency positive pressure ventilation. (See "Mechanical ventilation in neonates".)

High frequency oscillatory ventilation (HFOV), a technique of rapid ventilation with very small tidal volumes, appeared to be a promising alternative as it reduced lung injury in animal models compared to conventional ventilation. However, nearly all trials comparing HFOV to conventional ventilation performed in preterm infants with RDS (since surfactant replacement therapy has been available) showed no increased benefit in regards to mortality and development of BPD [33-35]. In one randomized study of 400 infants between 23 and 28 weeks of age, no difference in the composite primary outcome (death or chronic lung disease, diagnosed at 36 weeks of postmenstrual age) was observed between conventional ventilation or high-frequency oscillatory ventilation [34].

There is, however, one large study that reported a survival benefit with HFOV, contrary to the previously cited studies. In this trial of 500 preterm infants (601 to 1200 g birth weight), the proportion of infants who survived without BPD was slightly greater with HFOV than with conventional ventilation (56 versus 47 percent) [36]. But, this study was performed in centers experienced in the use of HFOV and strict protocols were utilized in patient management. Similar results may not be achieved at centers with less experience or without such strict protocols. In addition, there may be increased complications of HFOV in the hands of inexperienced clinicians [33,37]. At present, there is no evidence that favors the routine use of high frequency ventilation over conventional ventilation [34,37].

Conventional ventilators also can be classified by the mechanism used to determine the amount of gas delivery for each inspiration. Most centers, including ours, use pressure control that delivers inspiration based upon the selected peak inspiratory pressure (PIP) at a synchronized mandatory rate (SMV). Other ventilators control their delivery by tidal volume (volume control). In addition, there are ventilators that are patient-triggered requiring delivery based upon the inspiratory effort of the patients measured by chest movement or breath (assist/control ventilation), air flow or airway pressure.

There appears to be no significant advantage of one type of conventional ventilator over another. With respect to SMV versus assist/control, for example, one study randomly assigned premature infants (BW between 500 to 1249 g) requiring mechanical ventilation to either mode of ventilation [32]. There was no difference between the two groups in the length of time required for mechanical ventilation, the need for supplemental oxygen at 36 weeks postmenstrual age, or the proportion of infants alive and extubated at 14 days of age.

Summary — At the present time, there are no studies that suggest that any one mode of conventional ventilation is better than another regarding long-term outcomes [31]. Different modes may be beneficial in select clinical settings and is dependent upon the knowledge and experience of the clinician caring for the patient.

No matter which mode of ventilation is selected, it is crucial to minimize the time on mechanical ventilation and optimize management to facilitate weaning from ventilator support.

Criteria for mechanical ventilation — Assisted ventilation should be initiated when respiratory failure occurs. Respiratory failure is verified by one of the following:

- Respiratory acidosis, documented by an arterial pH <7.20 and a PaCO₂ >60 mm Hg
- Hypoxia, documented by an arterial PaO₂ <60 mm Hg despite oxygen supplementation of 70 percent on nasal CPAP
- Severe apnea

These are general guidelines for respiratory failure and the measurements need to be taken into the context of other assessments of the patient's cardiopulmonary function. If the patient meets the general criteria for respiratory failure in neonates, we initiate mechanical ventilation using these initial settings:

- Rate of 60 breaths per minute

- Inspiratory time of 0.2 seconds
- End expiratory pressure of 5
- Peak inspiratory pressure that adequately expands the chest wall that is titrated to the lowest level that will ensure adequate ventilation.

These initial settings meet the criteria for rapid rate low tidal volume ventilation that has been associated with lower rates of pneumothoraces and perhaps mortality compared to lower rate strategies [38,39].

Weaning the ventilator is a gradual process and is started when the patient is able to maintain acceptable oxygenation and ventilation on low peak inflation pressures of less than or equal to 20 cm H₂O.

INHALED NITRIC OXIDE — It is well established that inhaled nitric oxide (iNO) provides benefit in the treatment of term or late preterm infants with persistent pulmonary hypertension. In addition, animal studies demonstrated that iNO reduced lung inflammation, improved surfactant function, attenuated hyperoxic lung injury, and promoted lung growth [40-44]. (See "Persistent pulmonary hypertension of the newborn", section on 'Inhaled nitric oxide'.)

A number of randomized masked controlled clinical trials have been conducted to evaluate the safety and efficacy of iNO in preterm infants with respiratory distress [45-50]. These trials have significant differences in study design (eg, dose, duration, early versus late administration of iNO, and severity of illness).

Despite these variations in study design, a systematic review, which included 14 trials with 7 follow-up studies and one observational study, was performed to assess the efficacy and safety of iNO. The following findings were noted:

- There was no difference in mortality between the iNO and control groups (RR 0.97, 95% CI 0.82-1.15). Subgroup analysis based on dosing of iNO (5 ppm, 10 ppm, 20 ppm, or titrated to response) and birth weight also demonstrated no difference in mortality between the iNO and control groups.
- There was no difference in the incidence of BPD (despite variation in the definition of BPD used) between the iNO and control groups (RR 0.93, 95% CI 0.86-1.003).
- Subgroup analyses based on dosing showed no difference between the two groups when the iNO dose was 5 ppm, 20 ppm, or titrated to response. There was a decrease risk of BPD in the group that was treated with 10 ppm iNO compared with controls (RR 0.75, 95% CI 0.61-0.91).
- In one study, a lower risk of BPD was observed in infants with birth weights between 1000 and 1250 treated with iNO compared with controls (30 versus 60 percent, RR 0.5, 95% CI 0.32-0.79) [47]. However, there was no difference between the groups in infants with birth weights below 1000 g.
- There was a small difference of improved composite outcome of death or BPD in the iNO group compared with controls (RR 0.93, 95% CI 0.87-0.99). However, there was heterogeneity among the studies as eight reported no difference between the groups, whereas three showed a significant benefit of iNO over placebo. Two studies also demonstrated a reduction in the composite outcome of death or BPD in infants with birth weights above 1000 g [46,47].
- There was no evidence of increased adverse effects (patent ductus arteriosus, sepsis, necrotizing enterocolitis, severe retinopathy of prematurity, pulmonary hemorrhage, or air leaks) with the use of iNO compared with placebo.
- There were no differences in neurodevelopment outcome as follows:
 - There was no difference in the composite outcome of brain injury defined as intraventricular hemorrhage with ventriculomegaly, intraparenchymal hemorrhage, or periventricular leukomalacia between the two groups.
 - There was no difference in the incidence of cerebral palsy in follow-up assessments at 18 months, and 4 to 5 years of age.
 - There was no difference in cognitive ability between the two groups.
 - There was no difference in the incidence of neurodevelopmental impairment, which included assessment of cognitive, neuromotor and sensory function, between the two groups.

Cost-effectiveness — In the United State, iNo is an expensive intervention. Conflicting results were reported from two studies that evaluated the cost-effectiveness of this intervention in two of the previously discussed trials.

- In the first study, retrospective economic evaluation showed the cost of treating infants treated with iNO was similar to those in the placebo for the birth hospitalization (\$194,702 versus 193,125) [48,51]. The cost of the drug (estimated as \$12,000 for a course extending to 30 days) was offset by a decrease in days of ventilation and hospital admissions. In this analysis, daily costs were determined based upon respiratory support from a database of all daily charges for a similar group of infants cared for in a tertiary NICU. In a sub-group analysis, cost of iNO treated infants was lower than those in the placebo group. The authors concluded that iNO appears not to increase costs and is cost-effective if started between 7 and 14 days of life.
- In the second study, retrospective economic evaluation showed the cost of caring for infants treated with iNO was not statistically different than those in the placebo group during birth hospitalization and first-year of life (\$235,800 versus 198,300) [47,52]. The cost of the drug was set at \$125/hr to a cap of \$12,000 for a course extending to 30 days. In this analysis, costs were calculated by review of detail hospital bills from the NICU course for 80 percent of patients and by assigning costs for rehospitalization for days on the in-patient ward or intensive care unit. In a sub-group analysis, costs were significantly higher for iNO treated infants among infants in the lowest birth weight group of 500 to 749 g. The authors concluded that iNO, which was started within 48 hours of life until 21 days or extubation, did not lower costs and had a poor cost-effectiveness profile.

These two studies differed by the dose of iNO and the timing of iNO [47,48].

Our approach — Based upon the currently available data, we do not recommend the routine administration of iNO to preterm infants with RDS. Until an effective regimen is determined that demonstrates a substantial benefit of iNO justifying the cost, iNO administration should be limited to clinical trials [53]. This approach is consistent with the conclusions of an expert panel convened by the National Institute of Health that found the available evidence based on the above systematic review did not support the use of iNO in the treatment of preterm infants below 34 weeks gestation who require respiratory support [54].

POSTNATAL GLUCOCORTICOID — Postnatal glucocorticoid therapy, when given to premature infants in the first day of life, improves pulmonary and circulatory function and decreases the incidence of BPD. However, short-term complications, such as intestinal perforation, and metabolic instability; and more importantly, long-term abnormal neurodevelopmental outcomes in treated infants have led to strict restriction in the use of postnatal corticosteroid therapy. As a result, we do NOT recommend the routine use of postnatal glucocorticoid steroids to prevent or treat BPD.

A more in-depth discussion on the use and risk of postnatal corticosteroid therapy is found elsewhere in the program. (See "Postnatal use of glucocorticoids in bronchopulmonary dysplasia".)

SUPPORTIVE CARE — Additional supportive care for the preterm infants is needed to optimize the previously discussed specific measures for treating RDS.

Thermoregulation — Infants should be maintained in a thermal neutral environment to limit energy expenditure to maintain core body temperature. Proper thermoregulation reduces oxygen consumption and caloric needs.

Rectal temperatures should not be obtained in infants with RDS because of the greater risk of trauma or perforation associated with their use. As a result, abdominal temperatures should be used to set the servo-controlling temperatures in incubators and in radiant warmers. The ambient temperature should be selected to maintain an anterior abdominal skin temperature of 36.9°C in small premature infants (less than 1000 grams) and 36.5°C in larger infants, which correlates to a rectal temperature of 37°C.

Fluid status — Fluid status must be carefully monitored as excessive fluid increases the risk of patent ductus arteriosus, necrotizing enterocolitis (NEC), and BPD [55].

Fluid balance is complex as immature kidneys have limited concentrating abilities and insensible losses vary with gestational age, use of radiant heaters and phototherapy, and the water content of inspired air. Fluids should be adjusted to maintain a slightly negative water balance, and positive water balance should be avoided. In addition, as shown in a systematic analysis, there is no evidence to support the routine use of diuretics in preterm infants with RDS [56]. In addition, the administration of early nutrition is important in the overall care of these premature infants. (See "Prevention of bronchopulmonary dysplasia", section on 'Fluid restriction' and "Fluid and electrolyte therapy in newborns" and "Parenteral nutrition in premature infants".)

Cardiovascular management — Systemic hypotension and failure of closure of the patent ductus arteriosus increase the risk of developing NEC and BPD.

- Systemic hypotension occurs commonly in the early stages of RDS. In patients with moderate to severe RDS, continuous arterial pressure is monitored through the umbilical artery catheter. Hypotension is treated with vasopressor support and cautious use of crystalloid solutions for intravascular expansion. In patients with persistent hypotension unresponsive to vasopressor and volume therapy, assessing serum cortisol levels should be considered and treatment with stress doses of hydrocortisone may be necessary [57]. (See "Short-term complications of the premature infant", section on 'Systemic hypotension'.)
- Patent ductus arteriosus (PDA) is common in preterm infants with RDS. It may contribute to difficulties in weaning from mechanical ventilation and predispose the patient to BPD. The clinical features, diagnosis and management of PDA are discussed elsewhere in the program. (See "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants".)

COMPLICATIONS — Therapy with exogenous surfactant and antenatal corticosteroids have lowered the mortality and morbidity associated with RDS. Nevertheless, complications and deaths still persist. Complications are most often due to the therapeutic interventions, including placement of arterial catheters, supplemental oxygen, positive pressure ventilation, and the use of endotracheal tubes.

Endotracheal tube complications — Displacement or misplacement of the endotracheal tubes occurs commonly. Endotracheal tube placement into a main stem bronchus leads to hyperinflation of the ventilated lung and atelectasis of the contralateral lung. The hyperinflation may contribute to air leaks and the air-block syndrome. (See "Pulmonary air leak in the newborn" and 'Pulmonary air leak' below.)

Other complications from intubation include subglottic stenosis and atelectasis postextubation [58]. Esophageal and pharyngeal perforations rarely occur and may be confined to the mediastinum or extend into the pleural cavity [59].

Pulmonary air leak — Pulmonary air leaks, also known as air block syndrome, is the most common acute complication of RDS. Air leaks are due to the rupture of an overdistended alveolus usually from positive pressure due to mechanical ventilation. The air from the ruptured alveoli dissects along the perivascular connective tissue sheath. This dissection can move toward the hilum, resulting in a pneumomediastinum, or into the pleural space, producing a pneumothorax. Less commonly, air may dissect into the pericardial space, subcutaneous tissue, or peritoneal space, causing pneumopericardium, subcutaneous emphysema, and pneumoperitoneum, respectively. In the preterm infant, the perivascular connective tissue is more abundant and more compliant allowing air trapping in the perivascular space, resulting in pulmonary interstitial emphysema (PIE).

The clinical features, diagnosis and management of each of these pulmonary air leak disorders are discussed elsewhere in the program. (See "Pulmonary air leak in the newborn".)

Bronchopulmonary dysplasia — Bronchopulmonary dysplasia (BPD), also referred to as chronic lung disease of the neonate (CLD), is the main chronic complication of RDS. Despite improvements in the management of RDS, the incidence of BPD is still substantial.

The etiology of BPD is multifactorial. Inflammation, caused by volutrauma, barotrauma, oxygen toxicity, or infection, plays an important role in its development.

The lung appears to be most vulnerable before the alveolar stage of development (which occurs at approximately 31 to 34 weeks gestation), when alveolar formation is initiated. This is due to the premature lung's structural and functional immaturity, including poorly developed airway support structures, surfactant deficiency, decreased compliance, underdeveloped antioxidant mechanisms, and inadequate fluid clearance.

The pathogenesis, clinical features, prevention and management of bronchopulmonary dysplasia are discussed elsewhere in the program. (See "Pathogenesis and clinical features of bronchopulmonary dysplasia" and "Prevention of bronchopulmonary dysplasia" and "Management of bronchopulmonary dysplasia".)

SUMMARY AND RECOMMENDATIONS — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. Recommendations for prevention of RDS are discussed elsewhere (see "Prevention of respiratory distress syndrome in preterm infants").

- We recommend administration of surfactant therapy in infants with RDS (Grade 1A). The initial dose of surfactant is dependent on the surfactant product selected (table 1). (See 'Indications' above.)
- We recommend retreatment with subsequent doses of surfactant if there are persistent clinical findings of RDS (Grade 1B). In our clinical practice, persistent clinical disease is defined as a continual or recurrent oxygen requirement of greater than 30 percent. (See 'Continued therapy' above.)
- We recommend that infants with RDS be treated with CPAP rather than mechanical ventilation if the baby is active and breathing spontaneously (Grade 1B). CPAP promotes lung expansion and prevents atelectasis. (See 'Continuous positive airway pressure (CPAP)' above.)
- If respiratory failure occurs, intubation and mechanical ventilation is initiated. The use of mechanical ventilation should be minimized as it increases the risk of developing pulmonary air leaks and bronchopulmonary dysplasia. (See 'Criteria for mechanical ventilation' above.)
- Until an effective regimen is determined that demonstrates a substantial benefit of iNO justifying the cost, we recommend NOT administering iNO to preterm infants with RDS (Grade 1B). If utilized, iNO should be limited to clinical trials. (See 'Inhaled nitric oxide' above.)
- We recommend NOT administering postnatal glucocorticoid steroids due to the increased risk of long-term abnormal neurodevelopmental outcomes (Grade 1B). (See "Prevention of bronchopulmonary dysplasia", section on 'Glucocorticoids' and "Postnatal use of glucocorticoids in bronchopulmonary dysplasia".)
- Supportive general care includes providing optimal thermoregulation, close monitoring of fluid balance and avoiding fluid overload, maintaining adequate blood pressure and perfusion, and detecting and treating persistent patent ductus arteriosus. (See 'Supportive care' above.)
- Complications are most often due to the therapeutic interventions, including placement of arterial catheters, supplemental oxygen, positive pressure ventilation, and the use of endotracheal tubes. (See 'Complications' above.)

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Exogenous surfactant therapy in preterm infants

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INTRODUCTION — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. The lungs of preterm infants lack adequate pulmonary surfactant, a constituent of the air-liquid interface, that normally lines the alveolar surfaces and terminal airways. RDS is due to surfactant deficiency, which increases the surface tension at the air-liquid interface of the terminal respiratory units. This leads to atelectasis and increases ventilation perfusion mismatch.

Exogenous surfactant replacement therapy is directed toward correcting this deficiency. Exogenous surfactant replacement therapy has been widely used and is effective in reducing mortality and morbidity of RDS in preterm infants at risk [1-3]. Therapy provides surfactant that has not yet been produced into the lungs of preterm infants, preventing the development of RDS or (in some cases) diminishing the severity of RDS. It is effective both to prevent RDS and/or after RDS has been established.

Surfactant therapy can vary in the type of preparation. This discussion will review the different types of surfactant including their composition and clinical efficacy. The role for surfactant in the prevention and treatment of RDS is discussed separately. (See "Prevention of respiratory distress syndrome in preterm infants" and "Treatment and complications of respiratory distress syndrome in preterm infants".)

TYPES OF SURFACTANT PREPARATIONS — A wide variety of surfactant preparations have been developed. These include natural and synthetic surfactants:

Natural surfactants — Three natural surfactants are commercially available: poractant alfa, calfactant, and beractant (table 1). These are obtained by either animal lung lavage or by mincing lung tissue (eg, lung minces). These surfactants are subsequently purified by lipid extraction, removing hydrophilic components that include the hydrophilic surfactant proteins A and D. The purified lipid components retain surfactant proteins B and C, neutral lipids, and surface active phospholipids (PL) such as dipalmitoylphosphatidylcholine (DPPC). DPPC is the primary surface active component that improves alveolar surface tension.

Synthetic surfactants — There are currently no synthetic surfactant products available for clinical use. The one synthetic product, Colfosceril palmitate, that was available contained DPPC, cetyl alcohol, and tyloxapol. This preparation did not contain surfactant proteins but cetyl alcohol was used as a replacement spreading agent for DPPC.

In vitro studies have demonstrated that natural surfactants have superior physical properties to the synthetic products. Benefits include better surface adsorption, surface spreading and respreading, and film compressibility, as well as increased surface tension during cyclic compression. The superiority of natural products is attributed primarily to the presence of surfactant proteins B and C that are absent in synthetic products. These surfactant proteins aid in surface adsorption and spreading of DPPC. Beractant, a natural surfactant that contains lower concentrations of surfactant protein B, does not perform as well as the other two preparations in studies performed in vitro [4]. The next generation of synthetic products includes synthetic compounds that are thought to mimic properties of surfactant protein B.

Clinical trials — Both natural and synthetic surfactant preparations are effective. Compared with older synthetic preparations without protein B and C analogues, natural surfactants have been shown to be superior in clinical trials. In particular, natural preparations permitted relatively lower inspired oxygen concentration and ventilator pressures; this in part resulted in a decrease in mortality rates and complications of RDS in preterm infants [5-8].

However, limited data suggest that a new synthetic surfactant preparation that contains a peptide that is thought to be protein B analogue may improve mortality compared with natural surfactant [9]. This preparation is not commercially available.

Natural surfactant versus synthetic surfactant without protein analogues — The relative superiority of natural surfactant compared to older synthetic surfactants (without protein B and C analogues), particularly in terms of a decrease in mortality rate and risk of developing pneumothorax, was best illustrated by a meta-analysis of 11 randomized controlled studies of 4658 preterm infants (from 1975 to 2000) [7]. The following results were reported:

- In 10 studies, patients treated with natural surfactant had a lower mortality rate than those treated with synthetic surfactant (15.8 versus 18.4 percent; RR 0.86, 95% CI 0.76-0.98).
- In nine studies, there was a lower incidence of pneumothoraces in patients treated with natural surfactant than in patients treated with synthetic surfactant (6.9 versus 10.9 percent; RR 0.63, 95% CI 0.53-0.75).
- In seven studies, there was a higher incidence of intraventricular hemorrhage (IVH) in the patients treated with natural surfactant than in patients treated with a synthetic preparation (34.2 versus 31.5 percent; RR 1.09, 95% CI 1.00-1.19). However, there was no difference in risk for severe IVH (defined as grades 3 and 4) between the two groups.
- There was no difference between groups in the incidence of patent ductus arteriosus, sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (BPD), or chronic lung disease (CLD); CLD was defined as an oxygen requirement at 36 weeks adjusted age.

These results supported the use of natural surfactant over synthetic products without protein analogues [7].

Natural surfactant versus synthetic surfactant with protein analogue — Although unproven, some postulated advantages of synthetic surfactants over natural-derived products include [10]:

- Decreased immunogenicity
- Decreased potential to transmit animal-borne infectious agents
- Large quantities of material that is consistent in composition

These potential benefits of a synthetic product have led to continued efforts to develop new synthetic preparations that include protein analogues that mimic surfactant protein B and C [10]. One synthetic product, named lucinactant, contains a 21 amino acid peptide called KL, in which positively charged lysine molecules (K) are separated by 4 leucine molecules (L). KL4 appears to mimic surfactant protein B and combines with phospholipids. The relative efficacy of this agent compared to other synthetic surfactants and natural surfactants was evaluated in two well-designed studies:

- In one report, 1294 preterm infants (gestational age less than 32 weeks) were assigned to receive colfosceril palmitate, a synthetic surfactant without surfactant proteins, (509 patients), lucinactant (527 patients), or beractant, a natural surfactant, (258 patients) [9]. All forms of surfactant were administered within 20 to 30 minutes after birth. Compared with colfosceril palmitate, lucinactant significantly reduced the incidence of RDS at 24 hours of life (39 versus 47 percent) and BPD at 28 days (40 versus 45 percent). There was no difference between lucinactant and beractant in these outcomes. In addition, mortality due to RDS at 14 days was significantly lower with lucinactant versus both colfosceril palmitate (5 versus 9 percent) and beractant (5 versus 10 percent).
- In the second study, 252 preterm infants (gestational age less than 28 weeks), were randomly assigned to receive either lucinactant or poractant alfa, a natural surfactant, within 30 minutes after birth [11]. There were no significant differences in survival without BPD at 28 days of life and at 36 weeks postmenstrual dates. In addition, no significant differences were observed in the incidence of grade 3 or 4 IVH, NEC, PDA, pneumothorax, or retinopathy of prematurity. Nine patients died prior to receiving any form of surfactant (5 and 4 in the lucinactant and natural surfactant groups, respectively). A major limitation of this study was enrollment reached only one-half the sample size that was originally calculated.

A meta-analysis of the two trials demonstrated no differences between infants treated with synthetic surfactant versus those who received animal derived surfactant at 36 weeks adjusted gestational age in the rates of mortality (RR 0.81, 95% CI 0.64-1.03), chronic lung disease (RR 0.99, 95% CI 0.84-1.18), or the combined outcome of death and chronic lung disease (RR 0.96, 95% CI 0.82-1.12) [12].

In a subsequent report, participants from both of the two trials were evaluated at one year corrected age [9,11,13]. There was no difference in survival rate between the patients treated with lucinactant and those treated with natural surfactant (74 versus 71 percent, OR 0.83; 95% CI 0.61-1.12). The incidences of posthospital readmissions and respiratory illnesses, and neurologic outcome did not differ among the two groups.

These preliminary data are encouraging that an improved synthetic surfactant preparation with protein analogues may prove to be as effective and potentially safer than currently available products. However, further trials are need because of questions regarding early trial closure and limited statistical power [3]. In addition, there are concerns regarding the metabolic fate of lucinactant and its components, as well as safety issues prompted by the requirement of warming by a special cradle to convert lucinactant gel into liquid immediately before instillation [3].

Natural surfactant preparations — Comparative studies of different natural surfactant preparation in the clinical setting have been limited [14,15]. One trial was halted because of the inability to meet enrollment targets [14].

SUMMARY AND RECOMMENDATIONS — We recommend the use of natural surfactant products until trials are completed that adequately compare newer protein containing synthetic products with natural surfactant. In addition, synthetic surfactant products are not currently available. There are insufficient data to recommend a specific natural surfactant preparation over another (table 1) [8,14,16]. In general, the choice of natural preparation is based upon the availability at the site of clinical care.

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Management of patent ductus arteriosus in premature infants

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INTRODUCTION — During fetal life, the ductus arteriosus (DA) diverts blood from the pulmonary artery into the aorta, thereby bypassing the lungs (figure 1). After birth, the DA undergoes active constriction and eventual obliteration. A patent ductus arteriosus (PDA) occurs when the DA fails to completely close after delivery.

Preterm infants with moderate to large left-to-right shunts have a greater mortality rate than those without a PDA. They also have an increased risk of pulmonary edema and hemorrhage, bronchopulmonary dysplasia, and a decrease in perfusion and oxygen delivery to end-organs. As a result, management of preterm infants with clinically significant PDAs has been focused on PDA closure and prevention. The management of PDA in preterm infants will be reviewed here. The pathophysiology, clinical manifestations, and diagnosis of PDA in preterm infants are reviewed separately. (See "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants".)

OVERVIEW — Over the last several decades, research efforts have focused on preventing and closing PDAs in premature infants. However, current practice is focused on PDA closure as the benefit of preventive measures to

reduce the incidence of PDA appears to be outweighed by the adverse effects of prophylactic therapy. (See 'Prophylactic therapy' below.)

The current management of PDA in premature infants includes three different approaches:

- Conservative management with supportive therapy alone
- Pharmacologic closure using cyclooxygenase inhibitors (eg, indomethacin)
- Surgical ligation

The support for either medical or surgical closure is based on data from studies in the 1980s and 1990s that demonstrated PDAs in very low birth weight (VLBW) infants (birth weight below 1500) were associated with pulmonary edema, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis. As a result, many preterm infants with a gestational age less than 28 weeks have received either medical or surgical therapy for PDA closure. (See "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants".)

However, neonatal practice is continuously changing, and the increasing use of antenatal glucocorticoid therapy, postnatal surfactant therapy, and the adoption of lower targets of oxygen saturation may have affected both the incidence and impact of a clinically significant PDA shunt. Data are not available regarding the natural course of an untreated PDA in neonatal centers where these practices have become standard of care. In addition, there are no randomized controlled trials comparing outcomes of the three different approaches. Therefore, it remains unclear which approach is most advantageous for premature infants and whether clinical parameters or settings may favor one approach over another. This uncertainty has led to variation in the management of PDA in preterm infants not only amongst different neonatal intensive care units (NICU), but often within a single NICU.

SUPPORTIVE THERAPY — All neonates with PDA should receive the following supportive care regardless of the approach chosen to manage their PDA.

- A neutral thermal environment and adequate oxygenation that minimize demands on left ventricular function.
- The use of positive end-expiratory pressure (PEEP) to improve gas exchange in infants with respiratory compromise. In a study in preterm lambs, PEEP decreased left-to-right ductal flow and increased systemic blood flow [1].
- Maintenance of the hematocrit at 35 to 40 percent may increase pulmonary vascular resistance and reduce left-to-right shunting, although no trials have evaluated the effect of blood transfusion on PDA closure [2].

We do not recommend routine use of furosemide or any other loop diuretic, which stimulates renal synthesis of prostaglandin E₂, a potent vasodilator that maintains DA patency. In a trial of diuretic therapy in premature infants with respiratory distress syndrome, a PDA occurred more frequently in infants treated with furosemide compared with chlorothiazide (55 versus 24 percent) [3]. In a retrospective study of preterm infants below 32 weeks gestation, furosemide was associated with an increase in serum creatinine and hyponatremia but not an increase urine output [4]. We recommend the use of thiazide diuretics (eg, chlorothiazide) whenever diuretic therapy is being considered.

Fluid restriction is unlikely to promote ductal closure; however, excessive fluid administration (greater than 170 mL/kg per day) is associated with an increased incidence of PDA [5]. Moderate daily fluid restriction between 110 and 130 mL/kg is suggested to limit pulmonary edema in infants with hemodynamically significant PDA, especially in those with severe respiratory disease.

CYCLOOXYGENASE INHIBITORS — Prostaglandin E₂ (PGE₂) is a vasodilator that promotes ductal patency. In the 1970s, two studies demonstrated pharmacologic closure of PDA within 24 hours with the administration of indomethacin, an inhibitor of cyclooxygenase (COX), the pivotal enzyme in the synthesis of PGE₂ [6,7]. Currently, the two cyclooxygenase inhibitors used to medically close PDAs are indomethacin and ibuprofen.

The efficacy of these two COX inhibitors in PDA closure was illustrated by a systematic review of the literature that included 19 randomized trials that compared the intravenous administration of indomethacin and ibuprofen to placebo and to each other [8]. The following findings were noted:

- Indomethacin was twice as likely to close a PDA as placebo (pooled RR 2.39, 95% CI 2.05-2.78). There were no differences in the risk of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), chronic lung disease (CLD), and death between indomethacin and placebo.
- Ibuprofen was also twice as likely to close a PDA as placebo (pooled RR 2.4, 95% CI 2.03-2.84). There were no differences in the risk of NEC, IVH, and death between indomethacin and placebo. However, there was a trend towards an increased risk of CLD associated with ibuprofen compared with placebo (pooled RR 1.29, 95% CI 0.99-1.7).
- Indomethacin and ibuprofen were equally effective in PDA closure (pooled RR 1.0, 95% CI 0.93 to 1.08). There were no differences in the risk of NEC, IVH, and death between the two COX inhibitors. However, there was an increased risk of CLD associated with ibuprofen compared with indomethacin (pooled RR 1.28, 95% CI 1.03-1.8).

A major limitation of this study was the high level of heterogeneity in outcome effect, especially regarding CLD. This may be due to the use of different definitions for CLD or variation in baseline risk of respiratory morbidity among studies.

Indomethacin — It has been clearly established both by observational studies and randomized trials that indomethacin increases the rate of PDA closure within 24 hours of its administration [6,7,9]. Less clearly established are the optimal timing, dose, and duration of treatment [10].

Timing — Early administration (defined as when clinical signs first appeared) compared to late administration (defined as when signs of heart failure developed) of indomethacin for PDA closure is associated with less morbidity. This was illustrated by a meta-analysis that demonstrated early versus late administration of indomethacin in preterm infants with PDAs was associated with shorter duration of mechanical ventilation and decreased risk of bronchopulmonary dysplasia (OR 0.39, 95% CI 0.21-0.76), necrotizing enterocolitis (NEC) (OR 0.24, 95% CI 0.06-0.96), and need for surgical ligation (OR 0.37, 95% CI 0.20-0.68) [11].

As a result, when pharmacologic closure is considered, we suggest administration of indomethacin prior to the onset of signs of heart failure. (See 'Our approach' below.)

Dose — The pharmacokinetics of indomethacin vary among premature infants, and serum half-life decreases with postnatal age. In addition, ductal constriction and adverse effects of indomethacin do not correlate strongly with plasma concentrations. Although some studies suggest that obtaining indomethacin concentrations to adjust dosing may improve the rate of ductal closure, these measurements are not widely available [12-14]. More than one dose is typically required for sustained constriction. Based on these data, indomethacin is usually given intravenously as multiple doses that range between 0.1 and 0.2 mg/kg per dose administered at 12-to 24-hour intervals. In our practice, we give three doses (0.2 mg/kg per dose) at 12-hour intervals.

Others recommend dosing based on age as follows:

- Infants less than 48 hours of age – 0.1mg/kg per dose
- Infants greater than 48 hours but less than 7 days of age – 0.2 mg/kg per dose
- Infants more than one week of age – 0.25 mg/kg/dose

Results from one trial support a strategy of discontinuing indomethacin if there is an adequate response based on functional echocardiographic findings following an initial dose (0.1 mg/kg) [15]. In this study, there were no differences in the rate of PDA closure, reopening, and the need for surgical ligation between the echocardiogram-managed group and controls treated in a standard two or more doses regimen. The use of echocardiogram to determine initial response could potentially reduce the amount of indomethacin exposure and its potential adverse effects. However, there was a trend towards a higher incidence of intraventricular hemorrhage in the echocardiogram-managed group, although the number of patients was too small to accurately

assess neurologic outcome. Additional trials are needed to validate this approach before it can be adopted as a treatment option in preterm infants with PDA [10].

Duration — Because indomethacin suppresses prostaglandin synthesis only transiently, a prolonged course of indomethacin has been suggested to sustain ductal constriction while anatomic remodeling occurs. However, a systematic review of five randomized controlled trials showed that a prolonged (four or more doses) administration of indomethacin compared with a short course of therapy (three or less doses) did not yield statistically significant differences in PDA closure, retreatment, re-opening, or surgical ligation rates [16]. In addition, prolonged therapy appeared to be associated with an increased risk of NEC (RR 1.87, 95% CI 1.07-3.27) and a decreased risk of renal function impairment as demonstrated by a lower proportion of infants with diminished urine output (RR 0.27, 95% CI 0.13-0.6) and elevated serum creatinine (RR 0.51, 95% CI 0.33-0.77) [16]. Based upon this analysis, a prolonged course of indomethacin cannot be recommended for the routine treatment of PDA in premature infants.

Failure to respond — In premature infants who receive indomethacin, 15 to 20 percent will have a persistent PDA [11,17]. Risk factors associated with a persistent PDA include lower gestational age, lack of exposure to antenatal corticosteroid therapy, increased severity of respiratory distress, and intrauterine inflammation [17,18]. These factors may be associated with increased cyclooxygenase activity [18].

Complications — Indomethacin reduces cerebral, gastrointestinal, and renal blood flow. Preterm infants often develop reduced urine output that is transient and does not usually lead to permanent renal dysfunction [19]. Indomethacin may actually enhance renal function that is compromised by a symptomatic PDA. Dopamine may improve indomethacin-related tubular dysfunction and result in higher urine volume and fractional excretion of sodium [20]. In contrast, furosemide is of little benefit in reducing renal toxicity and is contraindicated when dehydration is present [21].

Indomethacin has been associated with isolated gastrointestinal perforation; although, as noted above, the risk of NEC is reduced by early symptomatic treatment of PDA [9].

Indomethacin also causes platelet dysfunction, which may promote bleeding.

Pulmonary hemorrhage — Indomethacin is associated with a decrease in pulmonary hemorrhage, mainly through PDA closure in infants with birth weights below 1000 g [22]. The mechanism of this reduction in pulmonary hemorrhage is thought to be reduced pulmonary overcirculation resulting from ductal constriction. This leads to reduced capillary engorgement in the lungs and thereby reduces the risk of hemorrhage.

Contraindications — Indomethacin is contraindicated in infants with the following:

- Proven or suspected infection that is untreated
- Active bleeding, especially those with active intracranial hemorrhage or gastrointestinal bleeding
- Thrombocytopenia and/or coagulation defects
- Necrotizing enterocolitis or suspected of having necrotizing enterocolitis
- Significant impairment of renal function
- Congenital heart disease in which patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (eg, pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).

Ibuprofen — Treatment of a PDA with ibuprofen is comparable to indomethacin. Similar adverse events are seen although there may be less oliguria associated with ibuprofen.

- In a study of 148 preterm infants who were randomly assigned to three intravenous doses of indomethacin (0.2 mg/kg every 12 hours) or intravenous ibuprofen (10 mg/kg followed by two doses of 5 mg/kg at 24-hour intervals), the rates of PDA closure and need for repeat treatment were similar [23]. Oliguria occurred less commonly with ibuprofen (7 versus 19 percent), although other complications were not significantly different.

- Similar results were seen in a trial of premature infants with a gestational age ≤ 28 weeks who were randomly assigned to either indomethacin (0.2 mg/kg followed by 0.1 or 0.2 mg/kg every 24 hours) or ibuprofen (10 mg/kg followed by 5 mg/kg every 24 hours) [24]. Closure rates were 88 percent in both groups and oliguria was less common with ibuprofen (7 versus 15 percent).

Although both indomethacin and ibuprofen interfere with the binding of bilirubin to albumin, thus potentially increasing the risk of kernicterus, indomethacin affects bilirubin binding only at plasma concentrations that far exceed those seen clinically [25,26]. However, ibuprofen interferes with binding at serum concentrations achieved by the usual doses of the drug [27]. As a result, the risk of kernicterus may be higher in jaundiced patients treated with ibuprofen compared with those who receive indomethacin [26,28]. (See "Treatment of unconjugated hyperbilirubinemia in term and late preterm infants".)

Dose — The dosing of ibuprofen for PDA closure is an initial dose of 10 mg/kg followed by two additional doses of 5 mg/kg given at 24 hour intervals. Ibuprofen is typically given as an intravenous preparation in developed countries. However, the intravenous preparation is expensive and many nurseries in developing countries are using oral ibuprofen for PDA closure. In one randomized Turkish trial of 102 VLBW infants, oral administration of ibuprofen was more effective than intravenous administration in PDA closure [29]. Oral ibuprofen also appeared to be associated with fewer side effects, although the study size was too small to detect significant differences in the rate of adverse events. Additional trials are needed to confirm that oral ibuprofen is as effective and safe as intravenous ibuprofen.

Contraindications — The contraindications for ibuprofen are similar to those for indomethacin. However, we have had notable success in treating patients with renal failure and large PDAs with use of ibuprofen.

Indomethacin vs ibuprofen — As demonstrated by the above meta-analysis there is little reason to prefer one drug over the other [8]. As a result, in most instances, individual, institutional, and economic preferences dictate the choice of drug. In infants with significant renal compromise, ibuprofen is the preferred drug.

SURGICAL LIGATION — Surgical ligation may be performed if the patient remains symptomatic after one or two courses of COX inhibitor or if COX inhibitor treatment is contraindicated. However, pharmacologic therapy remains the preferred initial treatment because ligation is associated with risks of blood pressure fluctuations, respiratory compromise, infection, intraventricular hemorrhage, chylothorax, recurrent laryngeal nerve paralysis, BPD, and death [30,31].

One study reported that surgical ligation was associated with increases in the blood flow velocity of the middle cerebral, celiac, and superior mesenteric arteries. The change in the cerebral vasculature was attenuated and occurred later than in the splanchnic vasculature (24 versus 3 hours) because of the acute adaptation of increased cerebral vascular tone [32]. Video-assisted thoracoscopic PDA ligation, if available, offers a less traumatic alternative to the conventional surgical approach [33].

CONSERVATIVE APPROACH — Results from a single study have supported the strategy of conservative treatment using supportive therapy alone in preterm infants with PDA [34]. In this cohort study, 10 of 30 preterm infants developed significant PDAs (defined as DA diameter ≥ 1.4 mm by echocardiography measurement) and were treated with fluid restriction (maximum intake of 130 mL/kg per day) and ventilator changes (lowered inspiratory time and increased positive end expiratory pressure). In all patients, the PDA closed without surgical or pharmacologic treatment. However, these results should be interpreted cautiously as the number of patients treated was small and the study was not controlled. (See 'Supportive therapy' above.)

Other experts in the field have also advocated conservative management of PDA in preterm infants based on the evidence that demonstrates a high rate of spontaneous closure and established adverse effects of both pharmacologic and surgical intervention, and the lack of evidence that treatment results in a decrease in neonatal morbidity [35,36]. This was illustrated by a review of pooled data from treatment trials of PDA in preterm infants regardless of methodological quality that were published before 2010 [36]. In this analysis, early trials with oral indomethacin suggested reduced mortality; however, subsequent larger studies that used intravenous indomethacin did not find a decrease in mortality.

COMPARISON OF MANAGEMENT APPROACHES — There have not been large randomized controlled trials comparing the different approaches of managing PDA in preterm infants.

Observational data are available, but often the treatment groups differ in gestational age, birth weight, and severity of illness [37,38]. This was illustrated in a study that evaluated 18-month outcome based on the management of PDA in infants with birth weights below 1000 g from the National Institute of Child Health and Human Development Neonatal Research Network Generic Data Base [37]. This study included 403 infants who were treated conservatively, 1525 treated with indomethacin alone, 135 with primary surgery, and 775 who received indomethacin initially followed by surgery. The following findings were noted:

- Infants who underwent either primary or secondary surgical closure had lower gestational age, birth weight, and Apgar scores but were less likely to be small for gestational age.
- There were no differences in the measured demographics between infants treated conservatively and those who only received indomethacin.
- There also were no differences between the conservatively and medically managed groups in mortality, neurodevelopmental outcome at 18 months, the composite outcome of mortality and neurodevelopmental outcome, or the risk of BPD or NEC.
- There were no differences between the primary or secondary surgical groups, and indomethacin groups in the composite outcome of mortality and neurodevelopmental outcome or rate of NEC. Patients who underwent secondary surgical closure compared to those treated with indomethacin alone were more likely to have BPD and neurodevelopmental impairment but had a better survival rate.

The study design, however, has a bias for increased survival in patients treated surgically because surgical deaths were only counted after the procedure, whereas deaths in the medically treated group were reported any time after the diagnosis of PDA.

Large randomized controlled trials are required to truly compare the different treatment approaches in regards to mortality and complications.

PROPHYLACTIC THERAPY — Although the use of prophylactic cyclooxygenase (COX) inhibitors had been proposed to reduce the incidence of PDA and improve neonatal outcome, prophylactic COX inhibitors appear not to be more effective at improving mortality, pulmonary outcome, or reducing the risk of NEC than early treatment of a symptomatic PDA [39]. In addition, prophylactic treatment of infants that do not develop symptomatic PDA may actually increase the risk of BPD as illustrated in the Trial of Indomethacin Prophylaxis in Preterms (TIPP trial) [40]. In this study, 999 preterm infants (birthweight 500 to 999 g) were randomly assigned to indomethacin prophylaxis or placebo at six hours of life. The following findings were noted:

- Infants who received indomethacin had a significant reduction in the incidence of PDA (21 versus 49 percent with placebo).
- Infants who received indomethacin had a similar incidence of BPD overall (45 versus 43 percent). However, among the subgroup of infants who did not develop PDA, indomethacin was associated with a higher incidence of BPD (43 versus 30 percent), a greater requirement for oxygen supplementation, and less weight loss. The last two findings may have resulted from a decrease in urine output with indomethacin leading to fluid retention, which promoted the development of BPD [41].

Several studies also showed that prophylactic ibuprofen versus placebo or no intervention decreased the incidence of PDA at day three of life and the need for therapeutic intervention [42-44]. However, the use of ibuprofen was associated with adverse side effects [42-44]. This was illustrated in a systematic review of four studies that compared ibuprofen with placebo or no medication [45].

- On day three of life, the incidence of PDA was lower in the ibuprofen compared to the control group (RR 0.37, 95% CI 0.29-0.49). There was a decreased need in the treated infants versus the control group for rescue medical treatment with indomethacin (RR 0.17, 95% CI 0.11-0.27) or surgical ligation (RR 0.34, 95% CI 0.14-0.81).
- In the control group, 60 percent of patients had spontaneous closure of their PDA by the third day of life.

- There were no differences in the mortality rate and incidence of severe intraventricular hemorrhage (grade III and IV) between the treated and control groups.
- In patients who received ibuprofen compared to controls, there was an increase in serum creatinine levels (RR 1.44, 95% CI 1-2.08) and a decrease in urine output. In one of the included studies [24], there were three cases of severe pulmonary hypertension in patients who received ibuprofen. In the meta-analysis, there was no statistical difference in the incidence of NEC, but in one of the trials [43], treated infants were more likely to develop NEC.

Based upon these results, prophylactic treatment to reduce the incidence of PDA with COX inhibitors is not recommended because many infants, who would not develop significant PDAs, are unnecessarily exposed to drugs with potentially serious adverse effects.

OUR APPROACH

Symptomatic PDA — Over the past several decades, management of symptomatic PDA has changed in our neonatal intensive care unit (NICU). Prior to the commercial availability of indomethacin in the 1980s, surgical ligation was performed in preterm infants with PDAs who were dependent on mechanical ventilation. Once indomethacin became available, our management strategy changed to include frequent evaluations to detect PDAs using echocardiograms and to treat all ventilator dependent infants with PDA with indomethacin. Currently, a more moderate approach is used based on initial supportive care and subsequent pharmacologic therapy to close PDAs in infants who remain dependent on mechanical ventilation.

As noted above, there are no data to determine the optimal management of PDA in preterm infants. As a result, there is variability in the treatment of PDAs amongst different centers, and among neonatologists at a single NICU including our own institution. The following is a consensus approach to the management of PDA in preterm infants based on the practice of the members of our NICU staff.

- An initial conservative approach with supportive care that includes:
 - Daily fluid restriction between 110 and 130 mL/kg.
 - Use of permissive hypercapnia, low PaO₂ targets, and PEEP in infants who are mechanically ventilated to facilitate weaning from the ventilator and extubation, thereby minimizing mechanical lung trauma that increases the risk of bronchopulmonary dysplasia.
 - Chlorothiazide may be used to treat infants who become fluid-overloaded or with signs of increased interstitial pulmonary fluid.
 - Maintenance of a hematocrit above 35 percent.
 - Neutral thermal environment.
- A course of a COX inhibitor is given to infants who remain dependent on mechanical ventilation after a few days and have a PDA confirmed by echocardiography. We do not routinely measure platelets prior to drug administration but do avoid COX inhibitor use in infants with coagulopathy. We do not use these drugs in patients with NEC because of the risk of decreased blood flow to the bowel. Feedings are withheld at the discretion of the individual attending clinician during drug administration. Urine output is monitored and if oliguria is present, low dose dopamine is administered. (See 'Indomethacin' above and 'Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants', section on 'Diagnosis'.)
- For infants with clinically significant PDA and suspected necrotizing enterocolitis, who are recovering from intestinal surgery, or who have renal failure, we will use ibuprofen for pharmacologic PDA closure. (See 'Ibuprofen' above.)
- A second course of cyclooxygenase inhibitor therapy is given if follow-up echocardiograms show failure of closure and the infant is still ventilator dependent.
- Surgical ligation of the PDA is rarely performed and is reserved for infants that remain on very high ventilator settings with large PDAs who have failed medical therapy. In our NICU, only 5 of 162 (3 percent) infants less than 28 weeks gestation with PDAs underwent surgical ligation in 2009. Surgery was performed in the infant's room with neonatology staff providing anesthesia and ventilator management.

Prophylactic therapy — We do not recommend the use of prophylactic cyclooxygenase inhibitors (ie, indomethacin and ibuprofen) to reduce the incidence of PDA because many infants, who do not have significant PDAs, are unnecessarily exposed to the adverse effects of these drugs.

OUTCOME — Mortality is increased in infants whose PDA persists despite attempted closure. In a retrospective study of 252 infants born at or below 28 weeks gestation, survival outcomes were compared among infants who never had a significant PDA, infants whose significant PDA had been successfully closed medically, and those who had a persistent significant PDA after unsuccessful medical closure [46]. Infants with a persistent PDA had a fourfold increased risk of death compared to infants who never had a significant PDA. There was no difference in mortality rate between the group of infants who had successful medical closure of their PDA and those who never had a significant PDA.

In another retrospective review from a single tertiary center in the United States, 41 VLBW infants with a persistent PDA (failed indomethacin therapy and not surgically ligated) had an eightfold increased risk of death compared to 260 infants with a closed PDA after adjustment for confounding factors that included perinatal factors, level of maturity, and disease severity [47].

In infants who receive intervention, it is unclear whether there is a difference in outcome between medical and surgical therapy.

- In a retrospective study of 426 extremely low birth weight infants with PDA from the Trial of Indomethacin Prophylaxis in Preterms (TIPP), there was a trend toward decreased mortality in patients whose PDAs were surgically closed compared to those who were treated without surgery [48]. However, in surviving infants evaluated at a corrected age of 18 months, neurosensory impairment, BPD, and severe retinopathy of prematurity (ROP) were more likely to develop in patients with surgically closed PDA compared to infants who were managed without surgery.

The observational design of this study makes it difficult to ascertain whether the increased risk of complications are directly related to the surgical procedure (including the effects of anesthesia) or if the surgical intervention included a subset of infants who were more critically ill and, hence, more likely to develop long-term complications. The study design also had a bias for increased survival in patients treated surgically because surgical deaths were only counted after the procedure, whereas deaths in the medically treated group were reported any time after the diagnosis of PDA.

As a result of these limitations, it is difficult to determine whether medical or surgical treatment for PDA closure is superior in long-term outcome in preterm infants.

- A retrospective review of 446 infants (gestational age <28 weeks) from a single tertiary center reported the clinical outcome of a standardized protocol utilizing prophylactic indomethacin. After initial prophylactic indomethacin, 15 percent had persistent PDA. Twenty-seven percent developed symptomatic PDA and the attending neonatologist decided upon the subsequent choice of treatment (indomethacin versus surgical ligation). Results, which were adjusted for gestational age, demonstrated no differences in the rates of mortality, NEC, and ROP between patients treated medically or surgically [49]. In contrast, increased risk for BPD was associated with surgical ligation.

A limitation of this study is that the subsequent choice of medical versus surgical treatment was not randomly selected, but was decided upon by the attending neonatologist. In addition, it is unclear whether the exposure to a symptomatic PDA differed between the groups, although there was a difference in the mean duration of exposure to a symptomatic PDA from 0.8 days before the initiation of indomethacin to 1.9 days for surgical closure.

Randomized trials that compare the clinical outcome of the different management approaches are required to decide upon the most efficacious and safe therapeutic intervention for premature infants with PDA. Until these data are available, we administer pharmacologic treatment to preterm infants with symptomatic PDA in our care as discussed above [50]. (See 'Symptomatic PDA' above.)

SUMMARY AND RECOMMENDATIONS — Preterm infants with clinically significant patent ductus arteriosus (PDA) have a greater mortality rate than those without a PDA. PDAs also are associated with an

increased risk of pulmonary edema and hemorrhage, and bronchopulmonary dysplasia. As a result, management has been focused on PDA closure and prevention. (See 'Outcome' above and "Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants".)

- Management of PDA includes the following three different approaches. (See 'Overview' above.)
- Conservative management with supportive care alone (See 'Supportive therapy' above.)
- Pharmacologic closure using cyclooxygenase inhibitors, such as indomethacin and ibuprofen (See 'Cyclooxygenase inhibitors' above.)
- Surgical ligation (See 'Surgical ligation' above.)
- The optimal current management approach is not known as there is a paucity of large randomized controlled trials comparing the three different approaches in the most recent era of neonatal practice. As a result, it remains unclear which approach is most advantageous and whether clinical parameters may favor one approach over another. This uncertainty leads to wide variability in the management of PDA amongst different neonatal intensive care units (NICUs) and even neonatologists who practice in the same NICU. (See 'Overview' above.)
- In our approach to managing preterm infants with symptomatic PDAs, the following therapeutic decisions are based on the severity of respiratory disease and the continued need for mechanical ventilation. (See 'Symptomatic PDA' above.)
- We recommend supportive care for all preterm infants with PDAs (Grade 1C). This includes providing a neutral thermal environment, using positive end-expiratory pressure to improve gas exchange, maintaining a hematocrit of 35 to 40 percent, fluid restriction between 110 and 130 mL/kg per day, and the use of permissive hypercapnia and low oxygen saturation targets to manage respiratory distress. If diuretic therapy is indicated, we recommend the use of thiazide diuretics (eg, chlorothiazide) over loop diuretics such as furosemide (Grade 1B). (See 'Supportive therapy' above.)
- In infants with a PDA who remain dependent on mechanical ventilation after two weeks, we suggest a course of cyclooxygenase (COX) inhibitors versus supportive care alone (Grade 2B). A second course of COX inhibitor is administered if follow-up echocardiograms demonstrate a persistent PDA and the infant remains ventilator dependent. (See 'Cyclooxygenase inhibitors' above.)
- We suggest that surgical ligation only be performed in infants with large PDAs who remain on high ventilator settings and have failed to respond to COX inhibitors (Grade 2B).
- We do not recommend the use of prophylactic COX inhibitors to reduce the incidence of PDA, because many infants, who would not develop significant PDAs, are unnecessarily exposed to drugs with potentially serious adverse effects (Grade 1B). (See 'Prophylactic therapy' above.)

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Etiology, clinical features, and diagnosis of neonatal hypertension

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INTRODUCTION — Hypertension can be detected in 1 to 2.5 percent of all neonates (both term and preterm infants) admitted to neonatal intensive care units (NICUs). The clinician needs to be knowledgeable about normative blood pressure (BP) values, the optimal method to measure BP in newborns, the underlying etiologies, and clinical manifestations, in order to identify and treat neonatal hypertension.

The definition, etiology, clinical features, and diagnostic evaluation of neonatal hypertension will be reviewed here. Treatment of hypertension in infants is discussed separately. (See "Management of hypertension in infants".)

DEFINITION — In children and adolescents, hypertension is defined as systolic and/or diastolic BP ≥ 95 th percentile based on normative data for age, gender, and weight [1]. (See "Definition and diagnosis of hypertension in children and adolescents", section on 'Definition'.)

Although this operative definition may also be used to define neonatal hypertension, there is a lack of robust normative BP data in this age group. In addition, there are a number of factors that affect normal BP values during the neonatal period (defined as the first 28 days of life). As a result, it is challenging to assemble reliable normative data for clinical use in this age group.

Normal BP — Normal BP in newborns varies with gestational age, postmenstrual (also referred to as postconceptional) age, and birth weight. BP values increase following birth, with greater rates of increase seen in preterm infants compared to term infants.

Useful data on BP in newborns were obtained in a study of 608 newborns admitted to 14 NICUs in the Philadelphia area (figure 1 and figure 2) [2]. Systolic BP and diastolic BP were measured by oscillometric device every eight hours for 1 to 99 days after delivery. The following findings were noted:

- On day one, systolic and diastolic BP correlated strongly with birth weight and gestational age.
- During the first five days after birth, systolic BP and diastolic BP progressively rose by 2.2 to 2.7 mmHg/day and 1.6 to 2.0 mmHg/day, respectively, regardless of gestational age or birth weight.
- Systolic and diastolic BP continued to increase after the fifth day of age, but at more gradual increments (0.24 to 0.27 mmHg/day and 0 to 0.15 mmHg/day, respectively).
- In a multiple regression analysis, the primary determinant of BP was postconceptional age (gestational plus postnatal age) (graph 1) [2].

Similar results were noted in a study of 373 hemodynamically stable infants (292 preterm and 81 term neonates) admitted to the NICU, in whom BP data were obtained utilizing an oscillometric device [3]. In this cohort, BP on day one of life correlated with gestational age and birth weight. In all infants regardless of gestational age, BP increased at a faster rate over the first week of life, followed by subsequent slowing. The rate of rise was more rapid in preterm infants compared with term infants [4].

Healthy term infants cared for in the normal nursery demonstrate a somewhat different pattern from the above studies. This was illustrated in an Australian prospective study of 406 term infants with a mean gestational age of 40 weeks born between 2003 and 2005, in whom blood pressure measurements were determined by oscillometry methods [5]. The following findings were noted:

- At 12 to 24 hours of life, median systolic, diastolic, and mean BPs were 65 (range 46 to 94), 45 (range 24 to 57), and 48 (range 31 to 63), respectively. Unlike what was seen in the studies of preterm infants, no difference in BP was seen on day one of life based on birth weight, length, or gestational age.
- Blood pressure measurements increased over the next four successive days by 1 to 2 mmHg/day. On days two, three, and four of life, median systolic BP measurements were 68, 69.5, and 70, respectively; median diastolic BPs were 43, 44.5, and 46, respectively; and median mean BPs were 51, 52, and 54, respectively. The differences between days three and four were not significant, suggesting an earlier leveling off of BP than observed in preterm infants.

In summary, the following observations about normal neonatal BP can be concluded from the above studies:

- The primary determinant of neonatal BP is postconceptional age.
- In neonates admitted to the NICU, BP varies with gestational age, postconceptional age, and birth weight. In all infants regardless of gestation, the rise in BP is higher during the first week of life. The rate of rise is more rapid in preterm compared with term infants.
- In healthy term infants, BP does not vary based on growth parameters or gestational age. BP does increase over the first three to four days of life but levels off sooner than what is observed in preterm infants.

These results demonstrate how challenging it is to establish normative values for neonatal BP, especially in preterm infants, because of the effects of gestational age and maturation on BP values. These issues, plus the lack of large scale, prospective, multicenter studies of neonatal BP, further complicate the problem of defining normative BP data for neonates, especially premature and ill term infants.

Nevertheless, based on a review of these data, a reference table of normal BP values at or after two weeks of age in infants between 26 and 44 weeks postconceptional age has been published (table 1) [6]. This table, which is based on the best available data through 2010, can be used clinically to identify infants with hypertension defined as persistent BP elevation greater than the 95th percentile. These infants require further evaluation and/or treatment. (See 'Evaluation' below and "Management of hypertension in infants".)

INCIDENCE — The incidence of neonatal hypertension varies depending upon the clinical setting. In otherwise healthy term infants, hypertension is exceedingly uncommon with a reported rate of 0.2 percent [7]. In infants admitted to a NICU, the incidence is higher with reported rates ranging from 0.7 to 3 percent [8-11]. Risk factors for hypertension include low gestational age and birth weight, specific diseases (eg, bronchopulmonary dysplasia [BPD] and acute renal injury), and the use of umbilical artery catheters.

In a retrospective Australian study of 2572 newborn infants born between 2001 and 2005, and admitted to the NICU, 1.3 percent of infants were diagnosed with hypertension (defined as systolic or mean BP >95th percentile for gestational age) at a median postnatal age of five days [11]. Hypertensive infants were more likely to have a lower gestational age, birth weight, and length than normotensive infants. Other factors associated with hypertension included antenatal steroid administration, maternal hypertension, umbilical arterial catheterization, postnatal acute renal injury, patent ductus arteriosus, and BPD.

In an earlier report, the incidence of hypertension was higher in infants with BPD (6 percent), patent ductus arteriosus (3 percent), and intraventricular hemorrhage (3 percent) [9]. Nearly 9 percent of infants with umbilical artery catheters developed hypertension.

Hypertension is also reported after NICU discharge. In a study of 654 infants seen in a neonatal follow-up clinic, 17 (2.6 percent) were found to have hypertension (defined as systolic BP >113 mmHg by Doppler) at a mean postconceptional age of 49 weeks [10]. Compared to a control group of 212 normotensive infants, the hypertensive infants tended to have lower birth weights, lower one minute Apgar scores, and longer lengths of stay in the NICU, but none of the differences were statistically significant.

MEASUREMENT — Comparison of an infant's BP to normative values requires proper measurement. BP can be measured invasively or noninvasively. The ideal setting to measure BP is while the infant is sleeping or resting, because crying, pain, feeding, and agitation all can increase BP [12].

Intra-arterial measurement — Direct intraarterial measurement through a catheter placed in the aorta or the radial artery is the most accurate technique. It also provides continuous readings. The degree to which radial pressures correlate with aortic pressures is uncertain. In adults, radial artery systolic BP measurements may be 20 to 30 percent higher than central values, although mean and diastolic measurements are comparable [13]. However, radial pressures appear to more closely mimic aortic pressures in newborns [14].

Complications associated with intraarterial catheters include thrombosis and infection. Thus, they should be used to monitor BP only when the catheter is needed for a significant clinical indication, such as frequent blood sampling, hypotension requiring pressor support, or severe hypertension requiring treatment with intravenous antihypertensives.

Noninvasive measurement — Numerous noninvasive devices are available to measure blood pressure. The most common technique is oscillometry, which permits continuous measurement of blood pressure and correlates well with direct measurements. Automated oscillometric devices measure the mean arterial pressure and calculate the systolic and diastolic pressures. The algorithms used for these calculations vary between manufacturers, so different devices may give different BP values in the same patient.

Cuff size — A critical component of noninvasive blood pressure measurement is use of an appropriate-size cuff [1]. The cuff bladder should measure two-thirds the length of the extremity, and 0.44 to 0.55 of the arm circumference. If the choice is between a cuff that is too small or one that is too large, use of the larger cuff will result in less error. Most normal blood pressure values are derived from upper arm measurements. Thus, BP usually is measured in an arm. In the term infant with a maximum arm circumference of 10 cm, the usual dimensions of an appropriated-size cuff bladder are 4 cm in width and 8 cm in length [1].

If a leg is used, an appropriate size cuff should be selected, that is, one that is two-thirds the length of the extremity. With appropriate size cuffs, lower- and upper-extremity BPs are nearly identical in the neonatal period [15]. The medical record should note the site of measurement.

Our approach — For non-critically ill infants in whom hypertension is suspected, we use the following standard protocol to measure BP [4]:

- BP measured by oscillometric device
- BP measurement preferentially performed 1.5 hours after a feed or medical intervention
- Infant lying in a prone or supine position
- Use of an appropriate sized BP cuff
- BP measurement performed in the right upper arm
- After cuff placement, the blood pressure should be measured several minutes after the infant has settled into a calm state.
- BP measurement performed while the infant is asleep or in quiet awake state
- Three successive BP readings are obtained at 2 min intervals

ETIOLOGY — Although numerous causes have been identified, the most common etiology of neonatal hypertension is umbilical artery catheter-associated thromboembolism, followed by chronic lung disease and renal parenchymal disease (table 2). However, sometimes no cause is identified. In patients with no identified cause, hypertension may be due to the presence of an undetectable renovascular event.

Vascular disease

UAC-associated thrombosis — The most common renovascular abnormality associated with neonatal hypertension is thrombosis associated with umbilical artery catheter (UAC) placement [16-19]. Thrombi that form on the tip or surface of the catheter can partially or completely occlude the abdominal aorta, thereby decreasing renal perfusion. These thrombi may then embolize into the renal vasculature, resulting in local areas of infarction and increased renin release.

Thrombi are common in newborns with UACs [16,18,19].

- In a prospective study, 18 of 19 patients had evidence of thrombus formation detected by contrast aortography [19]. In addition, there were several instances of clot fragmentation and embolization. Thrombosis was also seen at autopsy in 7 of 12 infants who had died.
- In a study using serial ultrasonography, abdominal aortic thrombi were detected in 32 of 99 consecutive patients (32 percent) after removal of an UAC [18].
- In another report, 11 of 12 newborns with hypertension had renal artery thrombosis demonstrated by radionuclide scan and/or angiography [20]. BP normalized with antihypertensive therapy and remained normal after discontinuation of treatment. At follow-up at a mean age of 5.75 years, scans remained abnormal, and five patients had unilateral renal atrophy.

The risk of UAC-associated thrombosis increases with increasing duration of UAC use, high UAC placement (ie, catheter above the diaphragm versus low placement, just above the aortic bifurcation) [21], the lack of use of heparinized infusate [22], and trauma to the endothelial surface while the catheter is in situ or during catheter insertion. In addition to hypertension, other serious long-term sequelae of umbilical artery catheterization include coarctation of the abdominal aorta due to scarring [23] and aneurysmal dilatation [24].

Other vascular causes — Other vascular causes of neonatal hypertension include:

- Coarctation of the aorta, which may be recognized by absent or diminished femoral pulses or a differential in BP between the upper and lower extremities. A rare variety of coarctation is the mid-aorta syndrome, in which there is segmental narrowing of the distal thoracic aorta or abdominal aorta and stenosis of branch vessels [25,26]. (See "Clinical manifestations and diagnosis of coarctation of the aorta".)
- Renal vein thrombosis, which classically presents with the triad of a flank mass, gross hematuria, and thrombocytopenia [27]. (See "Pathogenesis, clinical features, and diagnosis of thrombosis in the newborn", section on 'Renal vein thrombosis'.)
- Renal artery stenosis is a rare cause of neonatal hypertension [28,29]. Fibromuscular dysplasia accounts for the majority of cases of renal artery stenosis in childhood, although renal artery stenosis can be seen in genetic syndromes such as neurofibromatosis and Williams Syndrome. Renovascular disease is sometimes associated with congenital rubella infection [30,31]. (See "Congenital rubella syndrome: Clinical features and diagnosis" and "Epidemiology, risk factors, and etiology of hypertension in children and adolescents", section on 'Renovascular disease'.)
- Rare vascular causes include congenital abdominal aortic aneurysm [32] and idiopathic arterial calcification [33].

Renal parenchymal conditions — Renal parenchymal conditions associated with hypertension can be separated into congenital and acquired disorders.

Congenital disorders — Congenital renal and urologic disorders that are associated with neonatal hypertension include:

- Polycystic kidney disease: Both autosomal recessive (ARPKD) and autosomal dominant (ADPKD) polycystic kidney disease are frequently accompanied by hypertension. In a large series of children with ARPKD diagnosed after 1990 (median age 5.4 years), 65 percent had hypertension, which was detected at a median age of 16 days (range 5 to 165 days) [34]. ADPKD also can present in newborns, and in these patients, hypertension, although rare, may be present. (See "Autosomal recessive polycystic kidney disease in children", section on 'Hypertension' and "Autosomal dominant polycystic kidney disease in children", section on 'Renal manifestations'.)
- In contrast, hypertension is unusual in newborns with unilateral multicystic dysplastic kidney, although some cases have been described [35]. It sometimes occurs in later infancy or childhood [36]. (See "Renal cystic diseases in children", section on 'Multicystic dysplastic kidney'.)
- Obstructive uropathy — Hypertension may accompany obstructive uropathy, such as ureteropelvic junction obstruction [37,38]. The BP usually normalizes with surgical correction of the obstruction, but persistent hypertension has been described [39]. (See "Congenital ureteropelvic junction obstruction".)

Acquired renal parenchymal diseases — Acquired renal diseases associated with neonatal hypertension include:

- Acute kidney injury — Approximately 10 to 20 percent of newborns with acute kidney injury have hypertension. The most common cause in newborns is acute tubular necrosis, which is usually due to perinatal asphyxia, sepsis, or other causes of inadequate renal perfusion. (See "Acute kidney injury (acute renal failure) in the newborn", section on 'Etiology'.)
- Nephrocalcinosis is common in preterm infants. Affected infants rarely have hypertension, unless an obstructive calculus forms. However, infants with persistent nephrocalcinosis may develop hypertension. This was illustrated in a series of 83 of 201 preterm infants who had persistent nephrocalcinosis at term postmenstrual age [40]. Of these, systolic and diastolic blood pressures were >95th percentile at one and two years of age in 39 and 48 percent and 30 and 34 percent, respectively. (See "Nephrocalcinosis in neonates".)

Bronchopulmonary dysplasia — Systemic hypertension is common in infants with bronchopulmonary dysplasia (BPD) [41-43]. The incidence ranges from 5 to 40 percent, depending upon birth weight and severity of lung disease.

In a study of 73 very low birth weight infants (birth weight <1500 g), the incidence of hypertension was twice as great in those with BPD (n = 41 infants) compared with the overall cohort (12 versus 7 percent) [43]. The risk of hypertension appears to increase with severity of pulmonary disease [44].

The mechanism of hypertension in BPD is uncertain and may include increases in sympathetic activity and angiotensin II [44]. The association between hypertension and more severe BPD also suggests that hypoxemia may play a role. (See "Management of bronchopulmonary dysplasia", section on 'Systemic blood pressure'.)

Hypertension may not present until four to five months of age. It often is associated with the use of dexamethasone or other glucocorticoids [45-47]. If related to these drugs, it usually abates when therapy is discontinued. (See "Hypertension in infants between one month and one year of age".)

Iatrogenic causes — Iatrogenic causes of neonatal hypertension include fluid overload and medications. Medications that can cause hypertension include corticosteroids [45-47], pancuronium, and topical mydriatic agents [48].

Endocrine causes — Endocrine causes include hyperthyroidism [49] and mineralocorticoid excess, which, in neonates, is most often due to congenital adrenal hyperplasia (CAH) [50]. Hypertension and frequently hypokalemia, which are due to excess deoxycorticosterone, are typically present in CAH due to CYP11B1 (11-beta-hydroxylase) and CYP17 (17-alpha-hydroxylase) deficiencies. In neonates, CYP11B1 deficiency also is associated with ambiguous genitalia in females (clitoral enlargement, labial fusion, formation of a urogenital sinus), and penile enlargement in males. (See "Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency" and "Uncommon causes of congenital adrenal hyperplasia", section on 'CYP17 deficiency'.)

Miscellaneous causes — Other reported causes of neonatal hypertension include:

- Masses in or near the kidney, including mesoblastic nephroma [51], neuroblastoma [52], and Wilms tumor [53]. (see "Clinical presentation, diagnosis, and staging evaluation of neuroblastoma" and "Presentation, diagnosis, and staging of Wilms tumor")
- Increased intracranial pressure from cerebral edema or intracranial hemorrhage. (see "Clinical manifestations and diagnosis of intraventricular hemorrhage in the newborn")
- Hypertension occurs in 40 to 60 percent of patients during extracorporeal membrane oxygenation [54,55]. The underlying mechanism is unknown but is believed to be multifactorial, including fluid overload, altered renal sodium and water handling. Development of hypertension does not appear to be related to increased plasma renin activity, sodium or colloid loads, or their rates of infusion.
- Approximately one-third to almost one-half of neonates have hypertension after closure of abdominal wall defects [56]. The mechanism is attributed to increased intra-abdominal pressure causing transient changes in renal blood flow, rennin-angiotensin system, urine flow, and increased catecholamine secretion. The hypertension is usually transient and does not require any antihypertensive medication [57].
- Postoperative or procedural pain (eg, endotracheal intubation [58] or suctioning [59,60]). (see "Assessment of neonatal pain")
- Maternal cocaine and heroin use have been reported to cause persistent neonatal hypertension [61]. Withdrawal from long-term use of sedative and/or analgesics may also be associated with hypertension. (See "Infants of mothers with substance abuse".)
- For infants receiving prolonged parenteral nutrition (TPN), hypertension may result from salt and water overload, or from hypercalcemia caused either directly by excessive calcium intake or indirectly by vitamin A or D intoxication.

CLINICAL FEATURES — Most hypertensive newborns are asymptomatic, and the diagnosis is made by routine BP measurement. In patients with signs or symptoms, the magnitude of hypertension may not correlate with its presence or severity. These nonverbal patients may not manifest any symptoms even with severe hypertension.

Hypertension may be associated with the following cardiorespiratory, neurologic, and renal symptoms, and nonspecific signs such as lethargy, poor feeding, apnea, and irritability (table 3) [62]. In some instances, the underlying cause of hypertension is also responsible for the associated clinical manifestations.

- Cardiorespiratory signs include tachypnea, tachycardia, cyanosis, cardiomegaly, mottling, and, in severe cases, heart failure. Most resolve with correction of hypertension.

- Neurologic symptoms include irritability, lethargy, hypotonia, hypertonia, seizures, hemiparesis, nerve palsies, and hypertensive retinopathy (eg, vascular tortuosity, hemorrhages, exudates, and increased ratio of venous to arterial caliber) [63]. Some of these findings may be due to coexisting central nervous system abnormalities, such as intraventricular hemorrhage or cerebral thrombosis.
- Renal abnormalities include oliguria, polyuria, hematuria, sodium wasting, renal or bladder enlargement, and nephrotic range proteinuria [64]. Acute kidney injury may cause hypertension and most of these findings.

DIAGNOSIS — The first step in the evaluation is to confirm the diagnosis of hypertension by repeated, accurate measurements. In general, the diagnosis is supported by three or more elevated BP measurements over a 6- to 12-hour period. As noted previously, a standardized protocol for BP measurement when oscillometric devices are being used will help to ensure that accurate readings are obtained [4]. (See 'Our approach' above.)

EVALUATION — Once the diagnosis of hypertension is confirmed, an evaluation is performed to identify the underlying cause of hypertension, which may potentially be corrected. This includes a focused history, followed by physical examination and selected laboratory testing and imaging studies.

History — A focused history reviews pertinent prenatal exposures, neonatal course, and concurrent conditions. (See 'Etiology' above.)

- Prenatal history examines the possibility of maternal use of prescribed and illicit drugs, history of perinatal asphyxia, or prenatal ultrasound findings indicative of congenital renal or urologic disease.
- Neonatal history reviews the use of umbilical arterial catheter, current and past medications, and the presence of concurrent conditions associated with hypertension (eg, bronchopulmonary dysplasia, and congenital anomalies and/or syndromes associated with hypertension).

Physical examination — The physical examination may indicate the primary etiology of hypertension and may also detect pathophysiologic effects of hypertension, such as heart failure, hypertensive retinopathy, or neurologic abnormality.

- All infants with hypertension should have BPs measured in all four extremities to rule out coarctation of the aorta or an aortic thrombus occluding the thoracic or abdominal aorta. In these conditions, the femoral pulses typically are decreased or absent. (See "Clinical manifestations and diagnosis of coarctation of the aorta", section on 'Blood pressure and pulses'.)
- Abdominal distension or mass might be indicative of obstructive uropathy, polycystic kidney disease, hemocolpos, or abdominal/renal tumors.
- Signs of peripheral thrombi (eg, "cath toes", bluish discoloration of the toes caused by decrease perfusion) may sometimes be seen in hypertension associated with a umbilical arterial catheter.
- Newborns with hyperthyroidism may have tachycardia, flushing, and low birth weight. (See "Evaluation and management of neonatal Graves' disease", section on 'Clinical manifestations'.)
- Newborns with CYP11B1 deficiency typically have ambiguous genitalia in females (clitoral enlargement, labial fusion, formation of a urogenital sinus), and penile enlargement in males. (See "Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency", section on 'Clinical presentation' and "Evaluation of the infant with ambiguous genitalia", section on 'Congenital adrenal hyperplasia'.)
- Dysmorphic features may suggest an underlying syndrome (eg, Williams syndrome) that includes hypertension as one of its clinical manifestations. (See "Renal findings in Williams syndrome".)

Laboratory testing — Often the underlying cause is identified by the history and physical examination. Initial laboratory testing is directed towards assessing renal function and determining whether renal parenchymal disease is present. Routine testing includes urinalysis, urine culture, and measurement of blood urea nitrogen and serum creatinine, electrolytes, and calcium.

In some infants with renal artery thrombosis or embolism associated with a UAC, hypertension may occur in the absence of hematuria, proteinuria, or azotemia. Thus, their absence does not exclude this mechanism of

hypertension. Conversely, mild and transient hematuria, and proteinuria are common and nonspecific findings in ill newborns, and they cannot be used to diagnose renovascular disease.

Further testing is guided by the initial evaluation and individualized for the infant, and may include measurement of thyroid function tests, serum aldosterone, and plasma renin activity. Other studies may be needed to detect neurologic, drug, endocrine, or metabolic causes of neonatal hypertension.

Imaging studies — Renal ultrasonography with Doppler evaluation is the imaging modality of choice in neonatal hypertension and should always be obtained as part of the initial evaluation, when the cause has not been ascertained by the initial evaluation. It can identify renal masses, urinary tract obstruction, tumors, calculi, and renal cystic disease. Doppler flow studies can assist in detecting renal and aortic thrombi, and monitoring their course. Doppler studies are also essential to the diagnosis of renal venous thrombosis.

Radionuclide imaging is sometimes recommended when sonography is non-diagnostic. While a variety of isotopes are available to evaluate differential renal blood flow and glomerular filtration, useful diagnostic images are difficult to obtain in the neonatal period due to the immaturity of renal function. Given this, it may be best to defer radionuclide imaging until the infant has reached at least 44 weeks post-conceptual age. (See "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Dynamic renal scan' and "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT)", section on 'Static renal scan'.)

In infants with severe hypertension and no etiology detected by sonography, angiography should be considered. Although this test is invasive, it is the gold standard for the diagnosis of renovascular hypertension. Institutional expertise should guide the decision to perform angiography. In many instances, it will be appropriate to control the hypertension medically until the baby reaches a size at which angiography can be performed safely [65]. Noninvasive renal angiography, including computed tomography and magnetic resonance imaging, should not be ordered in infants because these techniques do not have sufficient resolution to reveal branch vessel disease in this age group.

Echocardiography — An echocardiogram should be obtained to detect possible left ventricular hypertrophy, left ventricular systolic dysfunction, or left atrial dilation and aortomegaly [5]. As in older children, detecting cardiac involvement would favor early institution of treatment with antihypertensive medications [1]. (See "Management of hypertension in infants", section on 'Who should be treated?'.)

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SUMMARY AND RECOMMENDATIONS — Neonatal hypertension is defined as persistent systolic and/or diastolic blood pressure (BP) that exceeds the 95th percentile for postconceptional age (graph 1 and table 1). (See 'Definition' above.)

- The incidence of neonatal hypertension varies depending upon the clinical setting. It is uncommon in healthy term infants with a reported incidence of 0.2 percent. The incidence is higher in infants who are admitted to the neonatal intensive care unit (0.7 to 3 percent), especially in very premature ill infants who are more likely to have risk factors for hypertension (eg, umbilical arterial catheter placement [UAC] and bronchopulmonary dysplasia [BPD]). (See 'Incidence' above.)
- BP can be measured either directly through intra-arterial measurement or noninvasively. Each center that cares for neonates should establish a standard approach for obtaining BP to ensure accuracy and consistency. In our center, we obtain BP measurements while the infant is either asleep or in a quiet state, and in a prone or supine lying position. For non-critically ill infants, BP is measured by an oscillometric device after an appropriate sized BP cuff is positioned on the right upper arm and preferably 1.5 hours after a feed or medical intervention. (See 'Measurement' above.)
- There are numerous causes of neonatal hypertension (table 2). The most common etiology is umbilical artery catheter-associated thromboembolism, followed by chronic lung disease and renal parenchymal disease. (See 'Etiology' above.)
- Most hypertensive newborns are asymptomatic. In those who are symptomatic, the magnitude of hypertension may not correlate with its presence or severity. Hypertension may be manifested by

cardiorespiratory, neurologic, and renal symptoms, and nonspecific signs such as lethargy, poor feeding, apnea, and irritability (table 3). (See 'Clinical features' above.)

- The diagnosis of hypertension is confirmed by repeated accurate measurements that demonstrate either systolic or diastolic BP that persistently exceeds the 95th percentile for postconceptional age (graph 1 and table 1). (See 'Diagnosis' above.)
- Once the diagnosis of neonatal hypertension is confirmed, an evaluation is performed to identify the underlying cause of hypertension, which may potentially be corrected. This assessment includes a focused history, followed by physical examination and selected laboratory testing and imaging studies. (See 'Evaluation' above and "Management of hypertension in infants", section on 'Correcting underlying cause'.)

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Gastroesophageal reflux in premature infants

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INTRODUCTION — Gastroesophageal reflux (GER), the passage of gastric contents into the esophagus, occurs commonly in newborn infants, especially those born prematurely. Physiologic GER typically is a developmental process that resolves with maturation. GER generally resolves on its own by one year of age. In infants who remain asymptomatic, no further evaluation or intervention is typically required.

In contrast, GER disease (GERD), as defined by the North American Society for Pediatric Gastroenterology and Nutrition, is clinically significant GER that causes morbidity [1]. Putative morbidities of GERD in preterm infants include frequent vomiting, aspiration pneumonia, irritability, failure to thrive, and exacerbation of respiratory symptoms, including chronic lung disease.

Gastroesophageal reflux (GER) in preterm infants will be reviewed here. GER in infants, children, and adolescents are discussed separately. (See "Gastroesophageal reflux in infants" and "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents" and "Management of gastroesophageal reflux disease in children and adolescents".)

MECHANISMS — Gastroesophageal reflux (GER) is extremely common in healthy infants in whom gastric fluids reflux into the esophagus 30 or more times daily. It appears that GER is more common in healthy preterm compared to term infants. The pathogenesis of GER in preterm infants appears to be multifactorial due in part to immature or impaired anatomic and physiologic factors that typically limit reflux.

Relaxation of lower esophageal sphincter — The most important mechanism of GER in preterm infants (similar to older infants and adults) is transient relaxation of the lower esophageal sphincter (LES) [2,3]. The LES is comprised of intrinsic smooth muscle of the esophagus and skeletal muscle of the crural diaphragm [4].

Transient LES relaxation is defined as an abrupt decrease in LES pressure below the intragastric pressure, which is unrelated to swallowing and allows regurgitation of stomach contents into the esophagus. Normally, the LES relaxes with the onset of esophageal contractions triggered by swallowing as food passes down the esophagus, and contracts when swallowing ceases in order to prevent reflux by maintaining a lower esophageal pressure that is higher than the intragastric pressure.

The frequency of transient LES relaxation is the same in preterm infants with and without GERD. However, infants with GERD are more likely to experience acid regurgitation during LES relaxation than those without GERD [5].

Gastric emptying — The time for gastric emptying increases with decreasing gestational age. This was illustrated in a study of preterm infants born between 25 to 30 weeks gestation that demonstrated emptying time decreased linearly with advancing gestational age at birth when emptying time was measured by breath tests using isotope labeled feeds [6].

The delay in gastric emptying in preterm infants may provide a greater gastric volume of liquid available for reflux. However, there are no data that show a delay in gastric emptying in preterm infants with symptomatic GER compared to asymptomatic patients [5].

Esophageal motility — In the preterm infant, esophageal motility may be immature and contribute to GER [7]. In one study that evaluated esophageal function during swallowing, increasing gestational age was correlated with increasing completion of secondary esophageal peristalsis, shortening of proximal esophageal sphincter contraction, and faster propagation velocity for liquids [7]. Another study that utilized high-resolution manometry confirmed that preterm compared to term infants were more likely to have incomplete esophageal peristalsis during swallowing [8]. Differences in swallow propagation during active sleep between preterm and term infants have also been reported [9]. However, there are no data showing differences in motility maturation directly correlating with an increased risk of symptomatic GER in preterm infants [10].

Respiratory disorders — GER may occur more frequently in infants who have respiratory disorders, such as bronchopulmonary dysplasia [BPD]. One possible mechanism contributing to increased reflux in infants with respiratory disorders may be that increased work of breathing results in a relative increase of intraabdominal versus intrathoracic pressures, which facilitates GER.

Gastric tube — The presence of nasogastric or orogastric tube, which is commonly used in preterm infants, may increase GER because it may cause greater LES relaxation and/or decreased gastric emptying [11,12].

CLINICAL MANIFESTATIONS

General symptoms — Because of the nonspecific nature of the symptoms associated with GERD, there is a wide variation among clinicians regarding their beliefs about the presenting signs and symptoms of GERD [13]. In general, symptoms include irritability, generalized behavioral discomfort, frequent bouts of emesis, posturing or grimacing, worsening of lung disease, and failure to thrive.

GER appears to be more frequent after feeding [14]. The reflux is less acidic and is higher in the esophagus.

Bronchopulmonary dysplasia — GER has been proposed as a contributor to the pathogenesis of bronchopulmonary dysplasia (BPD) due to aspiration of gastric contents into the lungs. This causal relationship

was supported by one study that demonstrated an increased pepsin concentration in the tracheal aspirates of preterm infants who develop BPD [15]. Another retrospective study reported an association between BPD and a diagnosis of GER among very low birth weight infants (birth weight <1500 g) at one year adjusted age [16]. However, this finding may be biased because of the possible greater diagnostic suspicion for GERD among infants with BPD, resulting in a more thorough reflux investigation in this group of infants. In contrast, two other studies did not find an association between GER and BPD [17,18].

Failure to thrive — Failure to thrive is a condition often attributed to GER. In a small match-controlled retrospective study of 23 preterm infants with clinically significant GER, there were no differences in the average weekly weight gain, caloric intake, and growth parameters between patients and matched controls. However, infants with GER took longer to achieve full oral feedings (32 versus 19 days) and had a longer length of hospital stay (99 versus 70 days) [19].

Relationship to apnea — A variety of physiologic protective reflex responses provide a plausible biological link between GER and apnea of prematurity [20]. As an example, evidence from animal models demonstrated fluid stimulation of the laryngeal mucosa inhibited normal respiratory patterns [21].

However, it is uncertain whether there is a causal association between GER and apnea of prematurity. Several studies performed in the 1970s and 1980s linked GER with apnea or respiratory arrest in neonates born at term and in older infants [22-25]. However, subsequent studies in preterm infants have mostly failed to demonstrate a temporal relationship between GER and apnea [26-33].

The lack of a temporal relationship between these two conditions has been demonstrated in studies that utilized cardiorespiratory monitoring, including respiratory inductance plethysmography, heart rate monitoring, oxygen saturation, and esophageal pH testing to detect acidic GER [27-30]. This was best illustrated in the largest of these studies from a single center that performed 12-hour cardiorespiratory monitoring in 119 premature infants with a mean gestational age of 28 weeks that resulted in 6255 recorded GER episodes [30]. The following findings were noted:

- Apnea ≥ 15 seconds was associated with only 1 percent of the GER episodes. There was no difference in the rate of apnea ≥ 15 sec before, during, or after GER episodes.
- Apnea ≥ 10 seconds was associated with 8.5 percent of the GER episodes. There was no difference in the rate of apnea ≥ 10 sec before or during GER episodes, but the rate decreased immediately after GER episodes.
- There was no difference between the mean duration of apnea before or during GER episodes (12.3 versus 13.9 sec).

Studies using multiple intraluminal impedance to detect nonacidic GER also demonstrated similar findings and failed to show a causal association of GER to apnea in preterm infants [31-33]. These data show that GER and apnea do occur in the same infant but generally as two separate events.

In a subsequent report of premature infants, motility studies in premature infants (postmenstrual age range from 34 to 37 weeks) demonstrated that apneic episodes were associated with a reduction in LES tone [34]. Similar results have been reported in a study of newborn piglets [35]. These findings suggest that apnea may precipitate GER rather than the opposite relationship of GER causing apnea.

DIAGNOSTIC EVALUATION — The diagnosis of GER is challenging in preterm infants because, as previously mentioned, symptoms are nonspecific, and diagnostic testing is limited due to technical problems and difficulties of interpreting results in the newborn.

In addition, the postconceptional age at which preterm infants can safely undergo procedures may be a limiting factor for diagnostic testing. Small, medically unstable infants may not be able to tolerate being transported for radiologic testing, or placement of a pH or multiple intraluminal impedance probe in the nostril, because it may compromise respiratory status or increase the risk of esophageal perforation from probe placement in the smallest infants, although this has not been reported in the literature. The size at which the diagnostic procedures may be safely accomplished will depend on institutional comfort and familiarity. In our institution, for instance,

we rarely place a multiple intraluminal impedance probe, which is stiffer than a pH probe, in infants with a weight less than 1600 g.

Thus, many clinicians use a therapeutic trial in infants in whom GER is suspected based upon the history and physical examination without performing an extensive diagnostic evaluation if testing is not available or if there is a concern that the infant safety may be compromised by attempting a diagnostic procedure. However, nonpharmacologic management should be the mainstay of therapy in the most immature and vulnerable patients who are at greatest risk for adverse events from procedures and pharmacologic therapy (figure 1). (See 'Management' below.)

History and examination — The nonspecific signs associated with GER include regurgitation of milk, vomiting, irritability, arching, grimacing, desaturation, and respiratory symptoms. In contrast, bilious vomiting, gastrointestinal bleeding, diarrhea, constipation, fever, lethargy, abdominal tenderness and distension, and hepatosplenomegaly suggest another diagnosis other than GER [36].

Diagnostic testing — In the premature infants, diagnostic testing includes esophageal pH probe and multiple intraluminal impedance.

Esophageal pH probe — Esophageal pH measurement to detect reflux of acidic gastric contents in the distal esophagus is the most widely employed diagnostic test for GER in preterm infants. The test, which may last up to 24 hours, is performed by the transnasal passage of a microelectrode containing a pH sensor into the lower third of the esophagus. The wide spectrum of size of preterm infants makes placement of the catheter challenging. However, placement is crucial, as misplacement may result in under- or overestimation of acid reflux, especially in the smallest infants in whom a small error in positioning could give rise to a potentially large error in the results [37]. The catheter is placed using the Strobel formula that correlates the patient's length to his/her esophageal length [38]. Placement is confirmed radiographically.

Various scoring techniques have been used to interpret the results of pH probe studies, and generally include the number of acid reflux episodes, average duration of the episodes, and overall proportion of time with a pH less than 4. The reflux index (RI), which consists of the sum of the periods in which pH is less than 4 as a percent of recording time, is a widely used scoring system. Data from term infants referred for screening for an increased risk of sudden infant death syndrome reported that the 95th percentile for RI was about 10 percent, and the 50th percentile was in the 4 to 5 percent range [39]. It is important to note that acid may not be detected postprandially in infants because milk will buffer acid contained in the refluxate, leading to underestimation of GER.

Intraluminal impedance — This newer technique, also known as multiple intraluminal impedance [MII], uses an esophageal catheter designed to measure impedance from multiple intraluminal recording sensors [40]. The method allows detection of GER based on changes in electrical resistance to electrical current flow between two electrodes when a liquid and/or gas bolus moves between them. Impedance detects GER if there is a sequential drop in impedance to less than 50 percent of baseline values, starting distally above the lower esophageal sphincter and propagating retrograde to at least the next two more proximal measuring segments. Therefore, anterograde swallows can be differentiated from retrograde boluses (GER). This emerging technology is being employed as both a clinical and research tool in preterm infants.

The obvious advantage of MII is the ability to assess postprandial reflux, which may be masked by milk neutralizing the acid content of the refluxant when only a pH probe is used. This was illustrated in one study of preterm infants (gestational age of 23 to 37 weeks, tested at a postconceptional age between 34 to 48 weeks) that showed more episodes of reflux and less acidic reflux contents after versus before a feed [14].

However, several reservations associated with the use of MII in preterm infants remain, particularly the lack of validated normative standards in neonates [41,42]. When compared to pH measurement, MII detects more frequent and shorter duration episodes, which are of uncertain clinical significance. Finally, it is important not to measure impedance based reflux alone, as there is a high incidence of acid reflux events detected by pH monitoring that is not identified by MII [43]. Acid reflux events missed by MII occurred most often in the least mature infants, possibly due to delayed esophageal fluid clearance in this immature population. To address this issue, MII has been combined with esophageal pH into a single probe [41,44].

Other techniques — Techniques used to detect GER in older infants and children, including endoscopy and esophageal manometry, are rarely employed in neonates because of size limitation. The need to perform biopsy to diagnose esophagitis is almost nonexistent.

Other studies that may be performed in neonates include:

- Upper gastrointestinal series — An upper gastrointestinal (UGI) series with small bowel follow-through should be performed in infants with severe GER. This study is used to evaluate esophageal, gastric, and intestinal anatomy because congenital anomalies in these structures may cause reflux or vomiting.

However, UGI is a poor method to demonstrate GER, because the procedure is performed under non-physiologic conditions that may provoke reflux that is not clinically important. Also, a UGI may not detect clinically significant GER because the period of fluoroscopic monitoring is brief, typically less than five minutes.

- Technetium scintigraphy — A nuclear medicine scintigraphy study, often commonly referred to as a milk scan, allows detection of esophageal reflux events, measurement of gastric emptying time, and detection of aspirated gastric contents in the lungs. However, this technique is more likely to miss reflux events than continuous pH or MII monitoring.

MANAGEMENT — The initial treatment for GER is conservative and consists of dietary changes and parental education [45]. Pharmacologic therapy is reserved for infants who fail conservative management and have excessive reflux demonstrated on diagnostic testing (figure 1). As discussed previously, diagnostic testing is difficult to perform in preterm infants, and a therapeutic time-limited trial often is used in patients suspected of having significant GER when testing is not feasible. The need for intervention should be reassessed every two to three weeks as maturation occurs.

Indications — About half of all infants between zero and four months of age regurgitate at least once per day, with symptoms peaking at four months of age when the majority of infants have clinical GER. As a result, the North American Society for Pediatric Gastroenterology and Nutrition generally recommends that "happy spitters" without any morbidity should not be treated for GERD [1]. However, these recommendations do not specifically address preterm infants in whom it is often difficult to distinguish between GER and GERD, especially when deciding to initiate treatment and evaluate the efficacy of different therapies. (See "Gastroesophageal reflux in infants", section on 'Natural history'.)

Because of the nonspecific symptoms associated with GERD, the indications used among clinicians to initiate therapy in preterm infants vary. In our practice, we initiate GER treatment for GER when there are significant symptoms and concern for harmful sequelae by initially starting with nonpharmacologic interventions.

Nonpharmacologic therapy — Initial nonpharmacologic therapy includes dietary changes and parental education [45]. We assure the parents that reflux is a common physiologic occurrence in preterm infants that will resolve on its own and generally does not need significant intervention.

Diet — In term and older infants with presumed symptomatic GER, several dietary manipulations have been investigated, including smaller more frequent feeds, thickened feeds, and a trial of cow-milk free diet. However, these dietary modifications have been not been adequately studied in preterm infants with GERD. In particular, the use of feeds thickened by rice cereal may be challenging in preterm infants with weak oromotor skills or who are fed by tube-feeds. In addition, it remains unclear whether this dietary manipulation is effective in preterm infants, as the available limited data report conflicting results [46,47]. (See "Gastroesophageal reflux in infants", section on 'Lifestyle changes'.)

Position — The optimal feeding and postprandial positions for premature infants remain uncertain despite extensive study, as demonstrated by the following discussion. In addition, the prone sleeping position is associated with an increased risk of sudden infant death syndrome (SIDS). Because there is no evidence of a preferred position to reduce GER, it is important to model supine positioning prior to discharge in the hospital and to educate families to use the supine sleeping position at home. (See "Sudden infant death syndrome".)

The following studies, which evaluated the effect of body positioning on GER in premature infants using a combination of pH and electrical impedance monitoring, failed to identify a preferred position to reduce the risk of GER.

- Prone versus supine positioning
 - In a study of 22 symptomatic premature infants (ie, frequent episodes of regurgitation and postprandial desaturation) with a median gestational age of 31 weeks (range 24 to 32 weeks) and birth weight of 1220 g (range 630 to 2250), prone position at median postmenstrual age of 36 weeks (range 33 to 38 weeks) was associated with the fewest number of acidic and nonacidic GER episodes (4.4 and 0.3 percent) followed by left lateral positioning (7.5 and 0.7), supine (17.6 and 1.3 percent), and right lateral positioning (21.4 and 1.2 percent) [48].
 - In a study of 21 premature infants at a median postmenstrual age of 36 weeks, although acid reflux index and obstructive apnea episodes were higher in the supine compared to the prone position, there were no clinically important differences in either parameter between the two positions [49].
- Right versus left lateral positioning
 - A study of 10 healthy asymptomatic premature infants with a median gestational age of 31 weeks (range 27 to 36 weeks) were evaluated at a median postmenstrual age of 36 weeks (range 33 to 38 weeks) either in the right or left lateral position during gavage feeds, which was changed to the opposite after one hour [50]. Although the frequency of GER episodes, primarily liquid GER, was greater with initial right compared to left lateral positioning, gastric emptying time was shorter with initial right side positioning. This resulted in a greatly reduced rate of liquid reflux during the second postprandial hour (when acidity of the reflux is increasing) with the initial right versus left lateral positioning.
 - In a study of eight healthy preterm infants (mean 36.1 weeks post menstrual age), more episodes of lower esophageal sphincter relaxation (LESR) and GER occurred when infants were placed in a right versus left lateral position [51]. In addition, LESR was triggered by lower continuously infused feeding volumes in the right versus left lateral position.
- Elevation of the head — Studies in term and older infants demonstrate that elevation of the head is not beneficial in reducing GER [52].

Available data do not identify a preferred position to reduce GER that outweighs the recommendation for supine position and that also reduces the risk of SIDS. As a result, preterm infants should be placed in the supine position for sleep even if they have reflux.

Pharmacologic therapy — In premature infants with GER, anti-reflux therapies are among the most commonly prescribed drugs in the neonatal intensive care unit (NICU) [53]. This was illustrated by a report from the National Institute of Child Health and Human Development Neonatal Research Network that demonstrated 25 percent of extremely low birth weight infants (birth weight below 1000 g) were discharged from the hospital on antireflux medications [54].

Therapy consists of two different approaches.

- Acid suppression agents increase gastric pH, and thereby reduce esophageal acid exposure during episodes of reflux. They include histamine 2 (H₂) receptor antagonists (eg, cimetidine, famotidine, ranitidine, or nizatidine) and proton pump inhibitors (eg, omeprazole and lansoprazole).
- Prokinetic agents improve gastric emptying and/or esophageal sphincter tone, and include metoclopramide or cisapride. These agents do not reduce the occurrence of transient lower esophageal relaxations.

Acid suppression — Acid suppression therapy is widely used in neonatal practice with little evidence of short- or long-term benefit.

- H₂ receptor antagonists, such as ranitidine, limit the action of histamine released from mast cells. Although the pharmacokinetics of ranitidine have been studied in the preterm infant, efficacy for relief of GERD in this population has not been demonstrated. It is logical to assume that reduction of gastric pH would be useful therapy for esophagitis, but this entity is not reliably diagnosed by symptoms alone in infants.
- Proton pump inhibitors (PPIs), such as omeprazole and lansoprazole, have become increasingly popular for GERD therapy because of their superior acid-reducing effect during short- and long-term therapy. PPIs act by irreversibly inhibiting H⁺/K⁺-ATPase in the parietal cell. The number of infants on PPIs in the US has dramatically increased in the last several years, and 49 percent of infants on PPIs are started in the first four months of life [55,56].

Limited data have shown that omeprazole compared to placebo reduces gastric acidity and the duration of acid exposure in preterm infants [57]. A small study of esomeprazole showed a decrease in acidity but not in the frequency, extent, or clearance of esophageal boluses [58].

However, symptoms, and not physiological measures, define the difference between GER and GERD. A double-blinded randomized multicenter trial of infants demonstrated no difference in the reduction of symptoms attributed to GER between lansoprazole compared to placebo [59]. There were more serious adverse effects, particularly lower respiratory tract infections, in the lansoprazole group. Although 44 of the 162 infants were preterm, a subset analysis was not performed due to the small number of patients. (See "Gastroesophageal reflux in infants", section on 'Pharmacotherapy'.)

In addition, potential adverse effects of the medications raise safety concerns as follows:

- Gastric acid suppression has been linked to necrotizing enterocolitis and altered gastric colonization in the NICU, and in some studies, increased pneumonia and gastroenteritis in older populations [59-66].
- One study of cimetidine in VLBW infants was stopped by the safety monitoring committee because of increased death or severe intraventricular hemorrhage in the cimetidine group [67]. Although this study hypothesis was about reducing oxidative injury in the lung, not GER, it is a cautionary tale in the use of unproven therapies in preterm infants.

Prokinetic agents — Use of prokinetic agents has been limited in preterm infants because of the uncertainty of benefit and the potential for significant adverse effects [68-73].

- The efficacy of metoclopramide remains uncertain, and it has several reported adverse effects including irritability, rare dystonic reactions, and extrapyramidal symptoms in infants [68,69].
- Cisapride was removed from the market in Canada and the United States because of the risk of ventricular arrhythmia [72,73].
- Baclofen, a gamma-amino-butyric acid B receptor agonist, promotes gastric emptying in children with GERD [71], but its safety and efficacy in preterm infants is not sufficiently established to warrant routine use in this population.
- Erythromycin does not decrease feeding intolerance, as shown by a meta-analysis of 10 randomized trials that demonstrated no benefit of erythromycin as a prokinetic agent [70].

These agents are discussed in greater detail separately. (See "Management of gastroesophageal reflux disease in children and adolescents", section on 'Prokinetics'.)

A small trial in preterm infants with a mean gestational age of 29 weeks found that a combined regimen of metoclopramide and ranitidine compared with placebo did not reduce, and may have increased, the episodes of bradycardia attributed to GER [74]. An important additional result was the observation that there was a decrease in the frequency of bradycardia episodes over time, which was unrelated to treatment. This may contribute to misleading conclusions in nonrandomized and unmasked trials, which do not take this finding into account.

Transpyloric feeding — Transpyloric placement of an enteral feeding tube in the duodenum or jejunum has the theoretical advantage of decreasing GER. However, there are technical challenges associated with correct tube placement and maintenance of position, as well as bypassing the gastric phase of digestion. A meta-analysis of

this technique failed to find any advantage with respect to growth or time to establish full oral feeds, and reported an increased incidence of gastrointestinal disturbance and possibly mortality [75].

Surgery — Surgical intervention is reserved for infants with severe GERD who have failed aggressive medical management. These patients often have major central nervous system and respiratory morbidity, or have suffered a life-threatening event associated with reflux. (See "Management of gastroesophageal reflux disease in children and adolescents", section on 'Surgery'.)

SUMMARY AND RECOMMENDATIONS

- Gastroesophageal reflux (GER) is common during infancy, especially in preterm infants. The increased risk of GER in preterm infants is thought to be due to immature or impaired anatomic and physiologic factors that typically limit reflux. Most infants remain asymptomatic from their GER and do not require further evaluation or intervention, as GER will resolve on its own by one year of age. (See 'Introduction' above and 'Mechanisms' above.)
- GER disease (GERD) is defined as GER that causes morbidity. Symptoms associated with GERD are generally nonspecific in preterm infants, and are thought to include irritability, generalized behavioral discomfort, posturing, grimacing, emesis, worsening of lung disease, and failure to thrive; although, definitive evidence for these associations is lacking. In particular, there is a paucity of evidence for a relationship between GERD and apnea of prematurity. (See 'Clinical manifestations' above.)
- The diagnosis of GER is challenging in preterm infants because symptoms are nonspecific, and diagnostic testing is limited due to technical problems and difficulties of interpreting results in the newborn. Many clinicians use a time-limited therapeutic trial in infants in whom GER is suspected based upon the history and physical examination without performing an extensive diagnostic evaluation. When feasible, diagnostic testing should be considered before the initiation of pharmacologic therapy in preterm infants. The most common diagnostic test performed in preterm infants is esophageal pH monitoring. (See 'Diagnostic evaluation' above.)
- Treatment should be reserved for infants in whom there is concern for reflux causing harmful sequelae (figure 1). Management initially is begun with nonpharmacologic measures that include dietary changes (eg, smaller frequent feeds, and thickened feeds) based upon evidence from term and older infants and parental education. (See 'Nonpharmacologic therapy' above and "Gastroesophageal reflux in infants", section on 'Lifestyle changes'.)

Pharmacologic therapy that has been used in preterm infants includes histamine H2 receptor antagonists, proton pump inhibitors, and prokinetic agents. They have not been definitively shown to be effective in improving symptoms and may be associated with adverse sequelae, and so should be reserved for infants who fail nonpharmacologic measures. (See 'Pharmacologic therapy' above.)

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Prevention of respiratory distress syndrome in preterm infants

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INTRODUCTION — Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the major cause of neonatal respiratory distress, especially in preterm infants. The lungs of preterm infants lack adequate pulmonary surfactant that normally lines the alveolar surfaces. RDS is a result of surfactant deficiency, which increases surface tension at the air-liquid interface in the alveoli and terminal airways; this leads to atelectasis, impaired gas exchange, and secondary lung injury.

As surfactant deficiency is due to lung immaturity, the best intervention for RDS is to prevent premature birth. Potential effective therapies have included cervical cerclage, use of tocolytic agents, prevention and treatment of infections, and smoke and alcohol cessation. (See "Prevention of spontaneous preterm birth".)

If premature birth cannot be prevented, a more directed therapeutic approach toward the neonate to prevent RDS includes:

- The use of antenatal steroid treatment to women in preterm labor, accelerating fetal lung maturation and surfactant production.
- The use of exogenous surfactant in the premature infant, providing adequate levels of surfactant and improving lung function.

The therapeutic approach to prevent of RDS will be presented here. The pathophysiology and clinical manifestations are discussed separately. (See "Pathophysiology and clinical manifestations of respiratory distress syndrome in the newborn".)

Despite the initiation of preventive care as outlined in this topic review, RDS may still develop and is associated with both acute and chronic complications. The treatment and complications of RDS are discussed separately. (See "Treatment and complications of respiratory distress syndrome in preterm infants".)

ANTENATAL CORTICOSTEROID THERAPY — Antenatal corticosteroid (ACS) therapy is used in pregnant women at risk for preterm labor, as it enhances maturational changes in lung architecture and biochemistry, resulting in improved neonatal lung function. These changes increase the synthesis and release of surfactant and other components necessary for surfactant function, decreasing the incidence of RDS.

We recommend antenatal corticosteroid (ACS) treatment for women at risk for preterm delivery prior to 34 weeks of gestation to prevent RDS as outlined by National Institutes of Health (table 1). The efficacy and use of antenatal corticosteroid therapy are discussed in greater detail elsewhere in the program. (See "Antenatal use of corticosteroids in women at risk for preterm delivery".)

SURFACTANT THERAPY — Exogenous surfactant replacement therapy is widely used and is effective in reducing mortality and morbidity in infants with RDS [1,2]. Therapy provides surfactant into the lungs of preterm infants, preventing the development of RDS or (in some cases) diminishing its severity. Surfactant therapy varies in the types of preparation and the timing of administration.

Types of surfactant — A wide variety of surfactant preparations, which include natural and synthetic products, have been developed. At the present time, only natural surfactant preparations are available (table 2). The different preparations of surfactant including their relative efficacy are more fully discussed elsewhere in the program. (See "Exogenous surfactant therapy in preterm infants".)

Timing of surfactant administration — Surfactant is administered in preterm infants using three different timing strategies.

- Prophylactic surfactant therapy, which is administered at the time of delivery to infants at risk of RDS
- Early therapy, which is administered by two hours of age frequently before the diagnosis of RDS is made
- Rescue surfactant therapy, which is given once the diagnosis of RDS is established

In all three strategies, surfactant therapy improves mortality and morbidity in preterm infants when compared to untreated patients [3,4]. However, clinical trials suggest that prophylactic or early therapy is superior to rescue therapy alone in infants at high-risk for RDS (below 30 weeks gestation) [5-7].

Prophylactic or early versus rescue therapy alone — The decision to administer prophylactic or early surfactant therapy versus rescue therapy is based upon the identification of the infant at risk for RDS who may benefit from preventive therapy.

The principal risk factor is gestational age, with infants less than 30 weeks gestational age being at the highest risk for the development of RDS, as well as having the highest risk of mortality and morbidity associated with RDS.

In at-risk infants, prophylactic or early treatment is associated with a decrease in morbidity and mortality compared to rescue treatment for established RDS. This was best illustrated in two separate meta-analyses [6,7].

The first meta-analysis compared early to rescue therapy in four randomized controlled studies with 3459 patients [6]. Early treated patients received surfactant preparation within the first two hours of life and qualified because they required intubation for early RDS, while rescue treated patients received surfactant after the diagnosis of RDS firmly was established. Two of the studies used natural surfactant and the other two synthetic preparations. The following results were reported:

- In all four studies, early treated patients had a significantly reduced mortality rate compared to rescue treated patients (19.5 versus 22.3 percent; RR 0.87, 95% CI 0.77 to 0.99).
- There was a significant decrease in complications in early treated patients compared to rescue treated patients including pneumothorax (11.9 versus 17.1 percent; RR 0.70, 95% CI 0.59 to 0.82), pulmonary interstitial emphysema (9.6 versus 14.8 percent; RR 0.63, 95% CI 0.59 to 0.82), and chronic lung disease (CLD) (8.7 versus 10.8 percent; RR 0.7, 95% CI 0.55 to 0.88).
- There were no differences in the incidences of patent ductus arteriosus, intraventricular hemorrhage (IVH), retinopathy of prematurity, bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC).

The second meta-analysis compared prophylactic to rescue therapy in eight randomized controlled studies with 2818 patients [7]. All patients were treated with natural surfactant preparations. Prophylactic treated infants were intubated in the delivery room and received surfactant therapy prior to the first breath or immediately after intubation and stabilization. Rescue treated patients received surfactant after the diagnosis of RDS was established. Studies selected infants at high risk for RDS using inclusion criteria of gestational age less than 32 weeks gestation. The results were as follows:

- In seven studies, prophylactic treated patients had a significantly reduced mortality rate compared to rescue treated patients (7.2 versus 11.7 percent; RR 0.61, 95% CI 0.48 to 0.77). In a secondary analysis of infants less than 30 weeks gestation, prophylactic therapy decreased mortality compared to rescue therapy (10.3 versus 16.3 percent; RR 0.62, 95% CI 0.49 to 0.78).
- There were decreases in the incidence of pneumothoraces and the development of pulmonary interstitial emphysema in infants treated with the prophylactic strategy compared to those treated with rescue strategy (3.3 versus 5.4 percent; RR 0.62, 95% CI 0.42 to 0.89) and (12.2 versus 19.8 percent; RR 0.54, 95% CI 0.36 to 0.82), respectively.
- There were no differences in the incidences of patent ductus arteriosus, IVH, retinopathy of prematurity, BPD, and NEC between groups.

These data indicate that for every 100 babies at high risk for RDS, prophylactic surfactant versus rescue therapy alone would result in approximately five fewer deaths.

Prophylactic versus early therapy — Although there are no clinical trials that compare prophylactic to early therapy, there is some indirect evidence to suggest that prophylactic therapy is superior to early therapy:

- Even short delays of administration of surfactant may worsen outcomes. In a randomized study of early versus delayed surfactant in 2690 infants at high risk for RDS, for example, the combined outcome of death and BPD was reduced by 11 percent in patients who received surfactant before two hours of life compared to those treated at three hours of life [8]. Although this study suggests earlier administration of surfactant is beneficial, it did not directly compare prophylactic administration in the delivery room to administration in the neonatal intensive care setting.
- There is evidence suggesting that spontaneous breathing or mechanical ventilation in infants with surfactant deficiency injures the lung within the first hour of life. This was demonstrated in an autopsy study of infants who died before 12 hours of life [9]. Nine infants who lived from 1 to 10 hours had evidence of hyaline membrane disease by histology.

These data suggest that the optimal timing for surfactant administration to prevent RDS is at the time of delivery for preterm infants at risk for RDS.

Gestational age — We do not routinely administer prophylactic surfactant to infants who are greater than 30 weeks gestation. These larger infants (usually greater than 1250 grams) are at a lower risk for developing severe RDS and clinical trials have not found a benefit of prophylactic over rescue treatment [10].

Our approach — Our clinical approach is to administer a natural surfactant preparation in the delivery room to infants at high risk for RDS. This approach is in concordance with a clinical report from the American Academy of Pediatrics published in 2008, which summarized the available literature and includes the following [5]:

- Intubation of infants born at or before 30 weeks gestation in the delivery room.
- Prophylactic natural surfactant therapy is administered through the endotracheal tube as soon as the infant is stable after intubation. We do not obtain a chest X-ray, as this would delay the administration of surfactant. Skilled personnel are required to ensure proper placement without the benefit of chest X-ray confirmation.

The recommended dose of surfactant is dependent upon the surfactant used (table 2). The dosing is expressed in mL per kg of body weight, but optimal dosing for each preparation has not been studied extensively. Studies comparing doses are limited, and firm conclusions about optimal dosing cannot be reached at this time. At present, dosing is based on the manufacturers' recommendations and is as follows:

- Poractant alfa — 2.5 mL/kg (200 mg phospholipid/kg)
- Calfactant — 3.0 mL/kg (105 mg phospholipid/kg)
- Beractant — 4.0 mL/kg (100 mg phospholipid/kg).

There are no current data to recommend a specific natural surfactant preparation over another. (See "Exogenous surfactant therapy in preterm infants".)

- After surfactant administration, extubation and stabilization on nasal continuous positive airway pressure (CPAP) can be considered if the infant is active, and exhibits spontaneous respiratory effort. (See 'Mechanical ventilation and CPAP' below.)
- For infants who are less than 30 weeks gestation who are born outside a level three neonatal intensive care unit, intubation and surfactant administration should be considered if competent personnel are available prior to transport.

An alternate approach is the initial use of continuous positive airway pressure alone, and subsequent intubation and administration of surfactant only in infants who develop significant respiratory symptoms. (See 'Surfactant and CPAP' below.)

COMBINATION OF STEROIDS AND SURFACTANT — The combination of antenatal corticosteroid and surfactant therapy appears to improve mortality rates and clinical outcome in survivors [11-16]. Although there is no single trial that has compared the use of antenatal corticosteroids alone, surfactant alone, combination of the two, and placebo, the use of combination therapy is recommended based upon overall observations. Interpretation of many of the studies is difficult since a few infants were not exposed to antenatal corticosteroid therapy. Despite this, the effectiveness of combination therapy is illustrated by the following:

- In one study, 430 preterm infants (gestational age between 23 and 29 weeks) were randomly assigned to receive prophylactic natural surfactant (100 mg of phospholipids/kg of Survanta) or placebo after initial stratification by birthweight and antenatal steroid exposure [15]. Treated patients could be given repeated doses of surfactant. Compared with placebo, surfactant resulted in a significant decrease in mortality rate (11 versus 19 percent), incidence of RDS (28 versus 57 percent), and incidence of pulmonary interstitial emphysema (23 versus 37 percent).
- In a retrospective study of 226 infants (<31 weeks gestation) who were treated with prophylactic surfactant, outcomes were analyzed based upon the administration and timing of antenatal steroids: group 1, no steroids; group 2, steroids within 24 hours before delivery; and group 3, steroids 24 hours to 7 days before delivery [16]. Group 2 had the lowest mortality rate and incidence of severe IVH. Compared with group 1, groups 2 and 3 also had significantly lower mortality rates and incidence of severe IVH.

MECHANICAL VENTILATION AND CPAP — Infants at risk for RDS are initially intubated to deliver the administration of exogenous surfactant. Subsequently, continuous mechanical ventilation has traditionally been utilized to help prevent atelectasis, even in infants without respiratory failure. However, it is increasingly appreciated that continued ventilation is associated with volutrauma, thereby contributing to the development of bronchopulmonary dysplasia (BPD) [17-19].

Among infants without respiratory failure, continuous positive airway pressure (CPAP) is an alternative to help prevent atelectasis and reduce the risk of BPD. Most of the data supporting the use of CPAP has been observational [17,20-22]. Results are less clear in the single trial comparing CPAP to intubation and ventilation.

In this multicenter trial of 610 infants who were born between 25 and 28 weeks gestation, patients were assigned to nasal CPAP (pressure of 8 cm H₂O) or intubation and ventilation if they required respiratory support at five minutes of age [23]. The administration of surfactant was not mandated and followed local clinical practice. The following findings were noted:

- At 36 weeks corrected gestational age, there was no difference in the primary outcome of death or BPD (defined as need for oxygen therapy) between infants with CPAP versus those who were intubated (34 versus 39 percent, OR 0.8, 95% CI 0.58-1.12.).
- About half (46 percent) of the CPAP group were intubated during the first five days of life.
- Surfactant use was halved in the CPAP compared to the intubated group and days of ventilation were fewer. There was, however, no difference in the fraction of inspired oxygen (FiO₂) or maximum PaCO₂ during the two groups during the first five days of life.
- The risk of pneumothorax was greater in the CPAP compared to the intubated group (9 versus 3 percent).

This study was limited in that treatment was not masked and there were variations in other interventions including administration of surfactant and methylxanthine treatment (which is associated with a lower incidence of BPD). Nevertheless, these results suggest that it may be possible to initiate CPAP in preterm infants born ≤ 28 weeks and treat them with surfactant only if they require intubation. (See "Management of apnea of prematurity", section on 'Methylxanthine therapy'.)

Surfactant and CPAP — CPAP alone, versus CPAP in conjunction with surfactant without mandatory ventilation, may decrease the need and duration for mechanical ventilation and air-leak syndrome including BPD [24-26]

This was best illustrated in the SUPPORT (Surfactant, positive pressure, and pulse oximetry randomized) trial that randomly assigned 1316 extremely preterm infants (gestational age between 24 weeks and 27 weeks 6 days) to intubation and surfactant therapy or nasal CPAP alone within the first hour of life [25]. Patients who were in the surfactant group remained intubated and ventilated until they met predefined criteria demonstrating the ability to maintain adequate spontaneous ventilation and oxygenation. Patients who were assigned to the CPAP group were intubated and received surfactant within the first 48 hours of life if they met predefined criteria that included a requirement of supplemental oxygen with a FiO₂ greater than 50 percent or showed evidence of hemodynamic. In this study, infants were also randomly assigned to one of two target ranges of oxygen saturation. The following findings were noted:

- Eighty-three percent of the infants in the CPAP group were intubated and about two-thirds received surfactant.
- After adjusting for confounding variables (ie, gestational age, center, and family clustering), there was no difference between the CPAP and surfactant groups at 36 weeks postmenstrual age (PMA) in the primary outcomes of mortality (14.2 versus 17.5 percent, relative risk [RR] 0.81, 95% CI 0.63-1.03) and the rate of bronchopulmonary dysplasia defined as the use of supplemental oxygen at 36 weeks PMA (40.2 versus 44.3 percent, RR 0.94, 95% CI 0.82-1.06).
- Secondary analyses demonstrated the CPAP alone was associated with a lower rate of postnatal corticosteroid use and a shorter duration of ventilation. There were no differences in other secondary outcome measures between the two groups, including the risk of necrotizing enterocolitis, air leaks, severe intraventricular hemorrhage, severe retinopathy of prematurity and patent ductus arteriosus.

Although these results suggest that outcome using CPAP alone is as good as intervention with intubation and surfactant, an accompanying editorial expressed the following concerns regarding the study design of this trial [27]:

- The criteria used for extubation in the intubated/surfactant group appeared to be more stringent than those used in prior clinical trials, and resulted in a longer median duration of ventilation compared to previous studies [23].
- Randomization was performed before delivery, and as a result, some of the infants in the CPAP group who exhibited respiratory distress immediately after delivery, were intubated after birth and did not receive CPAP.
- The surfactant and ventilator group required more resuscitation in the delivery room (intubation, chest compressions, and epinephrine) and may have been a sicker group to begin with based upon the support they required in the delivery room. The outcome analysis did not appear to be adjusted for this finding.

Finally, it remains uncertain whether CPAP alone is a better alternative to intubation and prophylactic administration of surfactant as over 80 percent of the CPAP alone group eventually were intubated and the majority received surfactant. It is unknown whether there was an impact in the delay of intubation and surfactant in any of these patients. Further studies including long-term developmental outcome studies are needed to determine whether CPAP alone is a better alternative to intubation and prophylactic administration of surfactant in premature infants less than 30 weeks gestation.

Our approach — Our current recommendation is that, after intubation and administration of surfactant, the infant should be extubated and placed on CPAP if the infant is active, exhibits spontaneous respiratory effort, and does not seem to require mechanical ventilation [28]. However, others have suggested initial use of CPAP and administration of surfactant only if the patient requires intubation, based upon the concern that intubation can be difficult and may destabilize an infant's condition [23].

Historical cohort studies have demonstrated a decline in the incidence of BPD when changes in delivery care using these approaches were implemented.

- In the first study, delivery room practice changes included intubation with the administration of surfactant and extubation followed by continuous positive airway pressure treatment at delivery. This delivery room practice change away from mechanical ventilation was combined with targeting lowered oxygen saturation, and administering early amino acid supplementation on the admission to the NICU [29]. These changes were associated with a decrease rate of moderate and severe BPD in infants with birth weights below 1000 g from 43 to 24 percent.
- In the second study, practice changes included lower oxygen saturation goals and selective intubation policy for infants born at or below 29 weeks gestation [30]. Before the changes in practice, infants were intubated, given surfactant in the delivery room, and were managed subsequently on mechanical ventilation. After delivery room practice changes were implemented, infants that were spontaneously breathing with a good heart were stabilized without mechanical ventilation, and nearly two-thirds received nasal CPAP. These changes resulted in a decrease rate of BPD from 47 to 21.5 percent.

An alternative approach is initial CPAP for all preterm infants below 30 weeks gestation in the delivery room and, the use of early rescue surfactant in infants who develop a FiO₂ requirement greater than 0.5 or 0.6 [25,31].

SUMMARY AND RECOMMENDATIONS — The administration of antenatal corticosteroid, and prophylactic or early surfactant therapy to high-risk preterm infants reduces the incidence and severity of RDS.

- We recommend that ACS should be given to any pregnant woman at 24 to 34 weeks of gestation with intact membranes at high risk for preterm delivery (table 1) (Grade 1A). (See "Antenatal use of corticosteroids in women at risk for preterm delivery".)
- We suggest that infants born at or before 30 weeks gestation be intubated and receive a prophylactic natural surfactant preparation (Grade 2B). The dose is dependent upon the surfactant product selected. In preterm infants without respiratory failure, an alternative option is the administration of continuous

positive airway pressure alone. (See 'Surfactant therapy' above and 'Mechanical ventilation and CPAP' above.)

- After administration of surfactant and if the infant is active and exhibits spontaneous respiratory effort, we recommend extubation and stabilization on CPAP rather than continued intubation and mechanical ventilation (Grade 1B). (See 'Mechanical ventilation and CPAP' above.)
- We recommend not administering prophylactic surfactant therapy for infants greater than 30 weeks gestation (Grade 1B). (See 'Gestational age' above.)

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Bronchiolitis in infants and children: Treatment; outcome; and prevention

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INTRODUCTION — Bronchiolitis, part of the spectrum of lower respiratory tract infection (LRTI), is a common cause of illness and hospitalization in infants and children younger than two years. Bronchiolitis is broadly defined as an illness characterized by wheezing and airway obstruction that is caused by infection with a

viral or, less commonly, a bacterial pathogen resulting in inflammation of the small airways/bronchioles. Respiratory syncytial virus is the most common cause. (See "Respiratory syncytial virus infection: Clinical features and diagnosis".)

The treatment, outcome, and prevention of bronchiolitis will be reviewed here. The epidemiology, clinical features, and diagnosis are discussed separately. (See "Bronchiolitis in infants and children: Clinical features and diagnosis".)

OVERVIEW — In healthy infants and young children, bronchiolitis usually is a self-limited disease. Therapy in most cases consists of supportive measures to ensure that the patient is well oxygenated and well hydrated [1]. Bronchodilator therapy may be beneficial in a subset of patients, as described below.

Factors that should be considered in management decisions include the age of the child, the stage of infection at the time supportive care was begun, the disease severity, premorbid diagnoses, and the cause and site of airway obstruction [2]. The stage of infection is important. Early in the course, airway obstruction and inflammation may be partially reversible with pharmacotherapy [3-6], whereas once the disease progresses to the point that airway obstruction has occurred [7] and hospitalization is necessary, it is not clear whether the course can be altered [4,8-10]. Early pharmacotherapy is controversial because it is unclear if the benefit is limited to children with a predisposition to asthma and because an insufficient number of infants with early signs and symptoms of bronchiolitis have been adequately studied. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Risk factors' and 'Systemic glucocorticoids' below.)

Severity assessment — The clinical practice guideline of the American Academy of Pediatrics (AAP) defines severe disease as "signs and symptoms associated with poor feeding and respiratory distress characterized by tachypnea, nasal flaring, and hypoxemia" [11]. Severe disease is indicated by persistently increased respiratory effort, apnea, or the need for intravenous hydration, supplemental oxygen, or mechanical ventilation. Assessment of disease severity in infants and children with bronchiolitis is discussed in greater detail separately. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Severity assessment'.)

Risk factors for severe disease and/or complications of bronchiolitis include gestational age <37 weeks, age <12 weeks, chronic pulmonary disease, congenital heart disease, immunodeficiency, congenital and anatomical defects of the airways, and neurologic disease. Environmental and other risk factors, such as passive smoking, crowded household, daycare attendance, concurrent birth siblings, older siblings, and high altitude (>2500 m) can also contribute to more severe disease. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Risk factors'.)

Indications for hospitalization — Children can be managed as outpatients if they are adequately hydrated, do not appear acutely ill, and do not have signs of moderate to severe respiratory distress (nasal flaring, retractions, grunting). Infants with bronchiolitis who are not hospitalized should be followed by their clinician for progression of disease.

Children with moderate to severe disease usually require hospitalization. Although there are no established criteria for hospitalization, a number of guidelines have been published [12-15]. In general, criteria for hospitalization include [12,15-18]:

- Toxic appearance, poor feeding, lethargy, and dehydration
- Moderate to severe respiratory distress, manifested by one or more of the following signs: nasal flaring, intercostal retraction, respiratory rate >70 breaths per minute, dyspnea, and/or cyanosis.
- Apnea
- Hypoxemia (oxygen saturation <95 percent on room air at sea level) with or without hypercapnia (arterial carbon dioxide tension >45 mmHg). Although the AAP guideline suggests that supplemental oxygen is indicated if the oxygen saturation is consistently below 90 percent, it does not provide a room air oxygen saturation threshold for hospitalization [11]. Among outpatient children with bronchiolitis, evidence differs on whether mild reduction in pulse oximetry (oxygen saturation <95 percent while breathing room air) predicts progression of disease [12,19].
- The parent is unable to care for the child at home.

However, clinical practice varies widely [20-22]. As an example, some clinicians recommend admission of infants with respiratory rates >50 breaths per minute if the oxygen saturation is <95 percent while breathing room air [22].

SUPPORTIVE CARE — Supportive care in both the outpatient and inpatient settings includes respiratory support and maintenance of adequate fluid intake.

Nasal congestion — Saline nose drops and nasal bulb suction may help to relieve partial nasal obstruction. There is little evidence to support routine "deep" suctioning of the lower pharynx or larynx in the inpatient setting [11].

Monitoring — Repeated clinical assessment is the most important component of monitoring for deteriorating respiratory status in both the outpatient and inpatient settings [23].

Hospitalized infants should have continuous monitoring of heart rate, respiratory rate, and oxygen saturation. Infants with severe distress or who have apnea should be monitored in the intensive care unit (ICU). An arterial or capillary blood gas measurement should be considered in children who require intensive care and should be repeated as clinically indicated.

A change from continuous to intermittent measurement of oxygen saturation may be instituted as the patient's clinical course improves [11]. Among children hospitalized for bronchiolitis, the perceived need for supplemental oxygen, based on low oxygen saturation values obtained by pulse oximetry, has been associated in some patients with an increased risk of prolonged hospitalization [11,17,24,25].

Respiratory support — Oxygen should be provided by nasal cannula, head box, or face mask to maintain the arterial oxygen saturation above 90 to 92 percent [2]. Data are lacking to support the use of a specific cutoff value. The AAP practice guideline recommends oxygen saturation <90 percent as the threshold to start supplemental oxygen. However, variability in the accuracy of oximeters, and the presence of fever, acidosis, and hemoglobinopathy favor the use of a higher cutoff value. In addition, there is evidence from other clinical settings to suggest that chronic or intermittent hypoxia (oxygen saturation 90 to 94 percent) may have long-term cognitive and behavioral effects [26,27]. Close monitoring is required as supplemental oxygen is weaned, particularly for children with hemodynamically significant heart disease, chronic lung disease, and premature birth [11]. (See "Oxygen delivery systems for infants, children, and adults".)

Infants with arterial carbon dioxide tension >55 mmHg, hypoxemia despite oxygen supplementation, and/or apnea may require mechanical ventilation. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Respiratory failure' and "Emergent endotracheal intubation in children".)

High-flow nasal cannula therapy — Heated humidified high-flow nasal cannula therapy (HFNC) is a noninvasive method of ventilatory support that permits high inspired gas flows (1 to 8 L/min) with or without increased oxygen concentration [28]. It has been used in an effort to prevent reintubation in preterm infants following extubation. (See "Oxygen monitoring and therapy in the newborn", section on 'High flow nasal cannula'.) In an observational study, HFNC was associated with decreased rates of intubation in children <24 months of age who were admitted to a pediatric intensive care unit with bronchiolitis compared with historical controls [29]. Additional studies are necessary before HFNC can be routinely recommended for bronchiolitis.

Fluid administration — Parenteral fluid administration may be necessary to ensure adequate hydration and avoid the risk of aspiration in infants and children with bronchiolitis [11,30]. Fluid and electrolyte status should be carefully monitored [31,32]. Children with bronchiolitis may have difficulty maintaining adequate hydration because of increased needs (related to fever and tachypnea) and decreased intake (related to tachypnea and respiratory distress). However, plasma antidiuretic hormone levels may be elevated [33,34], leading to fluid retention. Fluid overload should be avoided, since it may lead to pulmonary congestion.

Chest physiotherapy — We suggest that chest physiotherapy not be used in the management of bronchiolitis [11]. A systematic review of three randomized trials concluded that chest physiotherapy using vibration and percussion did not improve clinical score, reduce supplemental oxygen requirement, or reduce length of hospital

stay [35]. The use of chest physiotherapy is discouraged because it may increase the distress and irritability of ill infants.

PHARMACOLOGIC THERAPY

Bronchodilators — Although bronchodilators have not been shown to be effective in viral bronchiolitis in published studies where analysis of group outcomes is reported, it is difficult to sort out individual patients with a predisposition to airway reactivity or asthma from those with isolated viral bronchiolitis [36-38]. Thus, we suggest that infants and children with clinically significant bronchiolitis receive a trial of inhaled bronchodilators. The effects should be monitored by evaluating the child before and up to one hour after treatment. Inhaled bronchodilators should be continued if there is a documented clinical response using an objective means of evaluation [11].

Inhaled bronchodilators — Although widely used and studied, the efficacy of inhaled bronchodilators (albuterol, salbutamol, and epinephrine) in the treatment of bronchiolitis is uncertain, and the published results have been variable [39-51].

One of the major problems with interventional trials and meta-analyses on the use of bronchodilators in bronchiolitis is the difficulty in distinguishing bronchiolitis caused by primary infection from virus-induced wheezing or asthma [36-38]. Children in the latter categories often respond to bronchodilators (and glucocorticoids), and they are invariably included in interventional trials, thus making it difficult to determine the effects of these medications on true viral bronchiolitis. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Differential diagnosis'.)

The aggregate evidence from large randomized trials [39-44,52], meta-analyses [45-47], and systematic reviews [48-50] does not support the use of inhaled bronchodilator therapy for infants with bronchiolitis, as illustrated by the two meta-analyses described below:

- The first included eight trials comparing bronchodilators other than epinephrine to placebo [45]. There were no significant differences in improvement in clinical score between treatment and placebo groups, oxygenation, hospitalization rate, or duration of hospitalization. A modest improvement was noted in average clinical score, but, as noted above, the results may have been biased by the inclusion of studies that enrolled infants with recurrent wheezing/asthma. At most, one in four children treated with bronchodilators might have a transient improvement in clinical score.
- The second included 14 trials comparing nebulized epinephrine to other bronchodilators or to placebo [46]. Compared to placebo or salbutamol, epinephrine improved clinical score and oxygen saturation in the short-term (up to 60 minutes) but did not affect admission rate. Separate analysis of epinephrine versus albuterol/salbutamol in the outpatient setting found some evidence to suggest that epinephrine may be favorable to salbutamol and placebo.

One possible explanation for the lack of difference in admission rates that was not addressed in the systematic review summarized above is the common practice of observing children who have received nebulized epinephrine for up to several hours (which may require hospital admission) [53]. A randomized trial comparing nebulized racemic epinephrine to nebulized racemic albuterol that was performed after the meta-analysis addressed this issue [51].

Children <18 months of age who presented to two emergency departments with bronchiolitis were randomly assigned to treatment with three racemic albuterol nebulization treatments or nebulized racemic epinephrine followed by two treatments with nebulized saline [51]. They were assessed two hours after the first treatment. There was no difference in the proportion of children in each group who were successfully discharged, defined by lack of requirement for additional bronchodilators or hospital admission within 72 hours (approximately 50 percent; RR 1.08, 95% CI 0.92-1.26). However, when adjusted for severity of illness, patients who received racemic albuterol were more likely to be successfully discharged (adjusted RR 1.18, 95% CI 1.02-1.36). Although the study had methodologic limitations (eg, inclusion of children who had previous episodes of wheezing, inclusion of infants younger than one month of age who are often admitted because they are at risk for apnea), the results support the use of albuterol as the first-line agent when a trial of bronchodilator therapy is warranted [36].

Despite evidence to the contrary, many clinicians believe that a subset of patients have clinical improvement in response to bronchodilator therapy early in the course of their disease [39,54-57]. In addition, there is little toxicity from therapy.

The clinical practice guideline of the American Academy of Pediatrics (AAP) recommends that bronchodilators should not be used routinely in the management of bronchiolitis. However, it does state that a carefully monitored trial of bronchodilator medication is an option, with continuation only if there is a documented objective clinical response [11]. Various scoring systems to document clinical response have been used; most include some assessment of respiratory rate, oxygen saturation, wheezing, and respiratory effort [1,6,42]. One is available through the University of Cincinnati (www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/bronchiolitis.htm) [1].

In accordance with this option, we suggest a trial of inhaled bronchodilators. Each patient should be assessed before and up to one hour after treatment. Because inhaled albuterol is more appropriate for use in the home setting [11], we suggest using albuterol as the bronchodilator of first choice:

- Albuterol 0.15 mg/kg (minimum 2.5 mg; maximum 5 mg) diluted in 2.5 to 3 mL saline and administered over 5 to 15 minutes; or four to six puffs via a metered dose inhaler with spacer and face mask.
- If no benefit is observed in one hour, we administer a single dose of nebulized epinephrine:
- Epinephrine (0.05 mL/kg of 2.25 percent epinephrine diluted in 3 mL normal saline).

If no clinical response is seen within one hour of epinephrine treatment, we do not continue the use of these agents. If there is a response to either albuterol or epinephrine, bronchodilator therapy can be administered every four to six hours and discontinued when the signs and symptoms of respiratory distress improve.

Oral bronchodilators — We do not recommend the use of oral bronchodilators in the management of bronchiolitis. The efficacy of oral albuterol was evaluated in a randomized trial of 129 infants with bronchiolitis who were discharged to home from the emergency department [58]. Therapy consisted of a one-week course of albuterol or placebo. The median time to resolution of the illness was similar in the two groups. The lack of efficacy of oral beta-agonists has been noted in other studies [59,60].

Glucocorticoids — The antiinflammatory effects of glucocorticoids are thought to reduce airway obstruction by decreasing bronchiolar swelling. Whether glucocorticoids provide benefit in different subgroups of children with bronchiolitis is uncertain. Some patients presenting with bronchiolitis may be experiencing inflammation from asthma, and these patients can benefit from systemic glucocorticoids. However, randomized controlled trials have demonstrated no benefit of oral glucocorticoids in young children presenting with virus-associated wheezing [52,61]. (See "Treatment of virus-induced wheezing in young children".)

We recommend that glucocorticoids not be used routinely in healthy infants and young children with a first episode of bronchiolitis [3,11]. However, glucocorticoids may be beneficial for patients with chronic lung disease (bronchopulmonary dysplasia) and those with previous episodes of wheezing (ie, who may be at risk for asthma). (See "Acute asthma exacerbations in children: Outpatient management" and "Acute asthma exacerbations in children: Inpatient management".)

Systemic glucocorticoids — Similar to studies of bronchodilators, those investigating the use of glucocorticoids in bronchiolitis are hampered by the inclusion of children with virus-induced wheezing or asthma, which makes interpretation of the results difficult. (See 'Inhaled bronchodilators' above.)

A meta-analysis evaluating the use of systemic glucocorticoids (oral, intramuscular, or intravenous) for acute bronchiolitis in children (0 to 30 months of age) included 13 trials with 1200 patients [62]. Ten of the trials evaluated the use of glucocorticoids during the first 48 hours of hospitalization, and three trials evaluated the administration of glucocorticoids in the emergency department. In pooled analysis, no significant differences were found in length of stay, the clinical score on day three, hospital admission rates, or hospital readmission rates.

Small studies evaluating the administration of glucocorticoids in the emergency department have had mixed results [6,63,64]. A meta-analysis found no significant effect on hospital admission rate [62]. This finding was confirmed in two subsequent large randomized trials of previously healthy infants who presented to the emergency department with a first episode of wheezing and were diagnosed with bronchiolitis [52,65]. These findings support the recommendation against the use of glucocorticoids in healthy infants and young children with a first episode of bronchiolitis.

Data regarding the efficacy of glucocorticoids in children with bronchiolitis who require intensive care or mechanical ventilation are limited. A meta-analysis of three studies evaluating the use of systemic glucocorticoids in infants with bronchiolitis requiring admission to the ICU found no overall effect on duration of mechanical ventilation or length of hospitalization [66].

We recommend that glucocorticoids not be used routinely in previously healthy patients hospitalized with a first episode of mild to moderate bronchiolitis. This is similar to the recommendation in the AAP clinical practice guideline, which recommends that glucocorticoids not be used routinely in the management of bronchiolitis [11].

Data from randomized controlled trials call into question the benefit of oral glucocorticoids in young children presenting with virus-associated wheezing [52,61]. However, a short course of glucocorticoids may be beneficial for hospitalized infants with chronic lung disease and those with recurrent episodes of wheezing who might have an asthma component to their illness:

- Prednisone or prednisolone (1 to 2 mg/kg per day in one dose or divided into two doses per day for three to seven days). An alternative is dexamethasone (0.4 mg/kg per day in one dose for three to five days).

Additional data are required before systemic glucocorticoid therapy can be recommended in patients with less severe disease not requiring hospitalization [62,67].

Inhaled glucocorticoids — Inhaled glucocorticoids have not been shown to be beneficial in the treatment of bronchiolitis [50,68]. A randomized trial of nebulized budesonide versus placebo in 161 infants hospitalized with respiratory syncytial virus (RSV) bronchiolitis found no significant differences in symptom duration, readmission rates, or other endpoints between the two treatment groups [68]. The administration of inhaled glucocorticoids during the acute phase of illness does not prevent subsequent wheezing episodes [69].

Bronchodilators plus glucocorticoids — Several trials have evaluated the possibility of synergistic effects of combination therapy with bronchodilators (albuterol or epinephrine) and glucocorticoids [52,70,71]. Small trials in hospitalized patients suggested possible clinical benefit [70,71]. Similar to studies of monotherapy with bronchodilators or glucocorticoids, these studies are hampered by the inclusion of infants with multiple wheezing phenotypes (eg, virus-induced wheezing, asthma).

A large, multicenter trial evaluated the effectiveness of combination therapy in preventing hospitalization in 800 infants presenting to the emergency department with bronchiolitis (first episode of wheezing associated with signs of upper respiratory tract infection during RSV season) [52]. The infants were randomly assigned to one of four treatment groups: nebulized epinephrine and oral placebo; oral dexamethasone (1.0 mg/kg in the emergency department and 0.6 mg/kg per day for five days) and inhaled placebo; nebulized epinephrine and oral dexamethasone; and nebulized and oral placebo.

Outcomes in the dexamethasone and epinephrine monotherapy groups did not differ significantly from those in the placebo group. Treatment with dexamethasone and epinephrine was associated with a decreased rate of hospitalization one week after enrollment (17 versus 24 to 26 percent in the other groups), but the result was not significant when adjusted for multiple comparisons (relative risk, 0.65, adjusted 95% CI 0.41-1.03) [52]. The rate of hospitalization was not affected by RSV status, personal or family history of atopy, time of presentation, or illness severity.

These findings are consistent with the findings of a randomized trial in preschool children with acute virus-induced wheezing, in which oral prednisolone or placebo was administered in addition to nebulized albuterol [61]. Administration of prednisolone was not associated with decreased duration of hospitalization, decreased albuterol use, or improvement in clinical score. (See "Treatment of virus-induced wheezing in young children".)

The current data do not support combination therapy for most children with bronchiolitis. Additional studies specifically designed to compare bronchodilator-glucocorticoid combination therapy with placebo and additional information about long-term adverse effects of combination therapy is necessary before combination therapy can be considered for infants with a first episode of virus-induced wheezing [38,52].

Ribavirin — Ribavirin is not recommended routinely for treatment of infants and children with bronchiolitis. However, in immunocompromised patients and those with severe bronchiolitis due to RSV, antiviral therapy may still play a role. Although ribavirin is a nucleoside analogue with good in vitro activity against RSV, studies examining its effect in patients with bronchiolitis have been conflicting, and the cost for a course of therapy is substantial. As a result, ribavirin treatment remains controversial, and its use is generally reserved for infants with confirmed RSV who are at risk for more severe disease. Consideration of the use of ribavirin should be done early in the illness and on a case-by-case basis. (See "Respiratory syncytial virus infection: Treatment", section on 'Ribavirin'.)

Antibiotics — In children with bronchiolitis, antibacterial medications are warranted only when there is evidence of a coexisting bacterial infection (eg, positive urine culture, acute otitis media, consolidation on chest radiograph) [11,72-74]. Bronchiolitis does not increase the risk for serious bacterial infection. (See "Clinical features and diagnosis of urinary tract infections in children" and "Acute otitis media in children: Diagnosis" and "Clinical features and diagnosis of community-acquired pneumonia in children", section on 'Radiologic evaluation'.)

Such bacterial infections should be treated in the same manner as they would be treated in the absence of bronchiolitis. (See "Acute management, imaging, and prognosis of urinary tract infections in children" and "Acute otitis media in children: Treatment" and "Outpatient treatment of community-acquired pneumonia in children", section on 'Empiric therapy' and "Inpatient treatment of pneumonia in children", section on 'Empiric therapy'.)

Acute otitis media (AOM) in infants with bronchiolitis may be caused by RSV [75]. However, there are no clinical features that differentiate viral from bacterial AOM. In addition, in prospective studies of children with AOM and bronchiolitis, bacterial pathogens were isolated from as many as 94 percent of middle ear aspirates [75,76]. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Otitis media'.)

Nonstandard therapies

Heliox — Heliox is a mixture of helium (70 to 80 percent) and oxygen (20 to 30 percent). It can flow through airways with less turbulence and resistance than supplemental oxygen (nitrogen/oxygen), thus improving ventilation and decreasing the work of breathing [2]. (See "Physiology and clinical use of heliox".)

The use of heliox in the treatment of moderate or severe bronchiolitis has been evaluated in several small randomized trials with mixed results [77-81]. One study found no difference in the proportion of infants requiring mechanical ventilation, but the number of patients enrolled might have been too small to detect such a difference [77]. Other studies noted clinical improvement in some parameters [78-80] and decreased duration of ICU stay (3.5 versus 5.4 days) [79].

Administration of heliox is cumbersome and results in a relatively small benefit in a limited group of infants. We suggest that it not be used routinely in the treatment of bronchiolitis. (See "Physiology and clinical use of heliox", section on 'Technical issues'.)

Anti-RSV preparations — The use of intravenous immunoglobulin with a high neutralizing activity against RSV (RSV-IGIV, which has been discontinued) or RSV-specific humanized monoclonal antibody (palivizumab) has

failed to improve outcomes in infants with or without risk factors, hospitalized with RSV infection [82,83]. (See "Respiratory syncytial virus infection: Prevention", section on 'Palivizumab'.)

Surfactant — Clinical and laboratory evidence suggests that severe bronchiolitis may result in secondary surfactant deficiency [84-87]. Several small randomized trials have evaluated the effects of surfactant therapy in mechanically ventilated infants with bronchiolitis [88-90]. A meta-analysis of these trials concluded that surfactant therapy may shorten the duration of mechanical ventilation and duration of ICU stay in children with bronchiolitis [84]. However, additional data are needed before reliable estimates of the magnitude of the effects can be made.

Hypertonic saline — Hypertonic saline theoretically has the potential to reduce airway edema and mucus plugging, the predominant pathologic features of acute bronchiolitis [91]. Several trials have indicated a potential benefit of nebulized bronchodilator therapy administered with hypertonic (3 percent or 5 percent) saline compared with normal (0.9 percent) saline in hospitalized children with acute bronchiolitis [92-96]. Studies in the ambulatory and emergency departments have had conflicting results [97,98].

In a meta-analysis of three trials (189 patients), treatment of children hospitalized with acute bronchiolitis with nebulized 3 percent saline was associated with decreased mean length of stay (mean difference -0.94 days (95% CI -1.48-(-0.4) days)) [91-93,99]. No adverse events related to nebulized 3 percent saline were reported.

The protocol of the largest of the included trials (96 patients) did not require administration of bronchodilators with 3 percent saline, but bronchodilators could be added at the discretion of the treating clinician (albuterol or racemic epinephrine was added to 60 percent of treatments) [99]. In this trial, the benefit of 3 percent saline appeared primarily in a minority of children who stayed in the hospital for more than four days, raising the question of an inadequate sample size to control for potential differences between groups.

A multicenter study with a significantly larger sample size is required to determine the effectiveness and safety of hypertonic saline for the treatment of moderately ill infants hospitalized with bronchiolitis [100]. Additional studies also are needed to determine whether hypertonic saline has beneficial effects when administered with or without bronchodilator therapies and to determine the optimal delivery interval, concentration, and delivery device (eg, ultrasonic versus jet nebulizer) [91,92,97].

Montelukast — Cysteinyl leukotrienes are released during RSV infection and appear to play a role in airway inflammation in bronchiolitis [101-104]. The potential role of montelukast, a specific cysteinyl leukotriene receptor antagonist, in the treatment of acute bronchiolitis has been evaluated in two randomized trials with conflicting results [105,106].

Montelukast also has been evaluated as a potential means of ameliorating airway reactivity following bronchiolitis [107-110]. In a randomized controlled trial, 130 infants and young children (3 to 36 months, median age nine months) hospitalized with bronchiolitis were treated with montelukast for 28 days [107]. Montelukast therapy was associated with an increase in symptom-free days (22 versus 4 percent), a decrease in daytime cough, and a delay in exacerbations. However, there was no difference between groups at the eight-week follow-up (four weeks after discontinuation of montelukast). A subsequent large randomized placebo-controlled trial (N = 979) comparing two doses (4 mg and 8 mg daily) of montelukast over a 20-week period failed to show a benefit in respiratory symptoms of post-RSV bronchiolitis in children 3 to 24 months of age [109]. In a smaller trial (58 patients), treatment of children (≤ 24 months of age) with montelukast for three months following hospitalization for RSV bronchiolitis was not associated with a reduction in symptom-free days, disease-free days, exacerbations, unscheduled visits, or initiation of inhaled glucocorticoids [108].

Although additional studies may be necessary to determine what role, if any, leukotriene receptor antagonists play in the management of acute bronchiolitis or the prevention of symptoms following bronchiolitis [111,112], most studies to date do not support their use [105,108,109].

CLINICAL COURSE — In previously healthy infants who are older than six months and require hospitalization for management of bronchiolitis, the average length of hospitalization is three days [113]. The respiratory status typically improves over two to five days [17,114-118]. However, wheezing persists in some infants for a week or

longer. The course may be prolonged in younger infants and those with comorbid conditions (eg, chronic lung disease) [12,119].

In children who do not improve at the expected rate, chest radiographs may be helpful in excluding other conditions in the differential diagnosis (eg, foreign body aspiration, heart failure, vascular ring) [11]. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Differential diagnosis'.)

DISCHARGE CRITERIA — As with admission criteria, there are no established criteria for discharge, whether from the hospital or from an outpatient setting. One clinical practice guideline suggests the following [23]:

- Respiratory rate <70 breaths/min
- Caretaker can clear the infant's airway using bulb suctioning
- Patient is stable without supplemental oxygen
- Patient has adequate oral intake to prevent dehydration
- The resources at home are adequate to support the use of any necessary home therapies (eg, inhalation therapy if the trial was successful and this therapy is to be continued)
- Caretakers are confident they can provide care at home
- Education of the family is complete (as discussed below)

Education — Before discharge from the hospital or outpatient setting, the family should be educated regarding the expected clinical course, administration of necessary therapies (eg, nasal suctioning, inhalation therapy), indications for return to medical care, and means of preventing respiratory infections in children [11,23]. The prevention of respiratory infections is discussed below. (See 'Prevention' below.)

- Expected clinical course — The median duration of bronchiolitis for children younger than 24 months is 12 days. Approximately 20 percent of children remain ill after three weeks, and 10 percent still have symptoms after four weeks [120]. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Course'.)
- Proper techniques for suctioning the nose (table 1).
- Indications to contact primary care provider — apnea, cyanosis, poor feeding, fever, increased respiratory rate and/or work of breathing (retractions, nasal flaring, grunting).

OUTCOME — Bronchiolitis is a self-limited illness and resolves without complications in most previously healthy infants. However, severely affected infants, especially those born prematurely and those with underlying cardiopulmonary disease or immunodeficiency, are at increased risk for complications. (See "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Complications'.)

Mortality — The mortality rate for infants and children with bronchiolitis has remained stable since the 1970s, while the overall mortality from respiratory conditions has decreased [121,122]. The mortality from RSV among children with congenital heart disease also has decreased since the 1970s (from 37 to 3 percent between 1976-1980 and 1983-1990) [123].

The overall mortality rate in children hospitalized with RSV bronchiolitis is less than 2 percent [17,124]. Mortality is increased in young infants (6 to 12 weeks), those with low birth weight, and those with underlying medical conditions (eg, underlying cardiopulmonary disease, immune deficiency) [17,121,122], as illustrated below.

A study using data from death certificates in the United States from 1979 to 1997 provided the following information about bronchiolitis mortality in hospitalized children <5 years of age [121]:

- The mean annual mortality rate was estimated to be 2.8 per 100,000 live births.
- 79 percent of the deaths occurred in infants younger than one year.
- Death was 1.5 times more likely in boys than girls.
- Underlying medical conditions were listed in the death records of approximately 20 percent of deaths: 10 percent with congenital heart disease, 6 percent with lung disease, and 4 percent with premature birth; these conditions may have been underreported.

In another report, 55 percent of infant deaths due to bronchiolitis occurred between ages one and three months [122]. The mortality rate progressively decreased with increasing birth weight as follows:

- Birth weight <1500 g — 29.8 per 100,000 live births
- Birth weight 1500 to 2499 g — 6.4 per 100,000 live births
- Birth weight ≥2500 g — 1.3 per 100,000 live births

Despite the increased risk of mortality with very low birth weight, the majority of patients who died in this series weighed ≥2500 g at birth.

Possible association with asthma — Infants hospitalized for LRTI, especially RSV, are at increased risk for recurrent wheezing and reduced pulmonary function, particularly during the first decade of life [125-128]. In one report, LRTI with RSV increased the risk for subsequent frequent and infrequent wheezing (odds ratio 4.3 and 3.2, respectively) and was associated with reduced forced expiratory volume in children up to 11 years of age [129]. However, this association was lost by age 13 years, perhaps due to inadequate sample size.

Whether bronchiolitis in early childhood, especially that caused by RSV, is associated with the development of asthma is uncertain. In some studies, a correlation exists between infection with RSV and the later development of reversible airways disease. However, this may reflect the multifactorial nature of risk for asthma, including a genetic predisposition to airway reactivity, exposure to environmental pollutants such as smoke, immunologic mechanisms, and disruption of the growth and development of the lungs due to viral infection in early childhood [129-136]. (See "Respiratory syncytial virus infection: Clinical features and diagnosis", section on 'Airway reactivity'.)

PREVENTION — Standard strategies to reduce the risk of bronchiolitis and accompanying morbidity include careful hand washing (with soap or with alcohol-based rubs) to minimize transmission of infectious agents, minimizing passive exposure to cigarette smoke, and avoiding contact with individuals with respiratory tract infections [11].

Immunoprophylaxis with palivizumab, a humanized monoclonal antibody against the RSV F glycoprotein, decreases the risk of hospitalization due to RSV illness among infants with chronic lung disease, premature birth, and congenital heart disease. The indications and administration of palivizumab are discussed separately. (See "Respiratory syncytial virus infection: Prevention", section on 'Palivizumab'.)

Children younger than five years are at increased risk for influenza-related hospitalization or healthcare utilization. The Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommend influenza vaccine for everyone older than 6 months of age. Children aged 6 through 59 months and household contacts of children aged 0 through 59 months should be a priority. Vaccines to prevent RSV, rhinovirus, human metapneumovirus, or parainfluenza viruses, the most common causes of bronchiolitis, are unavailable. (See "Seasonal influenza vaccination in children", section on 'Indications'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Bronchiolitis (and RSV) (The Basics)")
- Beyond the Basics topics (see "Patient information: Bronchiolitis (and RSV) in infants and children")

SUMMARY AND RECOMMENDATIONS

- Bronchiolitis usually is a self-limited, mild disease. Therapy in most cases consists of supportive measures to ensure that the child is clinically stable, well hydrated, and well oxygenated. (See 'Overview' above and 'Supportive care' above.)
- Children with moderate to severe disease usually require hospitalization. Moderate to severe disease is indicated by persistently increased respiratory effort, apnea, and/or the need for intravenous hydration, supplemental oxygen, or mechanical ventilation. (See 'Indications for hospitalization' above and 'Severity assessment' above.)
- We suggest a trial of inhaled bronchodilators for children with bronchiolitis (Grade 2B). The bronchodilator response should be objectively assessed before and up to one hour after treatment. If there is a clinical response, aerosolized bronchodilator therapy can be administered every four to six hours and discontinued when the signs and symptoms of respiratory distress improve. (See 'Inhaled bronchodilators' above.)
- We recommend not using oral bronchodilators in the management of bronchiolitis (Grade 1A). (See 'Oral bronchodilators' above.)
- We recommend not using glucocorticoids routinely in the treatment of previously healthy infants hospitalized with a first episode of bronchiolitis (Grade 1A). However, glucocorticoids may be beneficial in infants with chronic lung disease (bronchopulmonary dysplasia) and those with recurrent episodes of wheezing suggestive of asthma. (See 'Glucocorticoids' above.)
- We recommend not using ribavirin routinely in the treatment of previously healthy children with bronchiolitis (Grade 1B). (See 'Ribavirin' above and "Respiratory syncytial virus infection: Treatment", section on 'Ribavirin'.)
- Antibacterial medications are warranted only when there are specific indications of a coexisting bacterial infection. (See 'Antibiotics' above.)
- The respiratory status of children with bronchiolitis typically improves over two to five days. However, wheezing persists in some infants for a week or longer. The course may be prolonged in younger infants and those with comorbid conditions. In children who do not improve at the expected rate, chest radiographs may be helpful in excluding other conditions in the differential diagnosis. (See 'Clinical course' above and "Bronchiolitis in infants and children: Clinical features and diagnosis", section on 'Differential diagnosis'.)
- Minimal clinical criteria for discharge from the hospital, emergency department, or office include respiratory rate of <70 breaths/min, patient is stable without supplemental oxygen, and oral intake sufficient to prevent dehydration. (See 'Discharge criteria' above.)
- Before discharge from the hospital or outpatient setting, the family should be educated regarding the expected clinical course, the administration of necessary therapies, the indications for return to medical care, and the methods of preventing respiratory infections in children. (See 'Education' above and 'Prevention' above.)

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Respiratory syncytial virus infection: Prevention

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INTRODUCTION — Respiratory syncytial virus (RSV) causes acute respiratory tract illness in persons of all ages. Almost all children are infected by two years of age, and reinfection is common [1]. The clinical manifestations vary with age, health status, and whether the infection is primary or secondary.

The prevention of respiratory syncytial virus infection will be discussed here. The epidemiology, microbiology, clinical manifestations, diagnosis, and treatment of RSV infection are discussed separately. (See "Respiratory syncytial virus infection: Clinical features and diagnosis" and "Respiratory syncytial virus infection: Treatment".)

GENERAL MEASURES — Prevention of RSV infection entails decreasing exposure to RSV and decreasing the risk of acquisition if exposure occurs. Strategies to decrease exposure and/or the risk of acquisition include [2]:

- Avoidance of exposure to tobacco smoke
- Restricting participation in child care during RSV season for high-risk infants (if possible)
- Hand washing in all settings, particularly when high-risk infants are at risk for exposure to respiratory infections from older siblings

NOSOCOMIAL INFECTION — RSV is highly contagious and can cause serious nosocomial infections [3]. The intensity of the precautions should be determined by the setting; prevention of nosocomial infection is most important for infants with congenital heart or lung disease, bone marrow and lung transplant recipients, and the frail elderly with multiple underlying conditions.

Rapid diagnosis, hand washing, and appropriate use of gloves are probably the most important infection control measures, but contact precautions, including surgical mask and eye protection for health care providers, should be used when there is a chance of exposure to aerosols of infectious respiratory secretions [4-12]. (See "General principles of infection control".)

Isolation of patients in private rooms or in rooms with other RSV-infected patients (cohorting patients), and limited transport of patients from their rooms also is recommended [6,11,13]. During outbreaks, personnel caring for RSV-infected patients should be restricted from caring for uninfected patients as often as possible [6,11,13].

Health care personnel should have continuing education on the symptoms, epidemiology, diagnosis, and transmission of RSV. Health care personnel and visitors with upper respiratory tract infections should be restricted from contact with high-risk patients as much as is practical, especially during the peak RSV transmission months [11,13,14].

IMMUNOPROPHYLAXIS — Data from epidemiologic studies suggested that infants with high titers of maternally acquired RSV-neutralizing antibody develop less severe RSV disease, even though antibody does not prevent infection [15]. This finding, and pilot studies indicating that monthly injections of intravenous immunoglobulin were safe and effective in decreasing the severity of subsequent RSV infections [16,17], led to the development of immunoprophylactic agents for RSV infection.

Immunoprophylactic agents

Palivizumab — Palivizumab (Synagis®), is a humanized monoclonal antibody against the RSV F glycoprotein (which is highly conserved among various isolates). It is licensed for use in selected infants and children younger than 24 months with BPD, preterm birth (≤ 35 weeks), or hemodynamically significant congenital heart disease [1,2]. Even before the discontinuation of RSVIG, palivizumab was preferred because of its ease of administration and lack of interference with immune response to MMR and varicella vaccines.

Motavizumab — Another more potent RSV-neutralizing antibody (MEDI-524, motavizumab, [Numax™]) was derived from palivizumab [18,19]. It appears to be more effective than palivizumab in animals [18]. A multinational phase 3 randomized trial compared motavizumab and palivizumab in 6635 preterm infants [20]. Both groups had low rates of hospitalization for RSV (1.4 and 1.9 percent, respectively) and medically attended lower respiratory tract infection (2.0 versus 3.9 percent). The overall rate of adverse effects was similar between groups, but cutaneous adverse effects were more frequent among motavizumab recipients (7 versus 5 percent). Motavizumab is not yet licensed by the United States Food and Drug Administration.

RSVIG — Respiratory syncytial virus immune globulin (RespiGam®, RSVIG), which is no longer available, was a polyclonal hyperimmune globulin prepared from donors with high serum titers of RSV neutralizing antibody. In controlled trials, RSVIG reduced RSV-associated hospitalizations among high-risk infants by 41 to 63 percent [21,22]. However, its use was associated with increased morbidity and mortality in infants with congenital heart disease, and it was never labeled for use in these infants [22,23]. In addition, as a blood product, RSVIG had the potential to interfere with the immune response to certain live virus vaccines (eg, measles/mumps/rubella and varicella) and to be contaminated adventitious agents.

Target groups for palivizumab — The American Academy of Pediatrics (AAP) recommends that immunoprophylaxis with palivizumab be considered for certain groups of children who are at risk for severe RSV infection. These include infants and young children with BPD, prematurity, and hemodynamically significant congenital heart disease [1].

In addition to these conditions, factors that may influence the decision to administer immunoprophylaxis include the presence of other conditions that predispose to respiratory illness (eg, neurologic disease), distance to and

availability of hospital care for severe respiratory illness, logistical difficulties of monthly administration, and cost [1,24,25].

Bronchopulmonary dysplasia — We suggest that palivizumab be administered to infants and children younger than two years of age with BPD who have required medical therapy for their pulmonary disease within six months of the anticipated RSV season [1].

Congenital heart disease — We suggest that palivizumab be administered to infants and children younger than two years of age who have hemodynamically significant cyanotic and acyanotic congenital heart disease [1,26]. Decisions should be made on the basis of degree of cardiovascular compromise (table 1). Infants in this category who require cardiac bypass during RSV season should receive a postoperative dose of palivizumab as soon as they are medically stable because the mean serum palivizumab concentration has been observed to decrease by more than 50 percent after cardiac bypass [1,27,28].

Prematurity — We suggest that palivizumab be administered to infants younger than 12 months of age who were born at ≤ 28 weeks, 6 days of gestation and to infants younger than six months of age who were born between 29 weeks, 0 days and 31 weeks, 6 days of gestation, particularly if they have risk factors for RSV, such as day care attendance or school-age siblings [1].

The risks, benefits, and cost of palivizumab for infants between 32 and 35 weeks must be carefully considered [1]. In 2009, the AAP Committee on Infectious Diseases (COID) revised its recommendations for palivizumab prophylaxis in this gestational age group to focus on infants at the greatest risk of hospitalization [1]. The COID suggests that prophylaxis may be warranted for infants born at 32 weeks, 0 days' through 34 weeks, 6 days' gestation who are younger than three months of age at the start of RSV season or who are born during RSV season AND have at least one of the following two risk factors: infant attends child care or infant has a sibling < 5 years of age. Prophylaxis is only administered until the infant reaches 90 days of age. (See 'Dose and schedule' below.) The revised recommendations were designed to balance benefit and cost but are somewhat controversial [29,30]. The original recommendations were based upon clinical trial data and the revised recommendations upon clinical judgment, in an effort to balance benefit and cost [1,29]. Some editorialists suggest that the decision to deliver doses beyond 90 days of age be made on a case-by-case basis [30].

Immunocompromised — The use of RSV immunoprophylaxis has not been evaluated in immunocompromised children in controlled trials. Nonetheless, children with severe immunodeficiencies (eg, severe combined immunodeficiency or severe acquired immunodeficiency, children younger than two years who have undergone lung transplantation or hematopoietic stem cell transplantation) may benefit from immunoprophylaxis [1].

Dose and schedule — The dose of palivizumab is 15 mg/kg intramuscularly (IM) once per month for a maximum of five doses. The first dose is administered before the RSV season begins (usually in November, but may vary by geographic region) [1]. (See "Respiratory syncytial virus infection: Clinical features and diagnosis", section on 'Seasonality'.)

Once an infant born at < 32 weeks' gestation (≤ 31 weeks 6 days) qualifies for initiation of prophylaxis at the beginning of the RSV season, all five doses should be administered, even if the infant becomes old enough that prophylaxis is no longer indicated [1,2]. As an example, an infant born at 29 weeks who is without BPD or congenital heart disease and turns six months old in January should still receive immunoprophylaxis in February and March. Fewer than five doses may be administered to an infant who qualifies for palivizumab and is born during the RSV season [1]. As a general rule, an infant born in February would receive only two doses (February and March), but may receive more if the local RSV season extends into April or May. The hospital laboratory or health department may have data to help determine when the local RSV season has ended.

Infants born at ≥ 32 weeks' through 34 weeks, 6 days' gestation who qualify for palivizumab should not receive palivizumab after 90 days of age [1]. The maximum number of doses varies depending upon the month of birth (three doses for infants born in October through January, two doses for those born in September or February, one dose for those born August or March, and zero doses for those born in April through July). The American Academy of Pediatrics Committee on Infectious Diseases (COID) decreased the maximum number of recommended doses from five to three in this gestational age group in 2009, in an effort to balance benefit and cost [1,29]. However, the recommendation is controversial [29,30]. The original recommendations were based

upon clinical trial data and the revised recommendations upon clinical judgment [1,29]. Some editorialists suggest that the decision to deliver doses beyond 90 days of age be made on a case-by-case basis [30].

Data from the Palivizumab Outcomes Registry, including nearly 20,000 infants who received palivizumab between 2000 and 2004, indicate that approximately 80 percent of palivizumab recipients received all five doses and between 65 and 70 percent of palivizumab recipients received the second through fifth doses within 35 days of the previous dose [31].

No association was detected between receiving all five doses and RSV hospitalization. However, infants who received the second through fifth doses of palivizumab within 35 days of the previous dose had a lower risk of hospitalization than those who did not (odds ratio 0.7, 95% CI 0.54 to 0.91) [31].

Immunoprophylaxis also should continue even if the infant experiences breakthrough infection [1]. This is because high-risk infants may be hospitalized more than once during an RSV season, and more than one strain of RSV may cocirculate in a community.

Home administration — Administration of palivizumab in the home setting may increase adherence to the schedule [31-34]. Administration in the home setting was associated with a decreased rate of RSV-associated hospitalization in the 2000-2004 Palivizumab Outcomes Registry (0.4 versus 1.2 percent when administered in the outpatient setting) [34].

Efficacy and effectiveness — The efficacy of palivizumab for preventing severe RSV infection in infants and children with prematurity, BPD, and congenital heart disease has been demonstrated in randomized controlled trials:

- In the IMpact-RSV Trial, 1502 patients with BPD and/or prematurity (<35 weeks) were randomly assigned to monthly treatment with palivizumab or placebo [35]. Palivizumab was associated with significantly fewer RSV-associated hospitalizations (4.8 versus 10.6 percent with placebo, a 55 percent reduction).
- In another trial, 1287 children with hemodynamically significant congenital heart disease were randomly assigned to monthly treatment with palivizumab or placebo [27]. Palivizumab was associated with fewer RSV-associated hospitalizations (5.3 versus 9.3 percent, a 45 percent reduction), fewer hospital days requiring oxygen (178 versus 658, a 73 percent reduction) and fewer total hospital days (367 versus 876, a 56 percent reduction). The mortality rates were similar in both groups (3.3 versus 4.3 percent). No deaths or adverse events were attributed to palivizumab.

Postlicensure surveillance indicates the RSV-associated hospitalization rates among high-risk infants who receive palivizumab are similar to or lower than the RSV-associated hospitalization rates described above [31,36-40]. Data from the Palivizumab Outcomes Registry indicate an RSV hospitalization rate of 1.3 percent among infants who received palivizumab during 2000 to 2004 [31].

Whether prevention of RSV LRTI with palivizumab affects the incidence of subsequent episodes of recurrent wheezing was evaluated in a cohort of 421 premature infants without chronic lung disease [41]. Of these, 191 received palivizumab prophylaxis and were not hospitalized for RSV, and 230 did not receive palivizumab (76 were hospitalized for RSV, and 154 were not). The incidence of clinician-diagnosed recurrent wheezing between 19 and 43 months of age was decreased in the palivizumab group (8 versus 16 percent). This preliminary finding suggests that prevention of RSV LRTI may reduce the risk of recurrent wheezing in premature infants without chronic lung disease [42].

Adverse events — Rare cases of severe hypersensitivity reactions (<1 per 100,000 recipients) have been described after an initial dose, as well as after reexposure [36]. In two studies evaluating the safety of palivizumab during two consecutive seasons, no serious adverse events were noted [43,44]. Only 1 of 118 children had a significant increase in antipalivizumab antibody titer, and the antibody response declined with continued dosing [43,44]. The development of RSV resistant to palivizumab is another potential adverse effect [45,46], although in a study of 458 palivizumab-treated infants, no escape mutants were detected [47].

Palivizumab does not interfere with routine childhood immunizations.

VACCINE DEVELOPMENT — There are multiple challenges to the development of a successful RSV vaccine. Immature immunity and possible suppression of an immune response by maternal antibody are issues in the target population of young infants. The vaccine must be protective against antigenically divergent strains. In addition, it must not potentiate disease in recipients who subsequently become infected with wild-type virus, as occurred in trials with a formalin-inactivated vaccine developed in the 1960s [48-52].

Live attenuated RSV vaccines are being developed and tested. Although several biologically attenuated candidate vaccines have induced an antibody response in young infants, they have been insufficiently attenuated for use in this age group [53]. Recombination technology has been used to produce an attenuated strain that was well tolerated by one- to two-month-old infants in one report [54]. However, only 44 percent of subjects had a detectable antibody response.

Subunit vaccines have been developed from RSV F and G glycoproteins. Trials conducted in adults, the elderly, pregnant women and children ≥ 12 months of age have been successful in demonstrating some rise in antibody titers but have not had a significant effect on clinical disease [55]. The utility of this approach in young infants is limited because of safety concerns.

A variety of gene-based vaccine vectors and novel adjuvants for candidate RSV vaccine are in preclinical development.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Bronchiolitis (and RSV) in infants and children")

SUMMARY AND RECOMMENDATIONS

- Prevention of respiratory syncytial virus (RSV) infection entails decreasing exposure to RSV and decreasing the risk of acquisition if exposure occurs. (See 'General measures' above.)
- Prevention of nosocomial infections should include rapid diagnosis, handwashing, and appropriate contact precautions (including masks and eye protection) for health care workers. (See 'Nosocomial infection' above.)
- We suggest immunoprophylaxis with palivizumab for (Grade 2A):
- Infants and children younger than two years who have bronchopulmonary dysplasia that required medical therapy within six months of the anticipated RSV season and/or hemodynamically significant congenital heart disease (table 1) (See 'Bronchopulmonary dysplasia' above and 'Congenital heart disease' above.)
- Infants younger than one year who were born at ≤ 28 weeks of gestation (See 'Prematurity' above.)
- Infants younger than six months who were born between 29 and 32 weeks of gestation (See 'Prematurity' above.)
- Palivizumab also may be indicated for infants younger than three months of age who were born between 32 and 35 weeks of gestation and immunocompromised children. (See 'Prematurity' above.)

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