Les troubles de la thermorégulation chez l'enfant : fièvre et hypothermie. Illustrations de quelques cas exemplaires

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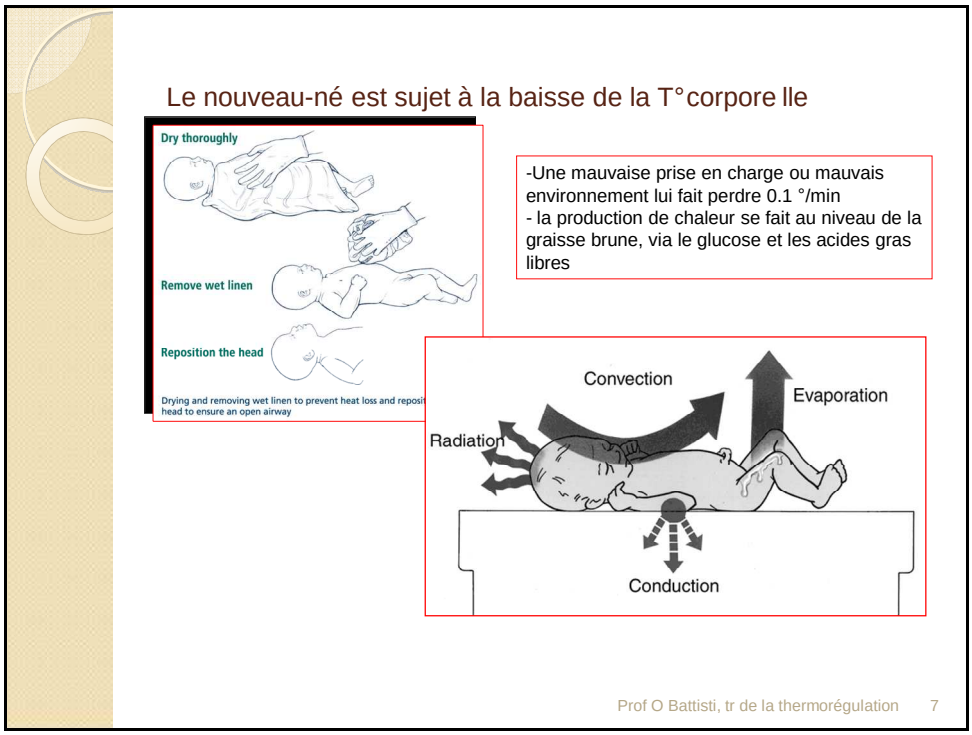
Sommaire



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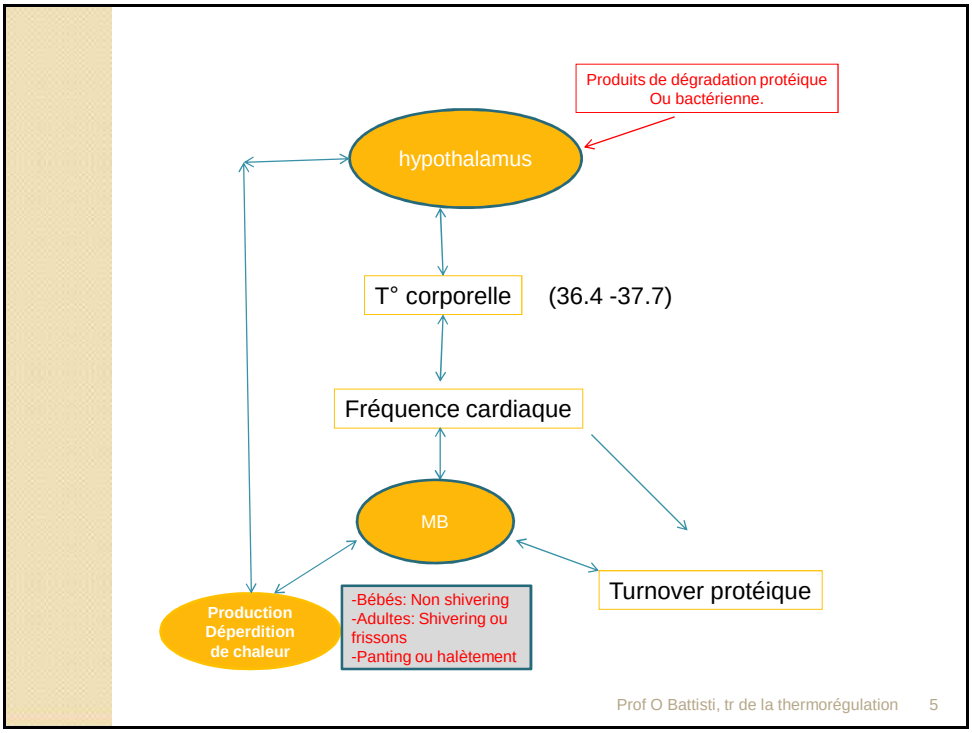
La thermorégulation

Physiopathologie de la fièvre



Le contrôle de la température corporelle est assuré par l'hypothalamus. L'hypothalamus antérieur contient des neurones thermosensibles, sensibles à la température sanguine ou en connexion avec les thermorégulateurs périphériques. L'induction de la fièvre se fait par deux voies principales : la voie prostaglandine indépendante est médiée par la MIP1 (macrophage inflammatory protein 1, protéine inflammatoire des macrophages 1) qui est sécrétée en réponse aux endotoxines, traverse la barrière hémato-encéphalique, agissant ainsi directement sur les centres de thermorégulation. Elle n'est pas inhibée par les inhibiteurs de la cyclooxygénase 1 ou 2.La voie prostaglandine dépendante est représentée principalement par la prostaglandine E2 (PGE2) via la cyclooxygénase 2 des cellules de l'hypothalamus. L'étape importante de formation de la fièvre est liée à l'augmentation de synthèse de métabolites de l'acide arachidonique et principalement PGE2. L'induction par PGE2 induit en quelques minutes une fièvre et la libération de pyrogènes tels que TU, IL6, TNFa et l'IFN y. Ce dernier stimule la production de PGE2.Une altération des rétrocontrôles de NU l'IL6, du TNFa et de l'interféron y peut donc se traduire par des fièvres récurrentes d'un point de vue clinique.

L'hypothalamus sécrète de manière physiologique des facteurs neuro-endocrines de régulation, l'hormone stimulant la mélanotropine (melanotropine stimulating hormon), l'arginine vasopressine et l'hormone libératrice de corticotropine (hormon corticotropine releasing), capables d'inhiber la synthèse des pyrogènes et donc la synthèse de la prostaglandine E2.

L'IL6 est le principal stimulateur de la production de protéines de l'inflammation. Les cytokines s'activent en cascade lors de l'activation des protéines de l'inflammation. Par exemple, le TNF a est le principal stimulateur de la production d'ILI chez des patients atteints de polyarthrite rhumatoïde ; l'IL 1 p peut augmenter ou diminuer la production de ses propres récepteurs ; l'élévation de l'IL6 chez la souris après injection de turpentine requiert l'IL1 [3, et l'IL6 inhibe la production du TNF a.

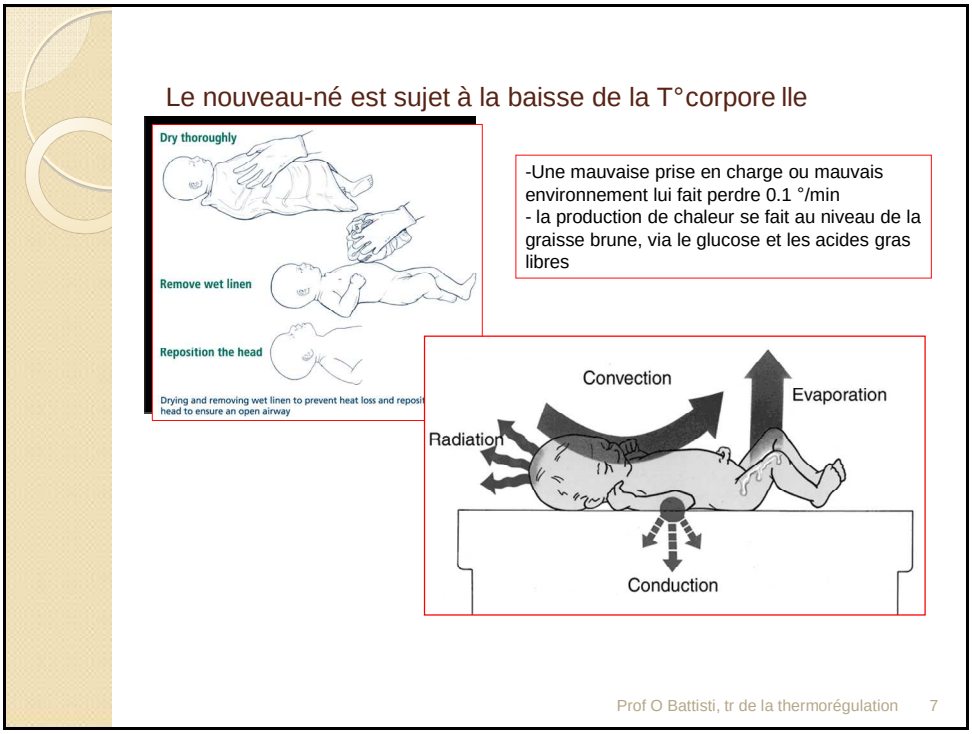
Les glucocorticoïdes augmentent généralement les effets stimulants des cytokines sur la production des protéines de la phase aiguë de l'inflammation.

L'élévation de la température permet la lyse ou l'atténuation de la virulence de certaines bactéries, comme le pneumocoque. L'élévation de la température augmente également la phagocytose, la bactéricidie des polynucléaires neutrophiles, et l'effet cytotoxique de certains lymphocytes.

La fièvre est représentative des changements neuroendocrines qui caractérisent la phase aiguë de l'inflammation. Les cytokines ne sont pas les seuls inducteurs de la fièvre : l'action du système vague est également importante. Les cytokines stimulent la production de la corticotropin releasing hormone, avec pour conséquence une stimulation de la production de cortisol ; et jouent également sur les surrénales.

La fièvre peut s'accompagner de signes d'accompagnement, tels que la somnolence, l'anorexie, la cachexie. Ces phénomènes sont médiés par les cytokines de l'inflammation, mais également par le système vague.

L'enfant hypothermique ou à risque d'hypothermie



Il faut distinguer l'hypothermie recherchée (et contrôlée) à visée neuroprotectrice (dans le cadre d'une circulation extra-corporelle, d'une encéphalopathie) de l'hypothermie non recherchée qui elle est neuro-délétère.

Ainsi, par exmple, le recours à l'hypothermie durant 24 heures pour traiter un traumatisme crânien grave chez l'enfant est inutile, car il n'améliore pas l'état du patient et pourrait même augmenter le risque de décès. ***Voilà la conclusion consternante d'une étude récemment effectuée par des chercheurs provenant de 17 hôpitaux du Canada, de la France et du Royaume-Uni.*** **«Nous avons été à la fois surpris et désolés»*, confie l'un des collaborateurs de l'étude, le pédiatre Jacques Lacroix, qui dirige l'axe Avancement et devenir en santé du Centre de recherche du CHU Sainte-Justine, à Montréal.* «Si nous avons mis cette technique à l'essai, c'est parce que nous étions convaincus qu'elle serait efficace et aurait des effets bénéfiques. »**

Des expériences probantes effectuées sur des animaux avaient convaincu les chercheurs qu'amener la température corporelle d'un patient jusqu'à un niveau d'hypothermie (32,5 °C) serait efficace si ce refroidissement était provoqué rapidement après le trauma et maintenu durant 24 heures. Ils ont alors mené une étude pendant cinq ans sur des enfants âgés d'un à 17 ans atteints de graves lésions cérébrales. Tous les patients devaient être traités dans les huit heures suivant le traumatisme. Sur les 1 441 patients atteints de lésions cérébrales qui se sont présentés à un des hôpitaux participants entre février 1999 et octo - bre 2004, 225 enfants remplissaient les critères de sélection de l'étude, et le consentement des parents à ce qu'ils y prennent part fut donné à temps. Un service téléphonique centralisé permettait aux chercheurs de placer les sujets au hasard dans le groupe expérimental ou dans le groupe témoin. Pour les enfants du groupe expérimental, la température corporelle était abaissée à 32,5ºC, alors que pour ceux du groupe témoin, elle était amenée à 37ºC, une valeur normale.

Au bout de 24 heures, on laissait la température corporelle des enfants du groupe ex périmental remonter jusqu'à la normale. Pendant cette période, plusieurs patients ont dû recevoir des soins à la suite d'une hypotension artérielle ou parce que le sang circulait moins bien dans leur corps et leur cerveau.

Chaque enfant a été suivi pendant une période de six mois ou plus après l'accident. Malheureusement, 23 sujets du groupe expéri - mental et 14 du groupe témoin sont décé dés. Dans chacun des groupes, neuf patients sont restés dans un coma végétatif ou sont demeurés aux prises avec de graves invalidités. Les enfants qui se sont remis de leurs lésions cérébrales et réussissaient à communiquer ont été soumis à un examen psychologique trois mois et douze mois après l'accident. Les chercheurs ont constaté que ceux qui avaient été mis en hypothermie possédaient nettement moins de mémoire que ceux du groupe témoin.

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Ces résultats, auxquels s'ajoutent un taux de mortalité supérieur et les effets secondaires du réchauffement du corps chez les patients du groupe expérimental, ont amené les chercheurs à contre-indiquer l'hypo thermie durant 24 heures comme mesure de traitement.des enfants admis en soins intensifs pour un traumatisme crânien grave.

« Nous savons maintenant qu'il ne faut pas abaisser la température corporelle de nos patients jusqu'à l'hypothermie», remarque Claude Mercier, neurochirurgien au CHU Sainte-Justine. *« Nous revenons aux traitements traditionnels pour nos patients atteints de traumatismes crâniens. Avant cette étude, nous ne prenions jamais en compte la température corporelle pour évaluer les résultats, mais nous essayions de la maintenir à un niveau normal. Nous n'avons plus recours à l'hypothermie. »*

PAR TRACEY ARIAL Réf. : Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. *New England Journal of Medicine* 2008;358(23):2447-2456.

La situation du nouveau-né est particulière.

L'hypothermie contrôlée chez l'enfant à terme asphyxié

Définition L'asphyxie à terme

Elle est relative (impossibilité de mesurer directement le niveau d'oxygénation du tissu cérébral), et l'on a recours à une combinaison de marqueurs indirects selon 4 critères:

- acidose sévère à la naissance : ph <7
- Apgar <3 à 5'vie
- Troubles neurologiques (hypotonie, convulsions, coma)
- Défaillance multiviscérale

L'association des tous ces critères pour définir l'asphyxie périnatale est controversée dans la littérature. Par contre, l'évaluation de la situation par un score clinique, le plus utilisé étant celui de Sarnat et Sarnat (mais il y en d'autres : celui de Ziegler et Amiel-Tison, celui de Fenichel et celui de Levene).

la classification de Sarnat et Sarnat

Item	Stade 1	Stade 2	Stade 3
Durée	< 24 h	2-4 j	Prolongée
Niveau conscience	Hyperalerte	Léthargie	Coma
Tonus	Normal	Hypotonie	Flacidité
Réflexes OT	Augmentés	Augmentés	Absent
Succion	Active	Faible	Absente
Moro	Exagéré	incomplet	Absent
Grasping	Normal à +	+++	Absent
Yeux poupées	Normal	++	- ou 0
Réf pupilles	Dilatées	Constriction	Variable
Respiration	Régulière	Périodique	Irrégulière, apnée
FC	N ou +	< 120b/m	Bradycardie
Convulsions	Non	Fréquents	Non fréquents
EEG	Normal	Voltage -, périodique ou paroxystique	Périodique ou isoélectrique
Mortalité	< 1 %	5 %	> 60 %
Handicap sévère	< 1 %	20 %	> 70 %

Retenir :

Asphyxie sévère = Apgar < 3 à 1 minutes

Asphyxie avec mauvaise récupération = Apgar < 6 à 5 minutes malrgé une bonne prise en charge.

Sur le plan clnique par après, on aura un stade de Sarnat et Sarnat de 2 ou 3

Epidémiologie :

-1,5 à 2/1000 naissances vivantes

- 15 à 20% décès

- 20 à 25% handicaps sévères chez survivants

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Physiopathologie : Encéphalopathie hypoxique-ischémique :

Lésions cérébrales post asphyxie

Précoces : min-heures

Anoxie - privation énergétique

phénomènes vaso-moteurs :

-réduction du débit sanguin cérébral avec perte de l'auto-régulation

=> hémorragie cérébrale

-puis ⍰ débit sanguin cérébral

=> lésions ischémiques

Tardives : après 12-48 h

cascades biochimiques aboutissant à la mort neuronal

-libération d'acides aminés neuro-excitateurs (glutamate,…) => dépolarisation membranaire

-production de radicaux libres

-↑ calcium intra neuronale => libération enzymes cytotoxiques

Prise en charge en salle de naissance : réanimation néonatale

-Débuter une réanimation sous air paraît possible :pas de ballon de ré-entrée

-Surveiller à tous moments une cyanose persistante: supplément d 'oxygène

-Valeurs normales SaO^2chez le NN sain : 1'= 65% , 5'= 85%, 10'= 95% → Emploi de l'oxymetre de pouls immédiatement

-Eviter l'hyperthermie

Prise en charge spécifique en cas d'encéphalopathie post-asphyxique :

- Glycémie : « sécure » si 75-100 mg/dl, éviter les hypoglycémies (<40 mg/dl) et les hyperglycémies (> 200) responsables par hyperosmolarité de lésions vasculaires cérébrales.

- Phénobarbital : *in vitro* : réduit l'action des radicaux libres, diminue la consommation d'O^2 et la libération d'acides aminés excitotoxiques. *In vivo* : peu d'arguments actuels d'utilisation systématique précoce de 20 ou 40mg/kg *iv (*→ à n'utiliser qu'en présence de convulsions et non de manière préventive).

- PaCo2 : 1mmHg => réduction de 3 % débit sanguin cérébral, pas de données de bénéfice d 'une hyperventilation sur la prévention HTAP => à éviter. Si absence d 'HTAP : viser normo ou hypercapnie modérée.

Hypothermie contrôlée

Principes généraux : éviter l'hyperthermie, qui est toujours nocive a chaque étape de l' encéphalopathie hypoxique-ischémique. ***Jamais d'hypothermie chez le prématuré*** .

Hypothermie :

effets favorables via de multiples raisons physiopathologiques :

1. libération aa excitotoxiques,
2. de la synthèse de NO ,
3. libération radicaux libres,
4. augmente interleukine 10,
5. de l'intensité et de la durée de la défaillance énergétique cellulaire,
6. réduit les mécanismes d'apoptose.

L'hypothermie sere pratiquée de manière contrôlée ; ellesera généralisée à tout le corps (et non seulement de la boîte crânienne), dont la température sera maintenue à 35 °C pendant 36 heures.

Les critères d'inclusions :

- PH <ou=7.0, BE >ou= -16 (sg cordon ou <1H)

- 7.01<PH<7.15, -10<BE<-15

- critères périnataux apgar <ou=5 à 10', ventilation assistée >10'

- Examen neurologique standardisé anormal : Encéphalopathie = 1 ou + signe(s) dans 3/6 catégories.

- EEG altéré:

modéré: tracé continu bas voltage

sévère: discontinu/burst suppression/inactif <10microV

Critères d'exclusion :

- >6H de vie, refus des parents
- Malformation congénitale
- PN<1800gr PC < -2DS
- Abstention de traitement
- Hémorragie c/nné
- Doses phénobarbital> 20 mg/kg
- HTAP (besoins O2 > 50%)

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La fièvre chez l'enfant

Objectifs

Fièvre aiguë chez l'enfant

1. Décrire les principaux types de courbe thermique que l'on peut observer chez le nouveau-né, le nourrisson et l'enfant.

2. Citer les signes d'accompagnement à rechercher par l'interrogatoire et l'examen clinique devant une hyperthermie.

3. Citer les risques majeurs de l'hyperthermie chez le nourrisson.

4. Décrire le tableau de l'hyperthermie majeure, en connaître le mode de survenue et les risques.

5. Décrire les explications à donner aux parents concernant les mesures physiques permettant de lutter contre l'hyperthermie chez un nourrisson.

6. Prescrire une ou deux médications fébrifuges ainsi qu'une thérapeutique préventive des convulsions au cours de l'hyperthermie.

Fièvre prolongée

1. Définir une fièvre prolongée.

2. Décrire l'interrogatoire des parents devant une fièvre prolongée de l'enfant.

3. Citer les examens complémentaires minimum à demander en cas de fièvre prolongée.

4. Définir la thermopathomimie et en donner les moyens de diagnostic.

5. Enumérer les principales causes de fièvre prolongée chez le nourrisson et en donner les principaux signes cliniques et biologiques qui en permettent le diagnostic.

1 La fièvre aiguë chez l'enfant

Symptôme très fréquent chez le nourrisson et l'enfant, la fièvre exige une double démarche : **diagnostique** impérativement guidée par un examen clinique (et O.R.L) complet qui orientera éventuellement les investigations complémentaires (biologiques et/ou radiologiques), **thérapeutique**, parfois urgente, car le symptôme fièvre peut avoir des conséquences graves chez le nourrisson. Il n'existe pas de parallélisme obligatoire entre l'importance de la fièvre et la gravité de l'affection causale, notamment en période néonatale. Si son étiologie la plus fréquente demeure l'infection, grave ou bénigne, bactérienne ou virale, la fièvre n'est pas toujours d'origine infectieuse : il est aussi en pédiatrie des fièvre métaboliques, inflammatoires ou néoplasiques.

1.1 Caractères en fonction de l'âge

- Chez le **nouveau-né**, la fièvre peut faire défaut dans les infections graves au cours desquelles on peut observer au contraire une hypothermie.
- Chez le **nourrisson**, l'hyperthermie peut constituer un risque neurologique et vital, quelle que soit son étiologie (Cf A - IV).
- Mieux supportée par **l'enfant**, elle pourra affecter différentes types : accès brefs ou fièvre prolongée épousant des allures variables : simple fébricule, fièvre en plateau, oscillante, ondulante, intermittente, rémittente, palustre ou pseudopalustre, désarticulée, voire hectique.

Outre son niveau, sa durée et son allure, on en précisera le mode d'installation (brutal ou progressif) et sa tolérance.

1.2 Signes d'accompagnement

Ils seront pris en considération : **frissons** traduisant des décharges bactériémiques ou une suppuration profonde, **douleurs** (rachialgies ou myalgies), **sueurs**, altération de l'état général, amaigrissement, asthénie,...
La symptomatologie fonctionnelle pourra orienter vers une localisation : dysphagie, toux et/ou dyspnée, troubles digestifs, arthralgies, syndrome méningé, signes fonctionnels urinaires,...
L'examen complet, appareil par appareil, devra s'attacher à rechercher les signes d'une localisation infectieuse (O.R.L notamment).

1.3 Conséquences et principaux signes

La gravité de l'hyperthermie réside dans le risque de voir survenir, surtout chez le nourrisson, deux complications : la déshydratation et/ou les convulsions.

1.3.1 La déshydration

Elle peut survenir en dehors de toute perte par vomissements et/ou diarrhée. On estime la perte d'eau liée à l'hyperthermie de l'ordre de 80 ml/m²/degré au-dessus de 37°. Cette perte sera souvent aggravée par un défaut d'hydradation (manque d'apport, refus de boire). Le plus souvent, les troubles digestifs associés aggravent rapidement cette déshydratation.

1.3.2 Les convulsions hyperthermiques (6 à 7% des enfants)

La brutalité du décalage thermique en est responsable chez les nourrissons prédisposés ; elle réclame un traitement symptomatique d'urgence et ultérieurement une thérapeutique préventive.

1.4 L'hyperthermie majeure

Elle réalise un tableau gravissime survenant surtout chez un nourrisson de moins de six mois, aussi bien en hiver qu'en été. A l'occasion d'une infection banale (rhinopharyngite,...), le nourrisson est retrouvé, le plus souvent le matin, en état de mal convulsif, inconscient ; sa température atteint 41° voire 42°. L'état de collapsus est attesté par une chute de la tension artérielle, une abolition des pouls périphériques, une lenteur à la recoloration des extrémités, une oligurie,. Un syndrome hémorragique, traduisant une C.I.V.D et/ou une atteinte hépatique, peut compliquer ce tableau. Malgré la mise en oeuvre de moyens de réanimation, l'issue fatale est à redouter, précédée par un syndrome de décérébration ; la survie n'est le plus souvent observée qu'au prix de lourdes séquelles neurologiques. C'est dire l'importance des mesures préventives visant à éviter ces hyperthermies chez le nourrisson et la nécessité de réduire au maximum la durée de toute hyperthermie à cet âge.

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1.5 Traitement de la fièvre

La fièvre réclame donc, chez le nourrisson, un traitement symptomatique indépendant de la thérapeutique de l'affection causale.

1.5.1 Mesure d'hygiène et moyens physiques :

- déshabillage : enfant dévêtu et si possible dans une pièce qui ne dépasse pas 20°C.
- bain tiède à une température initiale inférieure à 2°C à celle de la température de l'enfant. Les cheveux de l'enfant doivent être mouillés.
- hydratation suffisante : apport supplémentaire de boissons, en particulier nocturne.

1.5.2 Traitement médicamenteux :

- le paracétamol : 60 mg/kg/j en 4 prises. La voie orale est préférable, mais la voie rectale est possible. La voie injectable (Perfusalgan®), peut être administrée à des posologies de 60 mg/kg/j en 4 prises, ce qui correspond à une posologie quotidienne de 30 mg/kg/j de paracétamol.

- l'ibuprofène : 10 mg/kg/6-8h.

La toxicité respective de ces deux produits est encore discutée.

- l'aspirine : 60 à 80 mg/kg/j en 4 à 6 prises. La voie orale est préférable. Le traitement continu est nécessaire pour éviter les poussées hyperthermiques. L'absorption par voie rectale est incomplète (posologie de 20/mg/kg toutes les 8 heures). L'indication de la voie parentérale est celle de l'urgence et de la sévérité (10 à 20 mg/kg, 3 à 4 fois par jour). L'aspirine a été incriminée comme l'un des facteurs susceptibles d'induire un syndrome de Reye et les risques du paracétamol ont été sous-estimés. Il faut se méfier des automédications. L'association d'aspirine ou d'ibuprofène et de paracétamol en prescription simultanée ou alternée est largement réalisée mais en fait discutable.

- le Diazépam (Valium®) : 0,5 mg/kg en intra-rectal lors d'une convulsion fébrile.

Convulsions hyperthermiques

C'est une pathologie fréquente puisqu'elle touche environ 5% des enfants de 1 à 4 ans. Il faut d'emblée individualiser la convulsion fébrile bénigne largement majoritaire de la convulsion hyperthermique complexe. La conduite à tenir, le bilan et le pronostic sont différents.

1 Diagnostic clinique

Le diagnostic repose sur la **coexistence d'une crise convulsive et d'une fièvre élevée**, souvent supérieure à 39°C, en dehors de toute infection du système nerveux central (méningite, méningo-encéphalite).

1.1 Convulsion hyperthermique simple : 90% des cas

Les caractéristiques cliniques de la convulsion sont :

1. Age de survenue : entre 9 mois et 5 ans
2. Durée brève (inférieure à 10 minutes)
3. Crise généralisée, absence de déficit moteur post-critique
4. Absence de pathologie neurologique sous jacente

1.2 Convulsion hyperthermique complexe : 10% des cas

Les signes de gravité sont :

1. Age de survenue : < à 9 mois ou > à 5 ans
2. Durée de la crise > à 15 minutes
3. Caractère focal de la crise, touchant un hémicorps ou accompagnée d'un déficit moteur post critique
4. Retard psychomoteur antérieur à la crise convulsive ou examen neurologique anormal
5. Antécédents familiaux d'épilepsie

2 Conduite à tenir

Toute première convulsion hyperthermique doit être hospitalisée chez le nourrisson de moins de 2 ans et en cas de crise complexe.

2.1 Examens complémentaires

Le seul examen indispensable est la ponction lombaire. Elle permet d'éliminer une infection du système nerveux central dont les signes sont trompeurs chez le petit nourrisson.

Les dosages de la glycémie et de la calcémie sont fréquemment réalisés mais non obligatoires si l'enfant a récupéré rapidement et s'il prend bien sa supplémentation en vitamine D.

Recherche et traitement du foyer infectieux.

2.2 Cas particuliers : convulsion hyperthermique compliquée, convulsions hyperthermiques simples récidivantes (>2).

Un bilan neurologique est effectué comprenant au minimum un EEG et un scanner crânien.

Ce bilan sera complété par un examen ophtalmologique, un bilan biologique sanguin et LCR, une IRM en fonction des éléments d'orientation clinique.

3 Pronostic

Le pronostic est bon dans les convulsions hyperthermiques simples. La récidive est possible mais elle n'a pas de gravité propre. Lorsqu'il y a récidive, elle a lieu dans les 6 mois suivant la première convulsion fébrile dans 50% des cas et dans les 2 ans dans 90% des cas.

Le pronostic est plus réservé dans les convulsions hyperthermiques complexes. Le risque de récurrence est plus élevé (il est évalué à 50% lorsque la première convulsion fébrile survient avant l'âge de 1 an). Le risque d'épilepsie secondaire est également plus élevé, estimé à 2,8 à 3,5% selon les études.

4 Traitement

4.1 Traitement de la crise convulsive

Toute crise convulsive ne cédant pas spontanément en 10 minutes, doit être traitée par l'injection intra-rectale de **valium à la dose de 0,5 mg/Kg** (sans dépasser 10 mg/injection). Les parents et le personnel soignant doivent savoir utiliser le valium intra-rectal en cas de crise.

Si la crise persiste au bout de 10 minutes, une nouvelle dose de 0,5 mg/Kg peut être effectuée par le médecin. Au delà, si la crise persiste, il s'agit dun état de mal convulsif et le traiter comme tel (QS)

Des mesures de protection seront systématiquement associées: position latérale de sécurité, libération des voies aériennes supérieures.

4.2 Traitement préventif des convulsions hyperthermiques

Un traitement préventif des convulsions hyperthermiques est indiqué dans les convulsions hyperthermiques compliquées et discuté dans les formes simples mais récidivantes. Au delà de la deuxième ou troisième crise convulsive fébrile, on peut être amené à traiter si les crises sont proches dans le temps ou mal tolérées par le milieu familial.

Deux attitudes thérapeutiques sont possibles :

Traitement quotidien pendant 1 à 2 ans utilisant soit le valproate de sodium, soit le phénobarbital . La préférence va plutôt au valproate de sodium qui est mieux toléré cliniquement, notamment au niveau du comportement. Le valproate de sodium est utilisé à la posologie moyenne de 30 mg/ Kg/j en deux prises. Un bilan hépatique est nécessaire avant le début du traitement. La mise en route du traitement est progressive sur quelques jours.

Traitement préventif à la demande, en cas de fièvre, par du diazépam (VALIUM) à la dose de 1 mg/Kg/j réparti en 3 prises (= 0,33 mg/Kg/8h). A cette posologie, le diazépam a un effet préventif mais peut être responsable d'une ataxie, d'une somnolence ou d'une hyperactivité paradoxale. De plus, la convulsion est souvent révélatrice de la fièvre réduisant à néant toute prévention de ce type.

Dans tous les cas, le traitement de l'hyperthermie s'impose par le paracétamol et l'ibuprofène.

2 La fièvre prolongée

2.1 Définitions et diagnostic

Définie par la constatation d'une température centrale supérieure à 37°5 le matin et/ou 37°8 le soir (dans les conditions basales de repos), évoluant depuis au moins une semaine, la fièvre prolongée chez l'enfant exige :

- un interrogatoire très rigoureux : mode de prise de température (par les parents ou non), type de fièvre, régime alimentaire s'il s'agit d'un nourrisson, retentissement sur l'état général, symptomatologie fonctionnelle d'accompagnement, contage possible dans l'entourage, traitements éventuellement institués, vaccination BCG et état de l'allergie tuberculinique...

- un examen clinique complet et minutieux comportant obligatoirement un examen O.R.L et un toucher rectal.

- des examens complémentaires minimum : VS, hémogramme, culot urinaire, radiographie du thorax, réactions tuberculiniques, et d'autres guidés par la clinique (hémoculture, tests inflammatoires, séro-diagnostics,...).

A ce stade, il faudra se poser deux questions :
- **La fièvre est-elle authentique** ? C'est-à-dire éliminer une thermopathomimie : exclusivement observée chez l'enfant d'âge scolaire, plus souvent fille que garçon, en s'aidant du contrôle des prises thermiques, du caractère normal des examens complémentaires et en sachant qu'un tel diagnostic débouchera le plus souvent sur une investigation et/ou une prise en charge psychothérapique.
- **La fièvre est-elle organique ?**

- l'exercice musculaire peut être responsable de fièvre par augmentation de la thermogenèse (nécessité de prendre la température dans les conditions de repos).
- la thermolyse est parfois débordée (chauffage excessif) ou congénitalement déficiente (dysplasie anhidrotique),
- enfin, il est des fièvres iatrogènes (pénicilline, anticomitiaux,...).

2.2 Etiologie

La démarche étiologique d'une fièvre prolongée se pose différemment selon qu'il s'agit :

2.2.1 d'un nourrisson

2.2.1.1 L'infection

est de loin la cause la plus fréquente : respiratoire, virale ou bactérienne : rhinopharyngite, adénoïdite compliquée ou non d'otite moyenne voire d'antrite. Toute fièvre inexpliquée du nourrisson implique la recherche d'une infection urinaire (cf. cours). Plus rarement, il s'agira d'une primo infection tuberculeuse ou d'une fièvre typhoïde.

2.2.1.2 Les fièvres métaboliques

Elles ne sont pas exceptionnelles à cet âge : déshydratation au cours d'une gastro-entérite (virale ou bactérienne), d'un coup de chaleur, d'une mucoviscidose, d'un exceptionnel diabète insipide. Mais aussi fièvre du lait sec, observée avec le lait concentré sucré ou les laits en poudre, lorsque la concentration est excessive : la simple correction de la ration hydrique entraîne la normalisation de la température. Fièvre carentielle : l'hyperthermie fait partie du tableau du scorbut infantile et à un moindre degré de la carence martiale. Enfin, l'hypervitaminose D au cours de laquelle s'associent anorexie, soif et vomissements.

2.2.1.3 Les fièvres d'origine neurologique

Elles sont relativement rares chez le nourrisson : dérèglement thermique chez certains encéphalopathes ou chez des nourrissons porteurs de malformations cérébrales. En fait, c'est surtout l'hématome sous-dural chronique qu'il faut savoir évoquer (cf. cours) ; le diagnostic sera étayé par l'augmentation de volume du crâne, l'hémorragie au fond d'oeil, la ponction à l'angle externe de la fontanelle et/ou l'examen scanographique.

2.2.1.4 Le syndrome de Kawasaki

D'étiologie inconnue, mais très proche du tableau de périartérite noueuse du nourrisson, associe une hyperthermie prolongée, un exanthème avec glossite et chéilite, une adénomégalie : son pronostic est conditionné par le risque de complications cardiovasculaires (anévrismes coronariens et mort subite).

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2.2.2 Chez l'enfant

L'éventail étiologique est beaucoup plus vaste et toujours dominé par :

2.2.2.1 l'infection

Malgré la régression de l'endémie bacillaire, toujours penser à une **primo-infection** tuberculeuse (contage - radios poumons - intradermoréaction). Les **infections O.R.L** demeurent fréquentes à cet âge et les sinusites surtout maxillaires doivent être systématiquement recherchées (radiographie). Les **pneumopathies**, bactériennes ou virales, peuvent être muettes ou pauvres dans leur symptomatologie fonctionnelle et physique : nécessité d'un cliché pulmonaire. La **typhoïde** (du retour de vacances...), la **brucellose** (rare chez l'enfant) : suspectées sur des arguments cliniques, trouveront leur confirmation, suivant le stade évolutif, dans les hémocultures et/ou le séro-diagnostic. Le R.A.A (voir cours) est une infection inflammatoire (VS, fibrinémie, tests inflammatoires) post-streptococcique (ASL) susceptible d'entraîner des complications cardiaques (auscultation - ECG) nécessitant un traitement curatif (Prednisone + Pénicilline) suivi d'une prophylaxie des rechutes (EXTENCILLINE ou ORACILLINE). L'**endocardite** dont le diagnostic repose sur les hémocultures chez un enfant porteur d'une cardiopathie congénitale ou d'une valvulopathie rhumatismale. L'**abcès cérébral**, succédant à une infection ORL ou favorisé par une cardiopathie congénitale cyanogène, dont le diagnostic repose sur la clinique, les signes biologiques, le fond d'oeil, l'E.E.G et l'examen scanographique cérébral.

Parmi les **infections virales**, les plus courantes, responsables de fièvre prolongée chez l'enfant, on pensera à l'**hépatite** (surtout à virus A), le diagnostic est facile s'il existe un ictère et/ou une cholalurie ; les formes anictériques étant dépistées par l'élévation du taux des transaminases. La **mononucléose infectieuse**, due au virus d'Epstein-Barr, associe à la fièvre, dans sa forme habituelle, une angine avec polyadénopathie et splénomégalie ; le diagnostic évoqué par la formule sanguine (syndrome mononucléosique) repose sur la M.N.I test et la réaction de Paul-Bunnel et Davidsohn. La **maladie des inclusions cytomégaliques**, le plus souvent asymptomatique, peut déterminer un syndrome fébrile avec infection respiratoire haute et polyadénopathie également responsable d'un syndrome mononucléosique ; le sérodiagnostic en fera la preuve.

2.2.2.2 Les parasitoses

Responsables de fièvre prolongée chez l'enfant : la **toxoplasmose** acquise peut déterminer une polyadénopathie fébrile avec asthénie et parfois exanthème ; l'atteinte biologique hépatique est fréquente, le syndrome mononucléosique inconstant ; la sérologie en assure le diagnostic. Le **paludisme** (cf. C-V) sera suspecté de parti pris chez tout sujet fébricitant, venant d'une zone impaludée (voyage, migrant,...) et on demandera une recherche de l'hématozoaire (frottis sanguin ou goutte épaisse). La **distomatose hépatique**, le syndrome de **Viscéral larva migrans** (toxocarose) seront évoqués sur la constatation d'une hyperéosinophilie et confirmé par l'immunodiagnostic parasitaire correspondant. Le **Kala-Azar** (leishmaniose viscérale) associe chez un nourrisson ou un jeune enfant ayant séjourné en zone d'endémie (sud de la France, pourtour du bassin méditerranéen, Portugal.), une altération fébrile de l'état général avec importante splénomégalie et hépato-adénomégalie ; anémie, leucopénie, thrombopénie, hyperprotidémie et hypergammaglobulinémie. La certitude diagnostique est apportée par la mise en évidence des leishmanies au myélogramme ; des anticorps peuvent être recherchés par méthode immunologique. En l'absence de diagnostic et de traitement (Glucantime ; Lomidine) l'évolution est constamment mortelle en quelques mois.

2.2.2.3 Les affections malignes

- **la leucose aiguë lymphoblastique** peut évoluer initialement sous le masque d'une fièvre isolée sans modification importante de l'hémogramme ; il est donc important de rechercher des manifestations osseuses (cliniques et/ou radiologiques), une pâleur, une splénomégalie et/ou une intumescence ganglionnaire même modérée ; au moindre doute, toujours demander un myéolgramme qu'il faut parfois répéter.

- Plus rare chez l'enfant, la **maladie d'Hodgkin** associe une fièvre au long cours, des adénopathies superficielles et profondes, médiastinales. Le diagnostic repose, comme pour les lymphomes non hodgkiniens, sur l'examen anatomopathologique d'un ganglion périphérique.

- Les **tumeurs malignes** peuvent être responsables de fièvre prolongée. Après l'âge d'un an, le neuroblastome est métastasique dans la moitié des cas et se révèle souvent par une fièvre et une altération de l'état général.

2.2.2.4 Les collagénoses

Constamment fébriles, elles sont d'inégale fréquence chez l'enfant :

- Le **L.E.A.D**. est rare, associant une altération fébrile de l'état général, un syndrome polyarticulaire et des signes cutanés ainsi que des localisations viscérales diverses, rénales notamment, qui règlent le pronostic. On recherchera les cellules L.E., les anticorps antinucléaires, anti-DNA...

- La **périartérite noueuse**, affection aux masques multiples, d'observation peu fréquente en pédiatrie, associe également une altération fébrile de l'état général et des atteintes viscérales (nerveuses, cardiovasculaires, rénales) ; l'importante accélération de la VS, une hyperleucocytose avec polynucléose majeure, hypergammablobulinémie orienteront le diagnostic qui ne pourra être affirmé que par la découverte de lésions de nécrose fibrinoïde au niveau des artérioles à la biopsie musculo-cutanée. Rappelons les similitudes existant entre la forme du nourrisson et le syndrome de Kawasaki.

- La **dermatomyosite** de l'enfant, modérément et inconstamment fébrile, associe surtout un syndrome cutanéo-muqueux et des signes musculaires très évocateurs du diagnostic qui trouvera sa confirmation dans les signes électromyographiques et les données de la biopsie musculocutanée.

- moins exceptionnels, les **rhumatismes chroniques** de l'enfant peuvent débuter par un tableau fébrile important et réaliser une forme clinique très systémique (maladie de STILL) associant à l'hyperthermie prolongée et à l'atteinte articulaire, une hépatosplénomégalie, des adénopathies, parfois des rashs. L'atteinte cardiaque est possible ; le diagnostic repose sur la positivité des tests inflammatoires et immunologiques ; le recours à la ponction articulaire et/ou à la biopsie synoviale peut être requis dans les formes de diagnostic difficile.

- Le **syndrome de WISSLER-FANCONI** se caractérise par des poussées fébriles élevées et intermittentes, généralement bien supportées chez un enfant de 2 à 10 ans, associées à des rashs cutanés et à des manifestations articulaires fugaces (arthralgies), une splénomégalie et des adénomégalies peuvent se voir. Les poussées fébriles s'accompagnent d'accélération de la VS et d'hyperleucocytose importante. L'évolution se fait par poussées, parfois marquée par l'apparition ultérieure d'un rhumatisme chronique.

Professeur Oreste Battisti, la fièvre chez l'enfant,

Proposition d'attitude chez un enfant qui présente une fièvre sans cause apparente

Jeune nourrisson : Agé de moins de trois mois.

Fébrile : Température mesurée en rectale, et supérieure ou égale à 38°C.

La fièvre dans cette tranche d'âge ne doit jamais être considérée comme un symptôme banal ; le risque d'infection bactérienne invasive est plus important que chez l'enfant plus âgé.

Les difficultés diagnostiques à cet âge tiennent au caractère non spécifique et souvent paucisymptomatique à leur début, d'infections potentiellement sévères. Les signes sont d'autant moins spécifiques que l'enfant est plus jeune.

Les 2/3 à 3/4 de ces enfants ont une infection virale. Dans 20 à 25 % des cas, les infections sont d'origine bactérienne. Dans 5 à 10 %, ces nourrissons fébriles ont une bactériémie avec ses risques de complications. L'infection bactérienne la plus fréquente dans cette tranche d'âge est la pyélonéphrite aiguë.

Haut risque d'infection potentiellement sévère (un seul signe suffit):

Troubles du comportement

Troubles de la vigilance et/ou du tonus
Anomalies du cri
Anomalies de la réactivité (envers l'entourage familier)

Irritabilité et/ou inconsolabilité
Difficultés d'alimentation

Anomalies de l'hémodynamique
Anomalies de la coloration
Signes de détresse respiratoire
Signes de déshydratation
Signes en faveur d'une infection des parties molles ou du squelette
Purpura

Chez les nourrissons ne présentant aucun de ces signes, l'évaluation clinique ne permet pas à elle seule dans cette tranche d'âge d'exclure une infection bactérienne sévère, et des examens complémentaires sont indispensables

Les nourrissons à bas risque d'infection bactérienne sont définis comme ceux qui ne présentent aucun signe clinique définissant le haut risque et aucun signe biologique en faveur d'une infection bactérienne :
globules blancs compris entre 5 000 et 15 000 par mm3,
pas de syndrome inflammatoire : CRP < 10 mg/l ,
examen direct des urines (RUSU) fiable normal (ce qui n'exclut pas une infection urinaire !)

Il est par ailleurs possible de garder quelques heures en observation à l'HP (avec mesure répétée de la température rectale) un nourrisson avec une fièvre non quantifiée par les parents ou objectivée par les parents mais non retrouvée aux urgences, et dont l'état général et l'examen physique sont sans particularité. On envisagera un retour à domicile après avis du senior si l'enfant est resté apyrétique et stable et que sa biologie n'est pas perturbée.

AGE :	MISE AU POINT :	ATTITUDE :
< 1 mois	Biologie + hémoculture Rx thorax si symptômes respiratoires Ponction sus-pubienne./ sondage vésical PL d'office +/- PCR Herpès sur LCR $	Hospitalisation d'office Antibiothérapie d'office : CLAFORAN PENTREXYL AMUKIN +/- ZOVIRAX
1 mois à 3 mois	Biologie + hémoculture Rx thorax si symptômes respiratoires Ponction sus-pubienne./ sondage vésical PL d'office sauf avis senior	Hospitalisation et antibiothérapie selon résultats et avis senior : CLAFORAN PENTREXYL Et AMUKIN si RUSU +

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[$] La PCR Herpès sur le LCR est à réaliser chez tout nourrisson de moins de un mois, qui présente une anamnèse ou des signes cliniques cutanés, oculaires ou buccaux d'infection herpétique, ou qui présente des convulsions ou un état septique. Un traitement empirique par Zovirax sera dans ce cas instauré jusqu'à obtention des résultats de la PCR.

Chez un enfant neutropénique

FIEVRE CHEZ UN ENFANT NEUTROPENIQUE

NEUTROPENIE < (500 -) 1000 / mm^3

Fièvre > 38°

Hospitalisation pour 1er épisode de fièvre

OUI

NON

+

1) MERONEM : 100 mg/kg/j en 4x, IV5'

2) AMUKIN : 22 mg/kg 1x/j, IV1h

(3) DIFLUCAN : 5 mg/kg 1x/j, p.os ou IV1h)

Si mucite + ZOVIRAX : 10 mg/kg 3x/j IV1h

Réponse en 48 heures

OUI

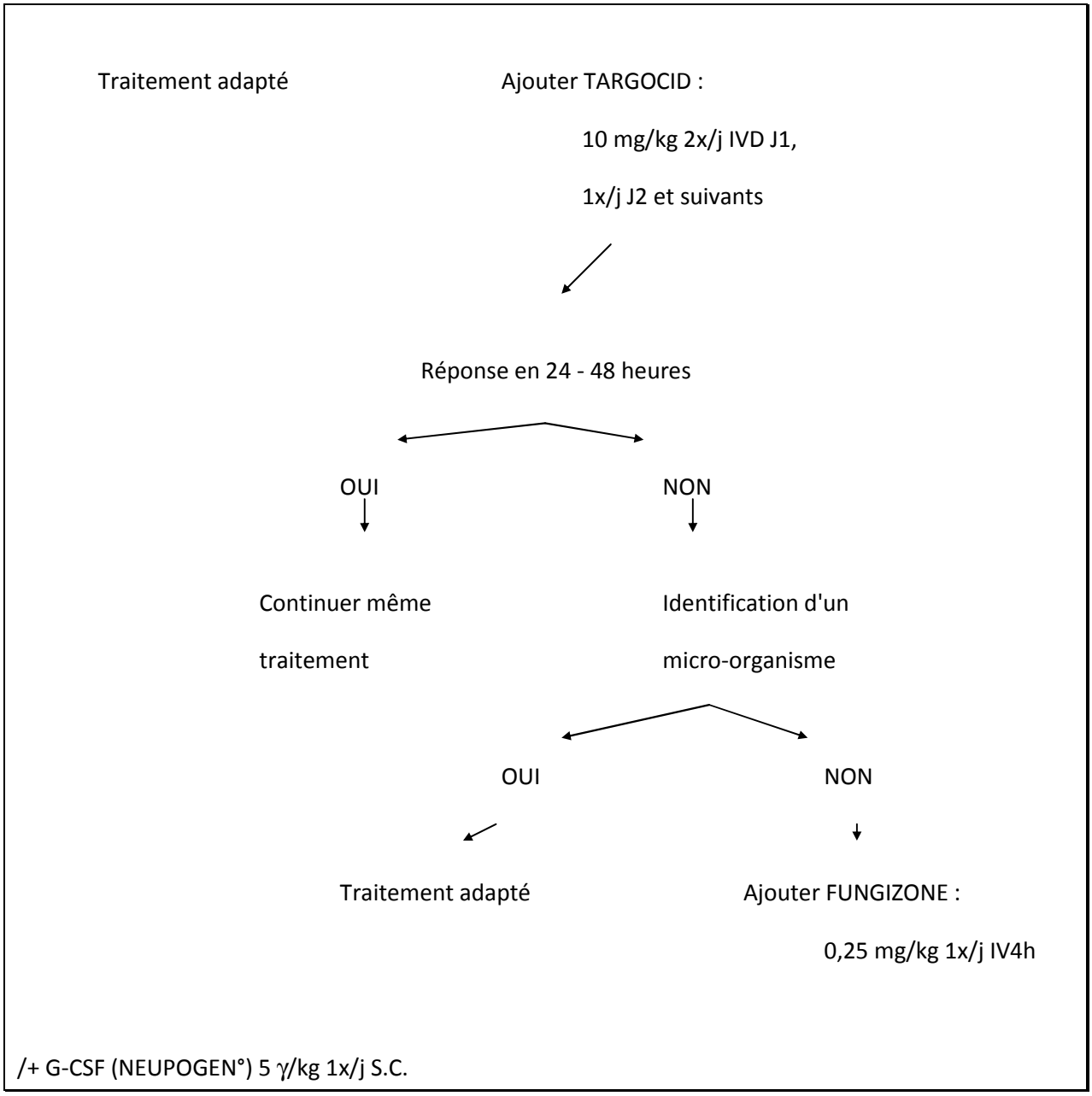
NON

Continuer même traitement

Identification d'un micro-organisme

OUI

NON


Traitement adapté
Ajouter TARGOCID :
10 mg/kg 2x/j IVD J1,
1x/j J2 et suivants
Réponse en 24 - 48 heures
OUI
NON
Continuer même
traitement
Identification d'un
micro-organisme
OUI
NON
Traitement adapté
Ajouter FUNGIZONE :
0,25 mg/kg 1x/j IV4h
/+ G-CSF (NEUPOGEN°) 5 γ/kg 1x/j S.C.

Les fièvres récurrentes :

Une fièvre récurrente que nous définirons comme une fièvre survenant à plusieurs reprises avec des intervalles libres, avec ou sans périodicité, peut donc traduire plusieursmécanismes

- soit une nouvelle rencontre avec le facteur déclenchant (nouvelle inoculation bactérienne, nouveau contact avec un allergène dans les réactions d'hypersensibilité...)

- soit une persistance de l'exposition avec le facteur déclenchant

- soit une anomalie du contrôle de la réponse immunitaire. Dans ce cas, la réaction fébrile initiale est une réaction normale, mais l'extinction de la réponse immune ne se fait pas. C'est le mécanisme impliqué dans la plupart des fièvres récurrentes héréditaires ou syndromes auto-inflammatoires.

Abord diagnostique.

Les étiologies des fièvres récurrentes de l'immunocompétent sont nombreuses. Dans les grandes séries, les étiologies se répartissent en 40% d'infections, 20% de fièvres paranéoplasiques et 15% de maladies systémiques (connectivites, vascularites et granulomatoses).

Sur le plan clinique, un interrogatoire minutieux et un examen clinique soigneux	**Aspect de la courbe**	**Orientation diagnostique**
Récurrente	Accès répétés survenant de manière régulière. Début et fin brutaux.	Paludisme, lymphomes, sodoku, leptospirose,
Rémittente	Fièvre irrégulière, oscillante subnormale le matin et élevée le soir.	Paludisme, suppuration profonde, abcès, tuberculose, cancers, collagénoses
Intermittente (pseudo-palustre)	Fièvre avec pics et retour à la normale entre deux pics.	Paludisme, pyélonéphrite, infection des voies biliaires
Hectique	Fièvre sans rythme, désarticulée, avec profonde altération de l'état général.	Septicémies, cancers
En plateau	Fièvre élevée, stable.	pneumopathie franche lobaire aiguë, salmonellose, tuberculose, viroses, grippe
Ondulante	Accès fébriles à début et fin progressifs alternant avec des phases d'apyrexie.	Brucellose, endocardite, lymphome

Tableau 1. Orientation diagnostique en fonction de l'aspect de la courbe thermique (7).

Sur le plan biologique, les données de l'hémogramme peuvent éclairer le tableau clinique devant une hyperéosinophilie, une leuconeutropénie, un syndrome mononucléosique. Le dosage de procalcitonine peut orienter vers une étiologie bactérienne. Un bilan immunologique incluant des FAN et un facteur rhumatoïde peut orienter vers une maladie systémique. Les sérologies orientées par les suspicions cliniques peuvent mettre en évidence une affection virale ou bactérienne.

Les investigations incluront des radiographies du thorax, des sinus et un panoramique dentaire, une échographie abdominale et une échographie cardiaque trans thoracique. L'IDR sera systématique.

2°) Etiologies des fièvres récurrentes.*Causes infectieuses :*

Les étiologies infectieuses les plus classiques sont résumées dans le **tableau 2.**

	Eléments d'orientation	**Diagnostic positif**
Septicémies		Hémocultures
Endocardite	Geste invasif, souffle cardiaque	Hémocultures, échographie
Brucellose	Profession, splénomégalie, leucopénie	Hémoculture, sérodiagnostic de Wright
Leptospirose	Morsure de rat, myalgies, évolution biphasique	Hémoculture, sérodiagnostic de Petit et Martin
Typhoide	Voyage, diarrhée jus de melon, splénomégalie, angine de Duguet, taches rosées lenticulaire, leucopénie	Hémocultures, sérodiagnostic de Widal
Légionellose	Pneumopathie atypique avec signes extrathoraciques	Immunofluorescence directe sur ECBC, antigénurie
Fièvre Q	Contact avec des animaux, arthromyalgies, hépatite,	sérodiagnostic
	pneumopathie	
Mycoplasme	Pneumopathie atypique, terrain	Sérodiagnostic
Tuberculose	Sujet transplanté, contage	Radiographie de thorax, IDR, tubages gastriques et ECBC
Miliaire tuberculeuse	Sujet âgé ou immunodéprimé, antécédent de tuberculose	Radiographie de thorax, IDR, ponction biopsie hépatique, myéloculture
Mononucléose infectieuse	Maladie du baiser, angine, polyadénopathie, splénomégalie, syndrome mononucléosique	Sérodiagnostic

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Infection à CMV	Polyadénopathies, hépatite cytolytique, syndrome mononucléosique	IgM anti CMV, virémie
Infection à VIII	Contage	Antigénémie p24, sérologie, charge virale
Paludisme	Voyage, fièvre tierce ou quarte, thrombopénie, anémie, hémolyse	Frottis sanguin, goutte épaisse
Toxoplasmose	Sujet jeune, polyadénopathies, syndrome mononucléosique	Sérodiagnostic

Tableau 2 : étiologies infectieuses les plus fréquentes des fièvres récurrentes.

Fièvres liées aux cancers et aux hémopathies :

Elles sont la conséquence de la sécrétion tumorale de cytokines pyrogènes, essentiellement l'interleukine 6. Elles s'observent principalement pour les lymphomes et, dans le cas de tumeurs solides, pour les cancers du rein. Elles sont décrites comme classiquement résolutives sous AINS.

Elles sont plus fréquentes en cas de maladie métastatique et leur existence a une valeur pronostique péjorative.

Fièvres des maladies systémiques :

Les maladies inflammatoires chroniques peuvent être à l'origine de fièvres prolongées qui peuvent parfois prendre l'allure d'un tableau infectieux.

1°) La maladie de Still en est l'exemple le plus caractéristique. La maladie de Still de l'adulte (MSA) est une affection systémique de cause inconnue dont la prévalence est de l'ordre de 1 à 2 pour 10 000 habitants. La maladie touche de façon similaire les deux sexes. Le pic de fréquence touche l'adulte jeune, puisque trois quarts des diagnostics sont posés entre 16 et 35 ans.

Diverses cytokines interviennent probablement dans la physiopathologie de cette affection, comme en témoigne l'élévation de NU de l'6, du TNF a et de l'interféron y.

Les manifestions cliniques associent :

une fièvre habituellement élevée, de l'ordre de 39 à 40°C, intermittente et hectique, prédominant le soir, s'accompagnant volontiers de frissons ; des arthralgies et des arthrites des petites et des grosses articulations, rarement destructrices, mais à l'origine d'un handicap fonctionnel majeur. Le liquide articulaire, lorsqu'il est prélevé, est très inflammatoire et d'une grande richesse cellulaire. Le tableau douloureux est complété par des myalgies intenses, sans déficit moteur ni élévation des CPK.

Un rash cutané fugace, volontiers maculeux ou maculopapuleux, de couleur rose ou saumoné, localisé sur le tronc ou sur la racine des membres. Les lésions cutanées accompagnent les pics fébriles et disparaissent typiquement au matin. Des douleurs pharyngées, parfois inaugurales et souvent invalidantes.

- Des adénopathies superficielles ou profondes, parfois une splénomégalie. - Des sérites et des manifestations systémiques ont étés rapportées.

Sur le plan biologique, on note :

une fréquente atteinte du bilan hépatique, souvent à type de cytolyse, parfois à type de cholestase ;

un syndrome inflammatoire quasi-constant avec une hyperleucocytose à polynucléaires neutrophiles, une élévation de la VS et de la CRP ; une anémie inflammatoire ;

une hyperferritinémie souvent majeure avec paradoxalement une diminution de la ferritine glycosylée qui, lorsqu'elle est inférieure à 15%, est un excellent argument pour la maladie de Still.

Le diagnostic repose sur un faisceau d'argument, associant deux critères majeurs et trois critères mineurs en l'absence de tout critère d'exclusion (voir **tableau 3).**

Il existe quatre formes évolutives prédominantes :

les formes systémiques et articulaires monoméliques évoluant d'un seul tenant et aboutissant à la guérison sans séquelle,

les formes systémiques récidivantes avec atteinte articulaire aiguë,

les formes systémiques monoméliques avec atteinte articulaire chronique souvent destructrice,

les formes systémiques récidivantes avec atteinte articulaire chroniques et risque de destruction articulaire.

Le traitement symptomatique par AINS ou aspirine forte dose est souvent nécessaire. Le traitement de fond repose sur la corticothérapie forte dose. Aucun autre traitement de fond ne fait l'objet d'un consensus, même si le methotrexate et les anti-TNF sont utilisés à titre d'épargne cortisonique dans les formes cortico-dépendantes.

Critères majeurs :

1. Fièvre > ou = à 39°C pendant au moins une semaine ;
2. arthralgies évoluant pendant au moins deux semaines ;
3. éruption cutanée typique, maculeuse ou maculopapuleuse, non prurigineuse, rose saumon, habituellement fugace et contemporaine des poussées fébriles ;
4. leucocytose (au moins 10 000 /mm^3) avec au moins 80% de polynucléaires neutrophiles.

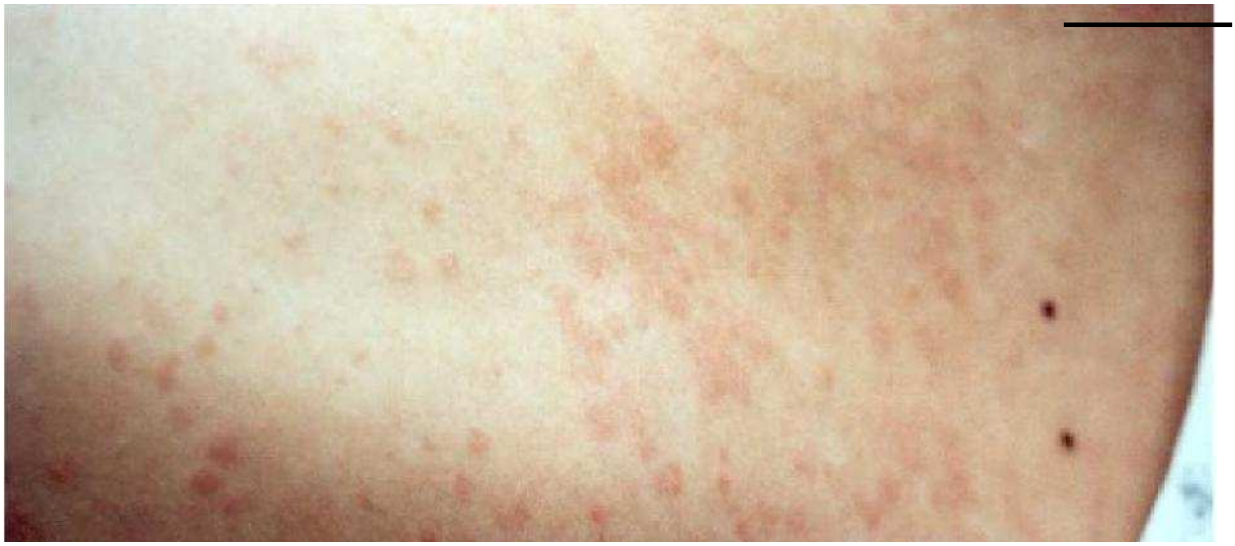
Critères mineurs :

1. douleurs pharyngées ;
2. adénopathies et /ou splénomégalie ;
3. perturbation du bilan biologique hépatique ;
4. absence d'anticorps antinucléaires et de facteur rhumatoïde.

Critères d'exclusion :

1. infections (tout particulièrement les sepsis et la mononucléose infectieuse) ;
2. néoplasies (tout particulièrement les lymphomes) ;
3. maladies systémiques (tout particulièrement la périartérite noueuse ou la polyarthrite rhumatoïde avec signes extra articulaire)

Tableau 3 : critères diagnostiques de la MSA (7).



Eruption saumonée fugace d'une maladie de Still.

2°) La *sarcoïdose systémique* peut s'accompagner de fièvre récurrente, rarement isolée, surtout présente au cours du syndrome de Ledgren.

La prévalence de la sarcoïdose en France est de l'ordre de 20/100 000 habitants.

Dans cette maladie chronique d'origine inconnue, des macrophages activés s'accumulent dans divers tissus, provoquant, par un mécanisme d'hypersensibilité de type W (hypersensibilité granulomateuse), la formation de granulomes souvent accompagnés de fibrose.

La découverte fortuite d'adénopathies médiastinales basses, bilatérales et symétriques, non compressives sur une radiographie de thorax réalisée à l'occasion d'une dyspnée, d'une toux irritative, d'une altération de l'état général, ou même de façon systématique dans le cadre de la médecine du travail représente 50% des diagnostics de sarcoïdose.

Dans un quart à un tiers des cas, la maladie sera découverte à l'occasion d'une localisation extra-thoracique.

Dans 10% des cas, la maladie débute de façon aiguë par un syndrome de Ledgren, associant des adénopathies médiastinales à des arthralgies ou des arthrites et à un érythème noueux.

La maladie se traduit essentiellement par une atteinte médiastino-pulmonaire qui est résumée dans le **tableau 4 :**

Type I (50% des cas) : adénopathies latérotrachéales sans atteinte interstitielle
Type II : association des adénopathies médiastinales avec une atteinte interstielle bilatérale et symétrique
Type III : atteinte interstitielle isolée sans adénopathies Type IV : fibrose pulmonaire destructrice et rétractile.

Tableau 4 : classification radiologique de la sarcoïdose pulmonaire.

Des formes extra-pulmonaires peuvent inclure :

adénopathies superficielles (20% des cas), avec ou sans hépatosplénomégalie atteinte oculaire avec uvéite antérieure ou postérieure

formes cutanées nodulaires : sarcoïdes ou lupus pernio, dans les atteintes chroniques (<10% des cas)

ostéite de Perthes-Jugling (5% des cas) : l'aspect le plus typique correspond à des microgéodes des métaphyses des phalanges ou du métacarpe.

atteinte musculaire

atteinte des glandes salivaires ou lacrymales, pouvant évoluer vers un syndrome de Mikulicz

atteinte cardiaque avec risque de troubles de la conduction ou de troubles du rythme, parfois responsables de morts subites

atteinte neurologique : paralysie faciale périphérique, méningite lymphocytaire, myélite, infiltration hypothalamo-hypophysaire

atteinte rénale avec hypercalciurie (la plus fréquente) ou néphropathie granulomateuse

Les éléments biologiques d'orientation : syndrome inflammatoire, hypercalciurie, hypercalcémie, élévation de l'enzyme de conversion de l'angiotensine, hypergammaglobulinémie, ne remplacent pas le diagnostic histologique. Les biopsies bronchiques étagées des éperons restent la technique de référence.

Le traitement varie en fonction de la sévérité clinique : si l'abstention thérapeutique est la règle dans la majorité des cas, une corticothérapie est nécessaire en cas d'atteinte oculaire ou neurologique ou devant une hypercalcémie.

3°) Dans la *périartérite noueuse,* la fièvre est présente dans environ trois quarts des cas. Elle est inaugurale une fois sur dix. Cette vascularite nécrosante touche essentiellement les artères de plus de 701.1m, c'est-à-dire les artères à destinée viscérale comme les artères rénales, hépatiques, coronaires, le tronc coeliaque et les vaisseaux mésentériques. Son incidence est de l'ordre de 5 à 10/100 000 habitants.

Outre la fièvre, qui oscille généralement vers les 38°C mais qui peut dépasser les 40°C, le tableau associe un amaigrissement (60 à 70% des cas), une neuropathie périphérique (60 à 70% des cas), des myalgies intenses (50 à 55% des cas), des arthralgies ou des arthrites (40 à 60% des cas), des signes cutanés à type de livédo ou de nouures sur les trajets artériels. Une atteinte rénale (néphropathie vasculaire) se voit dans 30 à 40% des cas et peut évoluer vers l'insuffisance rénale terminale Des manifestations digestives sont présentes dans 30 à 40% des cas : colite ischémique, hémorragies digestives, perforation. L'atteinte cardiaque est présente dans 20 à 30% des cas.

Sur le plan biologique, on constate un syndrome inflammatoire biologique et une hyperleucocytose à polynucléaires neutrophiles. Les ANCA sont rares. L'antigène et l'anticoprs HBs doivent être recherché, car il existe 10% des PAN liées au virus de l'hépatite B, ce qui modifie la prise en charge thérapeutique.

Le diagnostic peut être retenu en cas de présence de trois critères sur dix dans la liste de l'American College of Rheumatology **(tableau 5).**

Perte de poids >4kg chez l'adulte ou 10 % chez l'enfant.
Livedo
Douleurs testiculaires ou sensibilité à la palpation
Myalgies ou fatigabilité musculaire
Mono- ou polyneuropathie
Pression artérielle diastolique >90mm Hg
Augmentation de l'urée ou de la créatinine
Présence de l'antigène HBs ou de l'anticorps anti-HBs dans le sérum
Anomalie artériographique : microanévrysmes, occlusion des artères viscérales
Biopsie d'une artère de petit ou de moyen calibre évocatrice.

Tableau 5 : critères d'aide au diagnostic de la PAN (sensibilité 82%, spécificité 86%).

Le pronostic peut être évalué par les critères de Guillevin *et al.* **(tableau 6)**

Protéinurie > 1g/24h
Insuffisance rénale avec créatinine> 140fflol/L
Cardiomyopathie
Atteinte digestive sévère
Atteinte du système nerveux central

Tableau 6 : index pronostic de sévérité de la PAN. En l'absence de ces critère, la mortalité à 5 ans est de 12% ; lors de la présence d'un seul critère, la mortalité passe à 26% à 5 ans ; lors de la présence de plus d'un critère, la mortalité à 5 ans est de 46%.

Le traitement est basé sur une corticothérapie à forte dose relayée par un immunosuppresseur, essentiellement le cyclophosphamide. En cas d'hépatite B associée, des protocoles associent un traitement antiviral.

4°) Le *lupus érythémateux systémique* est un grand pourvoyeur de fièvre puisque le train fébrile est présent dans les trois quarts des poussées de la maladie. Il s'agit d'un symptôme prédominant une fois sur six.

Le lupus est la plus fréquente des connectivites après le syndrome de Gougerot Sjogren. Sa prévalence est évaluée à 15 à 50 cas pour 100 000 habitants.

Son diagnostic repose sur l'association de quatre des critères de l'American College of Rheumatology **(tableau 7) :**

Le traitement est fonction de la gravité du lupus. Dans les formes bénignes cutanées et articulaires, les antipaludéens de synthèse sont utilisés, parfois avec l'adjonction d'une petite corticothérapie. Le traitement des formes graves avec atteinte viscérale ou neurologique repose sur la corticothérapie à forte dose relayée par des immunosuppresseurs type azathioprine ou cyclophosphamide.

1.	éruption malaire en ailes de papillon
2.	éruption du lupus discoïde
3.	photosensibilité
4.	ulcérations buccales ou nasopharyngées
5.	polyarthrite non érosive
6.	pleurésie ou péricardite
7.	atteinte rénale : protéinurie > 0.5g/24h ou cylindres urinaires
8.	atteinte neurologique : convulsions ou psychose
9.	atteinte hématologique : anémie hémolytique avec hyper réticulose ou leucopénie < 4 000/mm3 ou lymphopénie < 1 500/mm3 ou thrombopénie < 100 000/mm3
10.	Désordre immunologique : présence de cellules LE ou d'anticorps anti DNA natifs ou d'anti Sm ou d'une fausse sérologie syphilitique
11.	présence d'un titre anormal d'anticorps antinucléaires

Tableau 7 : critères diagnostiques du lupus.

5°) La *maladie de Wegener* peut donner une fièvre traînante. Sa prévalence apparaît inférieure à 3/100 000 personnes.

La maladie débute habituellement par une atteinte ORL ou pulmonaire d'aspect infectieux, d'aggravation progressive. Les manifestations cliniques sont rappelées dans le **tableau 8.**

L'atteinte biologique retrouve un syndrome inflammatoire franc ; l'atteinte immunologique retrouve des c ANCA qui sont une aide précieuse au diagnostic.

Le traitement repose sur l'association de la corticothérapie à fortes doses aux immunosuppresseurs.

Type d'atteinte (fréquence)	**Manifestations cliniques**
Atteinte ORL (80-100% des cas)	Obstruction nasale, rhinorrhée chronique, croûteuse et sanglante, ulcérations nasales, pharyngées ou buccales, sinusite parfois expensive allant jusqu'à la destruction osseuse, perforation de la cloison nasale
Atteinte pulmonaire (80-100% des cas)	Toux, dyspnée, hémoptysie ; nodules et infiltrats parenchymateux multiples, bilatéraux, volontiers excavés, hémorragies alvéolaires, épanchements pleuraux
Atteinte rénale (70-80% des cas)	Protéinurie, Hématurie
Atteinte ophtalmique (40-50% des cas)	Episclérite, kératite, conjonctivite, uvéite ; névrite optique, vascularite rétinienne. Pseudotumeur de l'orbite sur granulome périoculaire ; exophtalmie.
Atteinte cutanée (40-50% des cas)	Purpura vasculaire, ulcérations, nodules sous cutanés, livédo, nécrose cutanée
Atteinte neurologique (20% des cas)	Multinévrite, polynévrite, hémorragies cérébroméningées, AVC ischémiques, thrombophlébites.
Atteinte articulaire (30-80% des cas)	Arthralgies voire polyarthrite
Atteinte cardiaque (10% des cas)	Péricardite, nécrose myocardique, troubles du rythme ou de la conduction

Tableau 8 : principales manifestations cliniques de la maladie de Wegener (7).

6°) Syndrome de Churg et Strauss. La fièvre fait partie des manifestations cliniques observées dans le syndrome de ***Churg et Strauss.*** Elle est présente dans 80 à 100% des cas et s'accompagne volontiers d'un amaigrissement. Un asthme est présent dans 95 à 100% des cas et précède souvent l'apparition de signes généraux. Les autres signes cliniques associent une neuropathies périphérique (60 à 80% des cas, typiquement une mononévrite multiple,

asymétrique, sensitivomotrice) ; une atteinte articulaire (40 à 60% des cas) avec arthromyalgies ; des signes cutanés (40 à 50% des cas :

purpura vasculaire, nodules sous cutanés, livédo, syndrome de Raynaud) ; une atteinte rénale (40 à 60% des cas) avec une protéinurie et une hématurie microscopique ; des douleurs abdominales dans 40 à 60% des cas ; et une atteinte coronaire ou myocardique dans 40 à 60% des cas.

L'hyperéosinophilie est l'un des critères diagnostiques essentiels. Elle peut varier de 1 000 à plus de 50 000 éosinophiles/mm3. Les p ANCA avec anticorps anti myéloperoxydase sont retrouvés dans 60% des cas.

Le traitement associe là encore une corticothérapie à des immunosuppresseurs.

7°) La maladie de Horton s'accompagne fréquemment d'un train fébrile. Cette vascularite des artères de gros calibre touche quasi-exclusivement les sujets de plus de 55 ans. Sa prévalence est évaluée à 10 à 20 cas pour 100 000 habitants de plus de 55 ans.

La clinique associe typiquement des signes généraux, avec une fébricule très corticosensible et un amaigrissement, à des signes rhumatismaux (arthromyalgies des ceintures) et à des signes vasculaires. Parmi ces derniers, les céphalées intenses superficielles provoquées par le moindre attouchement et la claudication douloureuse intermittente de la mâchoire, conséquence d'une sténose de l'artère faciale, sont les plus typiques. La palpation des artères céphaliques superficielles peut retrouver un cordon induré et douloureux. L'atteinte oculaire par l'atteinte de la carotide interne et de ses branches fait toute la gravité de la maladie.

Le syndrome inflammatoire biologique est souvent majeur, et peut être la circonstance de découverte de la maladie. Une élévation des phosphatases alcalines n'est pas inhabituelle. Le traitement repose sur une corticothérapie prolongée souvent pendant plusieurs années. Le méthotrexate peut être utilisé à titre d'épargne cortisonique dans les formes corticodépendantes.

8°) *La maladie de Behçet* peut se présenter par un syndrome fébrile inaugural accompagné d'une hyperleucocytose à neutrophiles. La coexistence d'aphtes bipolaires, d'arthralgies, de manifestations neurologiques ou ophtalmiques conduit au diagnostic.

Il s'agit d'une vascularite systémique d'origine inconnue. Sa prévalence prédomine en Moyen Orient et dans le bassin méditerranéen, particulièrement dans la communauté turque. Elle y est de l'ordre de 1/10 000.L'antigène HLA B5 constitue une prédisposition génétique.

L'aphtose bipolaire doit faire évoquer le diagnostic. Les signes cutanés à type de pseudo-folliculites ou de lésions papulopustuleuses sont fréquents. Les signes oculaires sont présents dans 60% des cas, essentiellement sous la forme d'uvéite antérieure ou postérieure. Des arthralgies ou des arthrites inflammatoires peuvent être présentes, mais le rhumatisme est non érosif. Les signes neurologiques atteignent 15 à 20% des patients et peuvent précéder les autres manifestations cliniques : méningites et méningo-encéphalites, myélites transverses, thrombophlébites cérébrales.

Les patients atteints d'une maladie de Behçet sont à risque de thromboses veineuses et artérielles, principalement la thrombophlébite cérébrale.

La biologie est marquée par un syndrome inflammatoire s'accompagnant volontiers d'une hyperleucocytose à polynucléaires neutrophiles.

Le diagnostic peut être porté devant l'association d'un critère majeur et de deux critères mineurs de l'International Study Group for Behçet's disease (1990) :

Critère majeur : aphtose buccale récidivante : 3 poussées au moins sur une période d'un an. **Critères mineurs :**

aphtose génitale récidivante

atteinte oculaire : uvéite antérieure ou postérieure, suspension cellulaire dans le vitré, vascularite rétinienne

manifestations cutanées : érythème noueux, pseudo-folliculite, lésions papulopustuleuses, nodules acnéiformes en dehors de la période pubertaire et de tout traitement corticoïde. Positivité de l'intradermoréaction à l'eau : pathergie observée par un clinicien (pustule aseptique développée au point de ponction à la 24-48ème heure).

Tableau 9 : Critères diagnostiques pour la maladie de Behçet selon l'International Study Group for Behçet's disease.

Le traitement repose sur la colchicine dans les formes bénignes, sur la corticothérapie et les immunosuppresseurs dans les formes sévères. Les anticoagulants et/ou l'aspirine sont employés pour éviter la survenue de thromboses vasculaires.

9°) Les ***rhumatismes inflammatoires et*** les *MICI* peuvent s'accompagner d'une fièvre.

Fièvres secondaires à des maladies générales :

Les maladies thromboemboliques peuvent bien évidemment s'accompagner d'un train fébrile. On peut évoquer aussi les thyroïdites, les hépatites chroniques actives, la cirrhose, la maladie des embols de cholestérol. On n'oubliera pas les rhumatismes microcristallins, souvent fébriles.

Fièvres d'origine génétique :

C'est le cas en particulier des syndromes auto-inflammatoires.

Les fièvres périodiques auto-inflammatoires sont traditionnellement décrites comme des maladies héréditaires se traduisant par des accès inflammatoires cliniques et biologiques intermittents, sans facteur déclenchant retrouvé. De transmission autosomique dominante ou récessive, ils débutent le plus souvent dans l'enfance. Les accès incluent de la fièvre et des signes focaux le plus souvent cutanés, digestifs et articulaires, ainsi qu'un syndrome inflammatoire biologique. Les poussées se reproduisent sans périodicité.

De grands progrès dans la compréhension de ces syndromes et de leur substratum génétique ont été faits ces dernières années. Ils sont liés pour la plupart à des anomalies d'une superfamille de protéines appelée CATERPILLER qui compte une vingtaine de protéines jouant un rôle dans la régulation de l'immunité. Les mutations des gènes entraînent dans certains cas la levée de mécanismes de régulation et un excès d'inflammation le plus souvent médié par l'interleukine 1 (9, 14, 17).

Nous allons rappeler brièvement les caractéristiques des syndromes auto-inflammatoires, car ils seront utiles pour la présentation de notre cas clinique.

a) la fièvre périodique méditerranéenne

Epidémiologie :

La fièvre périodique méditerranéenne est la plus fréquente des fièvres périodiques auto-inflammatoires. Elle est de transmission autosomique récessive. Elle touche les populations arabes, arméniennes, turques, kurdes, libanaises, italiennes et juives. Chez les juifs sépharades et les turcs, la fréquence à l'état hétérozygote de la mutation du gène responsable est de l'ordre de 20%.

Clinique :

La maladie débute avant 5 ans chez les deux tiers des patients. Il n'existe pas de facteur déclenchant évident mais les poussées pourraient être déclenchées par des épisodes de stress ou d'infection virale. La poussée associe des accès de fièvre durant classiquement de quelques heures à 72 H à des signes d'inflammation des séreuses. La fièvre est élevée, de début brutal, et s'accompagne de frissons. Des douleurs abdominales sont présentes dans 90% des cas. Le tableau peut être évocateur d'un abdomen chirurgical aigu. Sont ensuite touchés par ordre de décroissance la plèvre (40%), la vaginale testiculaire (10%) et le péricarde (1%). Une atteinte cutanée est fréquente sous la forme d'un pseudo-érésypèle des membres inférieurs, au regard des chevilles. Une atteinte articulaire avec des arthralgies mais également une monoarthrite des grosses articulations est possible. Des manifestations de type vascularite : myalgies, purpura, lésions des gros vaisseaux, ont été décrites. L'accès s'accompagne sur le plan biologique d'une élévation sérique de la SAA et de la CRP. Les biopsies des tissus touchés contiennent une infiltration par des polynucléaires

La survenue d'une amylose de type AA est la principale complication. Le rein est le principal organe atteint. Les autres organes atteints sont le tube digestif, la thyroïde et le coeur. Les dépôts amyloïdes sont formés de la protéine AA qui dérive par clivage de la protéine SAA, dont la concentration est multipliée par un facteur de 10 à 1 000 au cours de la réaction inflammatoire. L'amylose complique généralement des formes de la FMF (fièvre méditerranéenne familiale) typique mais peut aussi toucher des patients en l'absence même de tout accès inflammatoire clinique — ce que les auteurs israéliens ont appelé le phénotype de type 2 de la fièvre méditerranéenne familiale. L'explication de ce rare mais intrigant phénomène réside probablement en l'existence d'une inflammation sanguine infraclinique. Le sexe masculin est un facteur de risque d'amylose, ainsi que le génotype SAA1 du gène dont il existe différents allèles plus ou moins amylogènes.

Génétique :

Le gène MEFV (Mediterranean fever) , situé sur le chromosome 16, code pour une protéine appelée pyrine ou marénostrine *(mare nostrum :* nom latin de la méditerranée) qui a été identifiée en 1997. Le gène est spécifiquement exprimé dans les cellules myéloïdes, les neutrophiles, les éosinophiles et les monocytes.

La pyrine est membre de la superfamille des CATERPILLER. La proteine contient dans sa partie N terminale un domaine pyrine de 90 AA, des domaines CARDs, des domaines death-effector, et un domaine C-terminal appelé B30.2 qui est le plus souvent impliqué dans les mutations. Plusieurs isoformes existent.

Environ 40 mutations ont étés retrouvées dont 5 fréquentes (Exon 10: V726A, M694V, M694I, M680I, exon 2: E148Q). Trois exons (M694V, V726A et E148Q) expliquent 70% des cas.

Physiopathologie :

Les domaines pyrine sont capables d'engager des interactions homotypiques protéine/protéine et de former des homo ou des hétérodimères . La pyrine/marenostrine interagit, via son domaine pyrine, avec le domaine pyrine d'une autre protéine appelée ASC (apoptosis speck-like protein containing a CARD) afin de la réguler. La protéine ASC est impliquée dans l'activation de l'apoptose par la voie des caspases et dans l'activation de l'inflammation par l'intermédiaire de NF kappa B. La protéine ASC est aussi capable d'activer via son domaine CARD la pro-caspase 1 en caspase 1 qui clive l'IL1 bêta et permet la sécrétion de l'IL1 mature. Le résultat est la freination de l'inflammation médiée par l'ILLIn vivo, chez la souris knock-out pour la pyrine, les monocytes péritonéaux sécrètent de taux élevés de IL1 et la voie de l'apoptose y est interrompue. Ainsi la pyrine est-elle une protéine régulatrice de l'inflammation en régulant l'action de la protéine ASC.

Professeur Oreste Battisti, la fièvre chez l'enfant,

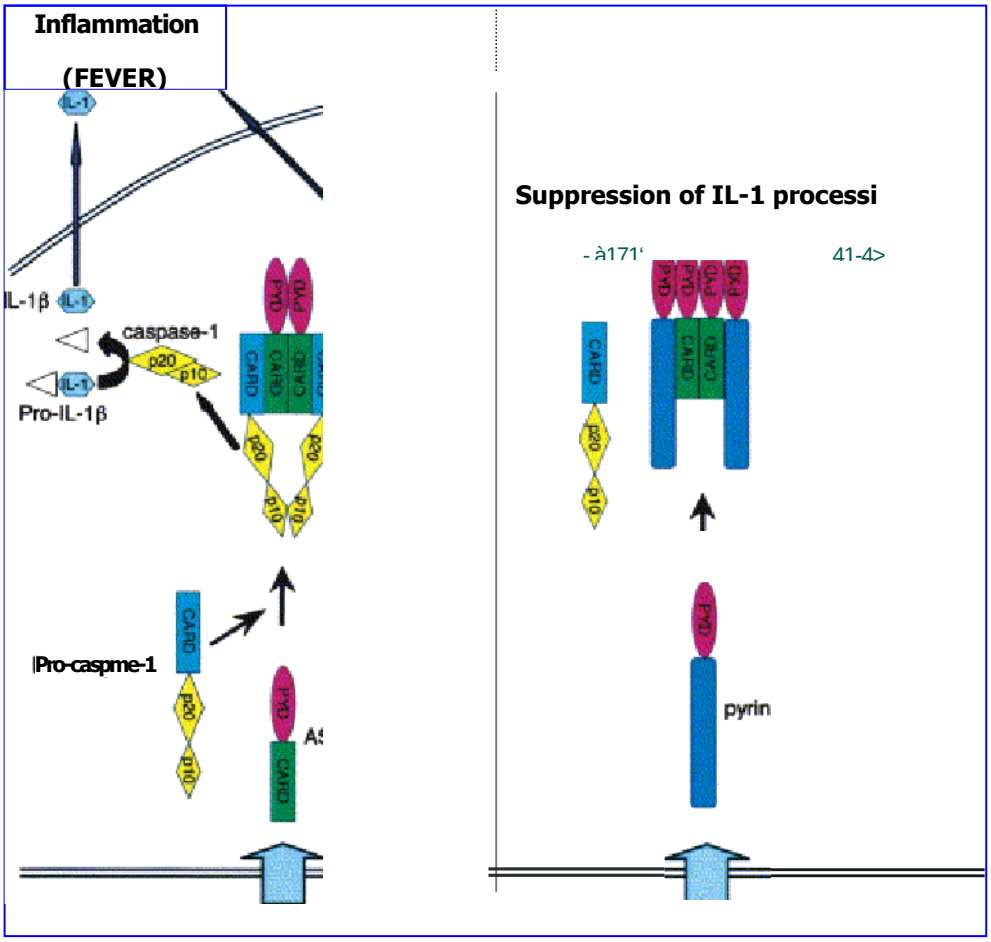


Figure 2 : mécanisme d'action de la pyrine (13).

Critères majeurs :

Crises typiques :

1°) Crise abdominale

2°) Pleurésie unilatérale ou péricardite

3°) Monoarthrite (hanche, genou, cheville)

4°) Fièvre isolée.

Critères mineurs :

Crises atypiques d'un ou plusieurs des organes suivants :

1°) Abdomen

2°) Thorax

3°) Articulations (autres que hanche, genou, cheville)

4°) Douleur des jambes à l'effort 5°) Efficacité de la colchicine.

Critères d'appoint :

1°) Contexte familial de maladie périodique

2°) Terrain ethnique prédisposé

3°) Début des signes avant l'âge de 20 ans.

Caractéristiques des crises :

4°) Grave, imposant le décubitus

5°) Rémission spontanée

6°) Intervalle libre entre les crises

7°) Syndrome inflammatoire biologique transitoire

8°) Protéinurie ou hématurie transitoires

9°) laparotomie « blanche » ou appendicectomie injustifiée

10°) consanguinité des parents

Le diagnostic repose sur la présence d'un critère majeur et de deux critères mineurs,

ou d'un critère majeur et de cinq critères d'appoint.

Tableau 10 : critères de Livneh pour le diagnostic de maladie périodique.

*Traitement :*La colchicine prévient les accès inflammatoires et l'amylose de la fièvre méditerranéenne familiale. L'usage de cette drogue est empirique, et son mécanisme d'action n'est pas élucidé. On peut suspecter, comme dans la goutte, un rôle anti-inflammatoire par l'action anti-prolifération des cellules inflammatoires.

Lorsque l'amylose est installée, la colchicine peut faire disparaître les signes cliniques d'atteinte rénale, même en cas de syndrome néphrotique. Une dose de 1 mg/jour est souvent suffisante pour prévenir les accès, mais des doses supérieures jusqu 'à 2,5 mg/jour sont parfois nécessaires. La mesure de la SAA sanguine peut permettre de monitorer la prise de colchicine.

b) fièvre périodique avec hyperimmunoglobulinémie (syndrome d'hyper-Ig»):

Epidémiologie :

Le syndrome de fièvre périodique avec hyperimmunoglobulinémie D (HIDS) commence presque toujours dans l'enfance, souvent au cours de la première année de vie. Cependant, certaines formes peuvent survenir à l'âge adulte.

Clinique :

Les accès fébriles dépassent fréquemment les 39°C, s'installent brutalement en quelques heures, s'accompagnent de frissons et fréquemment de prodromes à type de congestion nasale, pharyngite, céphalée, asthénie. Les accès inflammatoires durent typiquement 7 jours et reviennent assez périodiquement toutes les 2 à 6 semaines. Ils s'accompagnent de signes cutanés polymorphes (90% des cas), et dans 2/3 à 3/4 des cas de douleurs abdominales, diarrhées, vomissements, arthralgies ou arthrites. L'examen clinique retrouve une hépatosplénomégalie et des adénopathies cervicales douloureuses.

Biologie :

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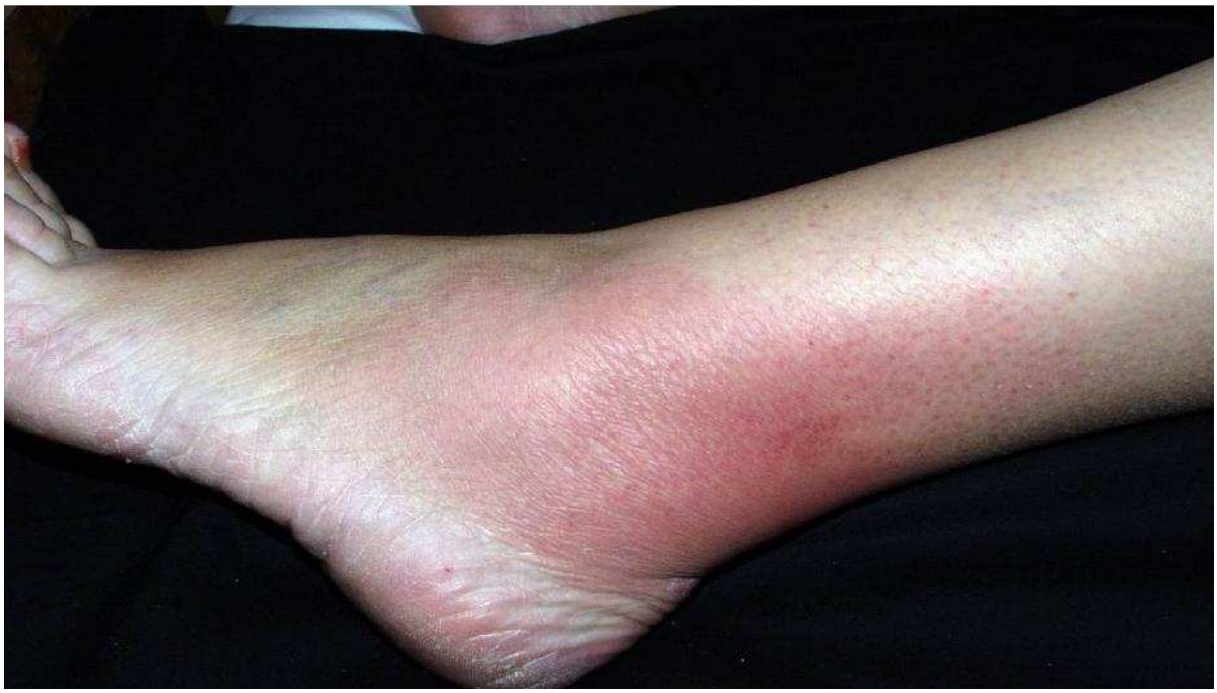
Il existe comme dans les autres fièvres auto-inflammatoires un syndrome inflammatoire biologique et une hyperleucocytose à polynucléaires neutrophiles. Les examens biologiques retrouvent un taux élevé d'immunoglobulines D circulantes mesurées deux fois à un mois d'intervalle. On peut mettre en évidence le déficit en mévalonate- kinase, soit en mesurant directement l'activité des enzymes dans les lymphocytes, soit en dosant le mévalonate (substrat de l'enzyme) dans les urines au décours d'une poussée.

Signes clinicobiologiques :

- élévation du taux des IgD mesuré à au moins deux occasions à un minimum un mois d'intervalle (> ou = 100U/mL)
- Poussées récurrentes
- Augmentation du taux des IgA (> ou = 2.6g/L) **Au cours des poussées :**
- augmentation de la VS, hyperleucocytose
- début brutal de la fièvre (> ou = 38.5°C)
- Adénopathies (cervicales notamment)
- Signes digestifs : diarrhées, vomissements, douleurs abdominales
- Signes cutanés : érythèmes maculeux et papuleux
- Arthralgies/arthrites
- Splénomégalie

Tableau 11 : critères diagnostiques de l' HIDS.



Pseudo-érésypèle dans un syndrome d'HIDS.

Génétique et physiopathologie :

La transmission est autosomique récessive, le gène MVK se trouvant en 12q24.

Le gène responsable du syndrome d'hyperimmunoglobulinémie D code pour la mévalonate-kinase, une enzyme de la synthèse du cholestérol. La synthèse par les mévalonate-kinases d'isoprénoïdes réduit l'action de l'ILL Le déficit en isoprènes induit une augmentation de la sécrétion d'ILI bêta par les cellules déficitaires. In vitro comme in vivo, l'activité de la mévalonate-kinase des fibroblastes de malades atteints du syndrome d'hyperimmunoglobulinémie D est diminuée lors des accès fébriles. Ces travaux suggèrent qu'une élévation minime de température comme une infection virale pourrait aggraver le déficit permanent en mévalonate-kinase, avec pour conséquence un déficit temporaire en isoprénoïdes et une poussée inflammatoire clinique médiée par l'IL1 .

Traitement :

Les traitements discutés incluent l'étanercept et la simvastatine, utilisée à titre de modulateur de la voie de synthèse du cholestérol et des isoprènes, dont une efficacité modérée sur les symptômes a été étudiée dans un essai randomisé (35).

c) Le TRAPS syndrome :

Les poussées durent classiquement d'une à plusieurs semaines. Les douleurs abdominales sont au premier plan. Des lésions cutanées sont observées dans plus de $^{3}/4$ des cas : lésions érythémateuses sensibles à la palpation, touchant les membres et le tronc (pseudocellulite). Ces lésions débutent à la racine et migrent au cours de l'accès vers l'extrémité du membre atteint .D'autres lésions maculeuses et des plaques érythémateuses existent. Il existe des myalgies souvent limitées à un groupe musculaire, en regard des lésions cutanées. D'autres signes, moins fréquents, peuvent co-exister : douleur thoracique, arthralgies, douleurs rachidienne, adénopathies satellites des lésions cutanées, oedème péri-orbitaire, conjonctivite aseptique.

Le gène responsable du TRAPS code pour le récepteur de type 1 A du TNF. Les mutations touchent des cystéines essentielles à la structure de la partie extracellulaire du TNFRSFIA. Le clivage physiologique du domaine extracellulaire conduit à la libération de la forme soluble du récepteur, dont l'action principale est de capter le TNF alpha circulant, donc de limiter son action. Certaines mutations empêchent le clivage du récepteur membranaire, ce qui conduit à une baisse du récepteur circulant laissant le TNF alpha libre de jouer son rôle pro-inflammatoire (1).

d) Urticaire familial au froid/syndrome CINCA/NOMID/Muckle Wells syndrome :

L'urticaire familial au froid (FCU : familial cold urticaria ou FCAS : familial cold autoinflammatory syndrome), le *syndrome de Muckle-Wells* (MWS) et le *syndrome CINCA/NOMID* (chronic infantile neurological cutaneous and articular/ neonatal onset multisystemic inflammatory disease) doivent être traités de façon conjointes, car on a découvert récemment que ces trois entités étaient liées à la mutation du même gène CIAS1 (8,13, 19-21).

Ces trois syndromes peuvent maintenant être considérés comme une seule entité avec différents degrés de sévérité ; le FCU serait le plus modéré, le syndrome CINCA/NOMID le plus sévère, et le MWS la forme intermédiaire.

Le syndrome de *l'urticaire familial au froid* est, comme les deux autres syndromes, autosomique dominant. Il débute dans les six premiers mois de vie. Il est caractérisé par la survenue d'une urticaire quelques heures après l'exposition à une atmosphère froide, associée à des arthralgies, une conjonctivite inconstante et une fièvre modérée. Ont également été décrites une dysmorphie faciale, une aphtose. On n'y trouve ni oedème périorbitaire (TRAPS) ni lymphadénopathies (syndrome d'HyperIgD).

Le *syndrome de Muckle Wells* est défini par l'association d'une urticaire, une amylose essentiellement rénale ; et d'une surdité neurosensorielle. Des signes oculaires à type de conjonctivite, des arthrites, peuvent coexister lors des accès. Selon les familles, d'autres signes ont étés décrits : anomalies endocrines, hernies abdominales, aphtoses, dysmorphies.

Le syndrome CINCA est une de maladies inflammatoires les plus graves de l'enfant. Il associe des signes neurologiques, cutanés et articulaires. L'âge de début des troubles est très précoce puisqu'ils débutent dans les premiers jours ou dans les premières semaines de vie. Le caractère intermittent des signes a quasiment disparu.

L'atteinte cutanée se présente sous forme d'un érythème diffus de type urticarien mais non prurigineux d'apparition néonatale. L'atteinte neurologique est sous tendue par une méningite aseptique à polynucléaires neutrophiles. Elle est responsable de céphalées chroniques, de crises comitiales, de déficits centraux. Un retard mental apparaît progressivement pendant l'enfance. Il existe aussi une atteinte neurosensorielle oculaire, avec notamment une conjonctivite, une uvéite, une papillite et une atrophie optique, pouvant entraîner une cécité ; et une surdité neurosensorielle progressive. L'atteinte articulaire aboutit à une arthropathie grave dès l'enfance. Une hypertrophie de la rotule est des cartilages de conjugaison est caractéristique. Les épiphyses des os longs sont également touchées. Ces manifestations entraînent des déformations majeures des genoux en particulier (aspect pseudo-tumoral) et un retard de croissance.L'atteinte chromosomique en 1q44 code pour un gène appelé CIAS1 (cold induced autoinflammatory syndrome 1) exprimé dans les leucocytes circulants, codant pour une protéine appelée cryopyrine. La cryopyrine est composée :- d'un domaine pyrine,d'un domaine d'oligomérisation dépendante de la liaison de nucléotides NBS (nucleotid binding site),et d'un domaine riche en leucine LRR (leucin rich domain) éventuellement impliqué dans la reconnaissance d'agent pathogènes et qui présentent des similitudes avec la famille des Toll récepteurs. Ces trois domaines définissent une nouvelle famille de protéines appelées NALP/PYPAF/PAN (la cryopyrine est aussi appelée NALP 3 ou PYPAF 1). Les NALP protéines (NACHT, LRR, and PYD containing protein) ont été récemment identifiées comme des membres de la superfamille des CATER PILLER. CATERPILLER signifie CARD, Translocation Enhancer, R purine binding, Pyrine, LRR. Elles incluent une vingtaine de gènes de la cascade inflammatoire. Avant la description du groupe CATERPILLER, ce groupe avait été appelé NACHT (NAIP, CIITA, HET-E, and TP1) ou PYPAF (Pyrin containing Apaf -1 like proteins). Les protéines CATERPILLER sont caractérisées par des domaines NBD pour nucleotide binding domain et LRR pour leucine rich repeat. De structure similaires, elles ont été décrites comme interagissant dans les mécanismes de la réponse immune. La plupart ont un domaine pyrine.

Comme la pyrine, la cryopyrine est capable d'interagir via son domaine pyrine avec ASC. La cryopyrine, la protéine ASC et les caspases 1 et 5 sont intimement liées dans un ensemble moléculaire appelé l'inflammasome. La cryopyrine interagit avec ASC via son domaine pyrine. L'activation de la procaspsase 1 aboutit à la transformation de la pro-IL 1 en IL1 et en l'activation de NF kappa B.

Dans une cellule, les voies de l'inflammation peuvent passer par le récepteur du TNF alpha. L'activation du TNF alpha induit la dégradation et la phosphorylation de I kappa B en les deux sous parties de NF kappa B, la p50 et la p65. La p65 est phosphorylée et migre secondairement dans le noyau pour stimuler l'expression des gènes de la cascade inflammatoire. Le TNF alpha et les ligands reconnus par des Tolls récepteurs induisent l'expression de CIAS1 dans les monocytes. L'expression de CIAS1 mène à une inhibition du TNF alpha, qui ne peut donc plus transformer I kappa B et NF kappa B. CIAS1 inhibe également la translocation de la partie p65 de NF kappa B dans le noyau.

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L'inhibition du TNF alpha via CIAS1 est médiée par les domaines NBD et LRR. Toutes les mutations décrites siègent dans l'exon trois, et la plupart touchent le domaine NBS.

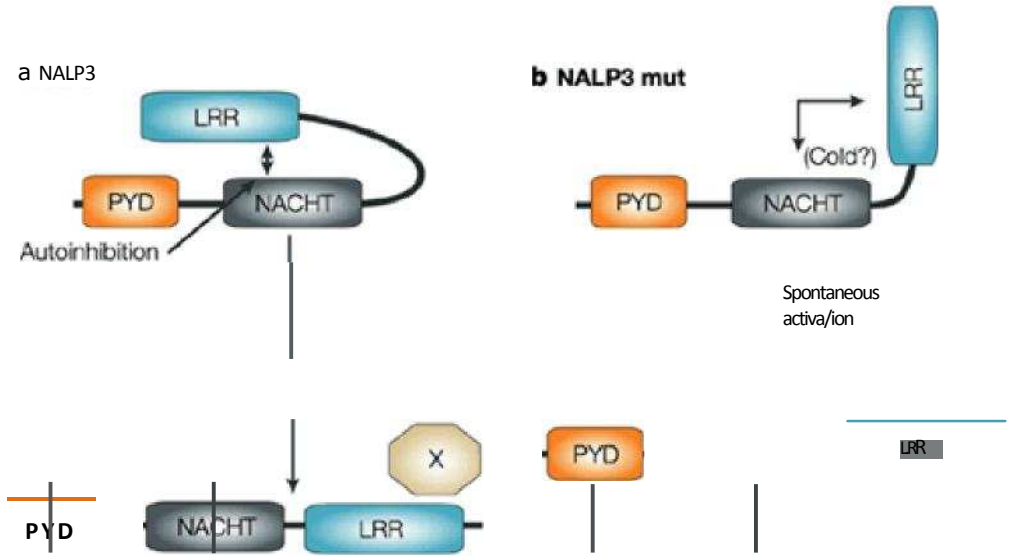

Figure 3 : mécanisme de CIAS1 (13)

Traitement :

Des réponses remarquables à l'anakinra ont étés décrites dans les MWS et les FCU. Malgré une amylose rénale s'exprimant par un syndrome néphrotique, le traitement a pu aboutir à une normalisation de la fonction rénale (12).

e) Le syndrome PAPA :

Le *syndrome PAPA* associe des destructions articulaires avec une atteinte cutanée sévère. PAPA est un acronyme pour pyogenic arthritis, pyoderma gangrenosum, acne. La transmission autosomique dominante est liée à des mutations de CD2BP1 (CD2 binding proteinl) également appelée proline serine threonine phosphatase interacting protein PSTPIP1. La physiopathologie du syndrome PAPA repose sur l'interaction de PSTPIP1 avec la pyrine. Les mutations A230T et E250Q qui ont été décrites dans la genèse du PAPA syndrome augmentent cette interaction.

f) Le syndrome de Blau

Le *syndrome de Blau* est une atteinte rare, autosomique dominante. Elle est caractérisée par une arthrite granulomateuse précoce, une uvéite, un rash et une camptodactylie.

Elle a été décrite initialement comme une forme de sarcoïdose pédiatrique sans jamais d'atteinte pulmonaire. Dans un second temps, des atteintes hépatiques, spléniques, des paires crâniennes, et une atteinte interstitielle rénale ont été décrites.

Physiopathologie :

Le gène de sensibilité pour le syndrome de Blau a récemment été identifié comme le gène CARD15/NOD2 qui était connu pour être le gène de susceptibilité de la maladie de Crohn.

CARD15/NOD2 code pour une protéine de 1040 acides aminés incluant deux domaines CARD, un domaine NBS et un domaine LRR. La protéine CARD 15 est exprimée par les monocytes et peut interagir via son domaine LRR pour activer NF kappa B.

Il est intéressant de noter que les mutations de LRR sont associées à la maladie de Crohn tandis que les mutations de NBS sont associées au syndrome de Blau (28,40).

	FMF	**HIDS**	**PAPA**	**MWS**	**FCAS**	**NOMID / CINCA**	**Blau Syndrome**	**TRAPS**
Mode de transmission	Autosomique récessif	Autosomique récessif	Autosomique dominant	Autosomique dominant	Autosomique dominant	Autosomique dominant	Autosomique dominant	Autosomique dominant
Gène	MEFV	MKV	CD2BP1/PSTPIP	CIAS1	CIAS1	CIAS	CARD15/NOD2	TNFRSF1A
Chromosome	16p13	12q24	15q24	1q44	1q44	1q44	16q12	12p13
Protéine en cause	Pyrine (marenostrine)	Mevalonate kinase	CD2BP1/PSTPIP	Cryopyrine	Cryopyrine	Cryopyrine	CARD15	TNF Receptor 1 (p55)
Atteinte cutanée	Pseudo-érésypèle	rash maculo-papuleux	Pyoderma gangrenosum, acne	Rash pseudo-urticarien	Rash pseudo-urticarien induit par le froid	Rash pseudo-urticarien	Rash granulomateux	Rash migrant dans le territoire des myalgies
Atteinte oculaire	rare	rare	Non rapportée	Conjonctivite, atrophie du nerf optique	Conjonctivite	Œdème papillaire, uvéite	Uvéite, ri docyclite	Conjonctivite avec oedème péri-orbitaire
Atteinte musculo-squelettique	Monoarthrite fréquente	Arthralgies occasionnelles oligoarthrites; rares myalgies	Arthrite stérile	Courbatures, arthralgies; arthrites	Arthralgies myalgies occasionnelles	Déformations épiphysaires	Arthrite granulomateuse	Sévères myalgies monoarthrite occasionnelle
Atteinte abdominale	Péritonite stérile-85%	Douleurs importantes	Néant	Parfois	Néant	Hépato-spléno-mégalie	Néant	Douleurs importantes
Eléments distinctifs	Pseudo-érésypèle	Lymph-adénopathies, hyperIgD,taux urinaire élevé de mevalonate pendant les accès	Inflammation destructrice et récurrente de la peau, des muscles et des articulations	Surdité neurosensortielle	Urticaire induit par le froid	Méningite aseptique chronique, surdité, arthropathies	Arthrites uvéites et rash granulomateux	Myalgies et rash migrateurs ; oedème périorbitaire

Tableau 12 : caractéristiques des syndromes auto-inflammatoires

Tous les syndromes auto-inflammatoires ne s'intègrent pas dans une histoire familiale. Il existe des mutations de novo et des formes sporadiques peuvent être décrites.

Fièvres médicamenteuses :

Les fièvres médicamenteuses sont consécutives à trois mécanismes : un effet pyrogène direct, une perturbation du centre hypothalamique de la thermorégulation, ou des mécanismes immuno-allergiques. Elles surviennent souvent sur un terrain atopique. La survenue est généralement précoce par rapport à l'introduction du médicament et on note une résolution de la fièvre en 1 à 3 jours après l'arrêt du médicament (sauf dans le cas du DRESS syndrome).

Les agents les plus fréquemment incriminés sont nombreux et de prescription courante : antibiotiques (bêta lactamines, macrolides, tétracyclines, sulfamides, isoniazide, rifampicine), psychotropes et neuroleptiques, AINS et aspirine, progestatifs, allopurinol, AVK, IEC, cordarone...

A part par sa présentation clinique se situe le DRESS syndrome que nous allons détailler.

Le DRESS syndrome :

Le DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) est une pathologie immuno-allergique décrite initialement, sous le nom de syndrome d'hypersensibilité, par Salzstein en 1959. D'emblée, il décrit des associations de ce syndrome avec des pseudo-lymphomes cutanés (5,26).

Ce terme se rapporte à un sévère syndrome d'idiosyncrasie,c'est-à-dire de susceptibilité personnelle innée et constitutionnelle. Ce syndrome associe typiquement un rash cutané exanthémateux et de la fièvre, souvent associé à une hépatite, des arthralgies, une polyadénopathie, et des anomalies hématologiques telles que l'hyperéosinophilie ou le syndrome mononucléosique.

Ce syndrome se développe après la prise de certains médicaments. Les agents antiépileptiques aromatiques (phénytoïne, carbamazépine et phénobarbital avec une réaction de 1/ 5000) et les sulfonamides (dapsone, sulfasalazine) sont les causes les plus fréquentes, mais d'autres médicaments ont étés incriminés, tels que la minocycline, les inhibiteurs de canaux calciques, la thalidomide, la mexiletine, la ranitidine, la D penicillamine,l'hydrochlorothiazide et l'amiloride, l'atenolol, les IEC, la cyclosporine, l'amitriptiline, et l'allopurinol. Le risque de développer un DRESS est cependant moindre avec ces traitements qu'avec les anticonvulsivants et les sulfonamides (38).

L'intervalle typique entre le début de la prise du traitement et le début des signes est de deux à six semaines, mais il existe des formes se déclenchant après plusieurs mois voire plusieurs années de traitement.

La fièvre et le rash sont les signes cliniques les plus fréquents, avec une prévalence de 87%. L'éruption cutanée est d'ordinaire indiscernable d'une éruption morbilliforme. La face, le haut du tronc et les extrémités supérieures sont les premières touchées, avec secondairement une atteinte des membres inférieurs. L'éruption maculopapuleuse peut devenir infiltrée et indurée. Un oedème de la face, souvent dans les régions périorbitaires, est évocatrice du diagnostic. L'éruption peut devenir purpurique, en particulier sur les jambes et lors de la guérison, une desquamation survient. Il existe une dermatose exfoliative dans 30 à 50% des cas.

La biopsie cutanée montre un infiltrat lymphocytaire dense et diffus, ou superficiel et périvasculaire. Des éosinophiles peuvent être retrouvés, mais ce n'est pas systématique. Les adénopathies (75%) sont fréquentes et le plus souvent liées à une hyperplasie lymphoïde bénigne.

La biopsie ganglionnaire retrouve à la fois une hyperplasie lymphoïde avec préservation de l'architecture du ganglion prélevé, ou un aspect de pseudo-lymphome avec oblitération de l'architecture normale du ganglion, qui est remplacée par un infiltrat polymorphe qui peut simuler un lymphome, avec des cellules atypiques, des zones de nécrose et d'oedème, avec des figures mitotiques mais sans cellule de Reed-Sternberg ou d'infraction capsulaire.

Des hépatites (51%), des néphrites interstitielles (11%), une hyperéosinophilie (30%) et des réactions mononucléosiques peuvent exister. L'atteinte du foie est la plus fréquente des atteintes viscérales. Une hépatomégalie peut être présente. Une hépatite avec une élévation isolée des transaminases est habituelle, mais une insuffisance hépato cellulaire peut survenir, grevant le pronostic. La biopsie du foie retrouve un infiltrat par des éosinophiles, ou des granulomes. Cette réaction s'accompagne d'une cholestase et de nécrose des hépatocytes. Dans les cas les plus graves, une nécrose massive ou disséminée explique l'insuffisance hépatocellulaire. L'hépatite peut persister et s'aggraver à distance de l'arrêt du traitement responsable, et peut mettre des mois à se normaliser.

L'hyperéosinophilie est probablement responsable de l'atteinte d'autres organes comme une néphrite interstitielle, des infiltrats pulmonaires, une myocardite à éosinophiles, une péricardite... L'aspect peut mimer un syndrome d'hyperéosinophilie idiopathique.

La physiopathologie est intéressante : les anticonvulsivants aromatiques (hydantoïne, carbamazépine et phénobarbital) sont susceptibles de donner les mêmes réactions ; Des réactions croisées sont d'ailleurs possibles entre ces agents. Tous ces traitements sont métabolisés par le biais du cytochrome p 450 en un métabolite commun. Ce métabolite est ensuite normalement détoxifié par l'epoxide hydrolase. Un déficit en cet enzyme conduit à l'accumulation du métabolite toxique, ce qui peut perturber les fonctions cellulaires et/ou stimuler le système immunitaire. Ce défaut de détoxification semble se transmettre par voie autosomique. Les

cellules des parents des patients ont un degré de sensibilité in vivo à ces toxiques intermédiaires entre le niveau des patients et celui des sujets contrôles.

Les mécanismes de la toxicité de ces médicaments et de leurs métabolites a été essentiellement étudiée au niveau du foie. La réponse immune est généralement associée avec une réponse immune CD4 et CD8. La destruction des hépatocytes est essentiellement achevée par les cellules T cytotoxiques. L'activité cytotoxique des cellules T cytotoxiques peut advenir par au moins deux mécanismes : dans la voie médiée par l'interaction perforine/granzyme, la perforine induit l'apoptose dans les cellules cibles. La voie Fas/Fas ligand induit elle l'apoptose par l'activation de la cascade des caspases (22, 31).

Le traitement le plus incriminé est essentiellement l'hydantoïne. Ce médicament induit une dépression du système immunitaire, et spécialement une diminution des lymphocytes T suppresseurs et une augmentation des T helpers, ce qui promeut la lymphoprolifération. La plupart des lymphomes malins suivant l'existence d'un pseudo-lymphome ont étés décrits avec ce médicament.

Une autre cause est le groupe des sulfonamides, en particulier la dapsone ou la sulfasalazine. Un phénotype d'acétylateur lent et une susceptibilité augmentée des lymphocytes in vitro aux métabolites hydroxylamine élève le risque de réaction d'hypersensibilité à la dapsone.

Parfois, les réactions immuno-allergiques ont lieu après de longues expositions à des médicaments. Cette longue période de latence suggère qu'un élément déclencheur extérieur interagit pour déclencher cette réaction. On a émis l'hypothèse que des réactivations des virus du groupe Herpès pouvaient aggraver ou déclencher des DRESS syndromes (37). Cette hypothèse est soutenue par :

- les réactions médicamenteuses plus sévères chez les patients atteints par le VIII,
- l'apparition de signes cutanés dans 95% à 100% des cas lors de la prise d'amoxicilline pendant une mononucléose infectieuse,
- des cas décrits dans la littérature de DRESS syndromes sévères survenant de façon contemporaine à la réactivation de HHV6. L'hypothèse que la réactivation de HHV6 pouvait interagir avec certaines voies de détoxification, comme celle du cytochrome p450, a été soulevée.

Des syndromes d'hypersensibilité ont étés décrits d'emblée en association avec des prolifération cellulaires mimant des lymphomes (pseudo-lymphomes)

- soit ganglionnaires,
- soit cutanés.

Parfois, les pseudo-lymphomes apparaissent dans le cadre d'un tableau clinique atténué.

Les lésions cutanées peuvent être solitaires ou multiples, localisées ou disséminées sous la forme de papules érythémateuses, de plaques ou de nodules pouvant parfois mimer un mycosis fungoides. Histologiquement, deux formes de pseudo-lymphomes peuvent être distinguées : les pseudo-lymphomes à cellules T et les pseudo-lymphomes à cellules B. Les pseudo-lymphomes à cellules T sont les plus proches cliniquement des mycosis fungoides. Par contraste, une atteinte nodulaire est plus fréquente dans les formes à cellules B.

Le DRESS syndrome peut être difficile à distinguer d'une vascularite, d'une maladie sérique, d'un lymphome malin. Peut-être parce que l'évolution est lente et le début tardif par rapport à l'introduction de la molécule, et en raisons des similitudes avec des pathologies infectieuses, le diagnostic est souvent retardé.

Après la phase aiguë où on évalue la mortalité à environ 10%, la guérison est le plus souvent totale, mais le rash et l'hépatite peuvent subsister plusieurs semaines. Un traitement par corticostéroïdes a été proposé, mais les études contrôlées à ce sujet manquent. La reprise du médicament responsable entraîne une récidive sévère.

L'apparition d'un véritable lymphome malin dans les suites de cet épisode est rare mais a été décrit. Dans la série de Saltzstein, un patient a développé un lymphome quatre ans après l'épisode allergique.

Bilan des fièvres récurrentes :

Au terme d'un bilan bien conduit, il persiste environ 10% de cas de fièvres récurrentes où l'étiologie n'est pas retrouvée. On peut alors discuter dans ces situations : soit un traitement anti-tuberculeux d'épreuve ;soit une corticothérapie dans l'hypothèse d'une connectivite.

Approach to the child with fever of unknown origin

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INTRODUCTION — Fever is a common presenting complaint in children, accounting for nearly one-third of pediatric outpatient visits in the United States [1]. The specific entity of "fever of unknown origin" (FUO), as opposed to "fever without a source" (FWS), has occupied a special place within infectious diseases since the first definition of and series about FUO by Petersdorf and Beeson in 1961 [2]. Although the original definition has been modified, the assessment of broad categories of illness (including infections, connective tissue disease, and malignancy) as a cause of FUO remains useful.

An approach to FUO in children will be reviewed here. Etiologies of pediatric FUO, FWS, and fever in unique host groups (eg, newborns, neutropenic children, or those with human immunodeficiency virus (HIV) infection) are discussed separately. (See "Etiologies of fever of unknown origin in children" and "Fever without a source in children 3 to 36 months of age".)

DEFINITIONS — The term FUO initially was reserved for adults with fever >38.4ºC (101.2ºF) on at least several measurements over three or more weeks without an established cause after at least one week of investigation in the hospital. This exacting definition probably was never rigorously applied in pediatrics.

We apply the following definitions for FUO and FWS:

- FUO — Children with fever >101ºF (38.3ºC) of at least eight days' duration, in whom no diagnosis is apparent after initial outpatient or hospital evaluation that includes a careful history and physical examination and initial laboratory assessment.
- FWS — Children with fever lasting for one week or less without adequate explanation after a careful history and thorough physical examination. (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Fever without a source in children 3 to 36 months of age".)

The above definition of FUO is a reasonable working definition for clinical purposes. However, an agreed-upon definition has not been used in published studies of FUO in children [3-11]. The required duration of fever for inclusion in various case series has ranged from five to seven days to three weeks [3-11]. Some series used different durations depending upon the setting (inpatient versus outpatient) [4,5]. Several made a distinction between FUO and "prolonged fever" [10,11].

FUO should be distinguished from FWS for three important reasons:

- The differential diagnoses and most frequent causes of each entity are distinct
- Children with FWS usually require immediate testing and evaluation, whereas those with FUO generally do not need an emergency assessment
- Expectant antibiotic therapy is not typically indicated in children with FUO, whereas treatment generally is recommended in a select group of infants with FWS

(See "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Fever without a source in children 3 to 36 months of age".)

ETIOLOGY — The number of infectious and noninfectious etiologies of FUO in children is extensive (table 1). FUO is usually caused by common disorders, often with an unusual presentation. This has been illustrated in several series of FUO in children, in which rare disorders (eg, Behçet syndrome, ichthyosis) are exceedingly uncommon [4-14]. (See "Etiologies of fever of unknown origin in children".)

Infectious diseases and connective tissue diseases are the most common etiologic categories of FUO in children; neoplastic disorders are less common and usually have manifestations other than fever [4-14].

In many cases, a definitive diagnosis is never established. In more recent series, there has been a trend toward an increasing proportion of undiagnosed cases [10,13,14]. Many of the classic FUO case series in children were published before the routine availability of the sophisticated diagnostic testing methods that are currently available [3-6,12]. With advances in diagnostic testing, children with diseases previously common in FUO series are now diagnosed earlier in their course of illness, leaving increasing numbers of children with difficult-to-diagnose conditions in FUO series [13-15].

DIAGNOSTIC APPROACH — Unless the child appears acutely ill, the evaluation for FUO usually begins as outpatient. If outpatient investigation fails to disclose a cause for the fever, admission to the hospital provides an opportunity to review the detailed history, physical examination, and available laboratory data, and to observe the child in a controlled setting.

Performing a detailed and thorough history and physical examination is the first and most important component of the diagnostic evaluation of the child with FUO. Incomplete histories, ignored physical findings, and failure to correctly interpret existing laboratory data delayed accurate diagnoses in a number of series of pediatric FUO cases [4-6].

The clinician must be prepared to repeat the clinical assessment on multiple occasions to reassess historical features or clinical findings that might have been missed previously. A patient or parent eventually may recall information that was omitted, forgotten, or deemed unimportant when the initial history was obtained. New physical findings can appear, and subtle abnormalities not originally appreciated can become apparent. In one of the pediatric FUO series, significant physical findings that were not present at the time of admission developed in more than 25 percent of children during hospitalization [4].

We suggest that some basic tests be performed in the initial evaluation of all children with FUO. Subsequent diagnostic testing is guided by "potential diagnostic clues" from the serial clinical assessments and initial laboratory and radiographic evaluation [16,17]. (See 'Diagnostic testing' below.)

HISTORY — FUO is usually caused by common disorders, often with an unusual presentation. Although it is important to ask questions related to uncommon diseases, an uncommon presentation of a common entity always should be entertained.

Fever — It is essential to obtain as much detail about the fever as possible. Important aspects include:

- The duration, height, and pattern; parents can mistake normal variations in body temperature (eg, temperature elevations after exercise or late in the afternoon) for febrile episodes.
- How was the fever assessed (eg, by touch, forehead strip, or measured with a thermometer; if measured with a thermometer, which type was used)? Rectal temperature is most accurate; however, in an older child, temperature recorded with an oral thermometer is usually adequate.
- Was the fever confirmed by someone other than the caregiver?
- Are there specific circumstances that precede the temperature elevation?
- Does the child appear ill or develop any signs or symptoms during the febrile episode? Absence of malaise or other generalized signs in a child with a history of high fevers can signal factitious fever.
- Whether and how quickly the fever responds to antipyretic drugs and whether other constitutional symptoms (eg, myalgias, headache, malaise, etc.) persist when the fever abates; the persistence of constitutional symptoms is more worrisome. Lack of response to nonsteroidal-antiinflammatory antipyretics may indicate a noninflammatory condition as the cause of FUO (eg, dysautonomia, ectodermal dysplasia, thalamic dysfunction, diabetes insipidus) [18].
- Is there associated sweating? Patients with fever, sweating, and heat intolerance may have hyperthyroidism, whereas those with fever, heat intolerance, and absence of sweating may have

ectodermal dysplasia. (See "Clinical manifestations and diagnosis of hyperthyroidism in children and adolescents" and "The genodermatoses", section on 'Ectodermal dysplasias'.)

Fever pattern — The pattern and duration of fever generally are not useful in making a specific diagnosis in children with FUO [4,6]. However, the fever pattern, such as that observed in cases of malaria, occasionally can be illuminating. It is best documented by asking the family to keep a fever diary.

- Intermittent — Intermittent fevers with a high spike and rapid defervescence (often termed a hectic or spiking fever) suggest pyogenic infection but also can occur in patients with tuberculosis, lymphoma, and juvenile idiopathic arthritis (JIA, formerly juvenile rheumatoid arthritis, or JRA). (See "Tuberculosis disease in children" and "Overview of Hodgkin lymphoma in children and adolescents" and "Systemic onset juvenile idiopathic arthritis: Clinical manifestations and diagnosis".)
- Remittent — Remittent fevers are characterized by fluctuating peaks and a baseline that does not return to normal; they can appear to be intermittent if antipyretic agents are administered. Remittent fevers are seen most commonly with viral infections but also may occur with bacterial infections (especially endocarditis), sarcoid, lymphoma, and atrial myxoma.
- Sustained — Sustained fevers persist with little or no fluctuation but can appear to be intermittent if antipyretic agents are administered. Typhoid fever, typhus, brucellosis, and many other infections characteristically follow this pattern. (See "Epidemiology, microbiology, clinical manifestations, and diagnosis of typhoid fever" and "Clinical manifestations, diagnosis, and treatment of brucellosis".)
- Relapsing — Relapsing fevers with periods during which patients are afebrile for one or more days between febrile episodes may be seen with malaria, rat-bite fever, Borrelia infection, and lymphoma. (See "Clinical manifestations of malaria" and "Rat bite fever" and "Clinical features and management of relapsing fever" and "Overview of Hodgkin lymphoma in children and adolescents".)
- Recurrent — Recurrent episodes of fever over periods of more than six months' duration suggest metabolic defects, central nervous system (CNS) dysregulation of temperature control, periodic disorders (such as cyclic neutropenia, hyperimmunoglobulin D syndrome, and deficiencies of selected interleukin receptor sites), and immunodeficiency states. (See "Etiologies of fever of unknown origin in children", section on 'Other causes'.)

Associated complaints — It is important to ask, and ask again, about past or current abnormalities or complaints. As examples:

- Red eyes that resolved spontaneously may suggest Kawasaki disease. (See "Kawasaki disease: Clinical features and diagnosis".)
- Nasal discharge may suggest sinusitis. (See "Acute bacterial sinusitis in children: Clinical features and diagnosis", section on 'Acute bacterial sinusitis (ABS)'.)
- Recurrent pharyngitis with ulcerations may suggest the periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA). (See "Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome)".)
- Gastrointestinal complaints may suggest Salmonellosis, an intraabdominal abscess, hepatosplenic cat scratch, or inflammatory bowel disease.
- Limb or bone pain may suggest leukemia, osteomyelitis, or infantile cortical hyperostosis. (See "Overview of the presentation and classification of acute lymphoblastic leukemia in children" and "Clinical features of hematogenous osteomyelitis in children" and "Differential diagnosis of the orthopedic manifestations of child abuse", section on 'Infantile cortical hyperostosis (Caffey disease)'.)

Exposures — It is important to ask specifically about the following exposures:

- Contact with infected or otherwise ill persons.
- Exposure to animals, including household pets, domestic animals in the community, and wild animals (table 2). (See "Zoonoses from cats" and "Zoonoses from dogs" and "Zoonoses from pets other than dogs and cats" and "Microbiology, epidemiology, clinical manifestations, and diagnosis of cat scratch disease".)
- Travel history (including place of residence), extending back to birth. A number of diseases acquired in endemic areas can reemerge years after departure (eg, histoplasmosis, coccidioidomycosis, blastomycosis, malaria). The travel history should include:

- The site(s) of travel
- Prophylactic medications and immunizations before travel
- Measures taken to prevent exposure to contaminated food and water
- Whether artifacts, rocks, or soil from other geographic areas were brought into the home
- Exposure to other persons with a recent history of travel

- Tick bites can be a clue to Rocky Mountain spotted fever, ehrlichiosis, tularemia, tick-borne relapsing fever, or Lyme disease. North American mosquitoes and some ticks carry a variety of arboviruses. (See appropriate topic reviews).
- Consumption of game meat, raw meat, or raw shellfish may be a clue to brucellosis, toxoplasmosis, tularemia, or hepatitis.
- A history of pica, specifically eating dirt, may be associated with diseases such as visceral larva migrans and toxoplasmosis.
- Exposure to medications (including prescription, topical, and nonprescription drugs) and nutritional supplements. (See "Drug fever".)
- History of surgical procedures; patients with a history of abdominal surgery have an increased risk of developing an intraabdominal abscess.

Ethnic or genetic background — Certain conditions associated with fever tend to occur among members of certain ethnic groups. As examples:

- Nephrogenic diabetes insipidus in Ulster Scots [19]. (See "Diagnosis of polyuria and diabetes insipidus".)
- Familial Mediterranean fever in those of Sephardic Jewish, Armenian, Turkish, and Arab descent. (See "Clinical manifestations and diagnosis of familial Mediterranean fever".)
- Familial dysautonomia in those of Ashkenazi Jewish decent. (See "Hereditary sensory autonomic neuropathies", section on 'HSAN3 (Familial dysautonomia)'.)

EXAMINATION

General assessment — The patient with FUO should be evaluated while febrile. This is necessary to assess how ill the patient appears, to determine the effect of fever on sweating and the heart and respiratory rates, and to document any accompanying symptoms (eg, malaise or myalgias) or signs. The rash of JIA is characteristically evanescent and may be present only during fever (picture 1).

The physical examination should begin with a general assessment of the patient's appearance, activity, vital signs, and growth parameters.

Although it is important to evaluate the patient for weight loss, this is a nonspecific finding. Certain chronic diseases, such as inflammatory bowel disease (IBD), or endocrine abnormalities, such as pituitary gland impairment related to an intracranial lesion, characteristically result in disproportionate deceleration of linear growth or short stature. (See "Causes of short stature", section on 'Diseases that may cause growth failure and short stature'.)

Certain findings on physical examination help to signal a variety of conditions, as those described below.

Skin and scalp — Skin lesions, abnormalities, and rashes are a component of a number of conditions that may cause FUO; if skin findings are not present initially, the skin should be examined repeatedly. Examples include:

- The absence of sweat during fever may suggest dehydration related to diabetes insipidus, ectodermal dysplasia, or familial dysautonomia.
- Petechiae in infectious endocarditis (IE), bacteremia, and viral and rickettsial infections.
- The rash of Rocky Mountain spotted fever, which typically begins on the ankles and wrists and spreads to the palms and soles and centrally. (picture 2).
- Papular lesions in cat scratch disease (picture 3).
- Eschar in tularemia (picture 4).

- Erythema migrans in tick-borne diseases: Lyme disease (picture 5A-B) and southern tick-associated rash illness (picture 6).
- The macular salmon-pink rash of JIA (picture 1).
- Malar erythema in systemic lupus erythematosus (SLE) (picture 7).
- Palpable purpuric lesions in vasculitis (eg, polyarteritis nodosa) (picture 8).
- Urticarial and/or serpiginous macular rash and band of erythema at the lateral aspects of the hands and feet (picture 9) in serum sickness.
- Erythema nodosum (picture 10) may be present in children with infection, JIA, SLE, malignancy, and inflammatory bowel disease. (See "Erythema nodosum".)
- A seborrheic rash can indicate histiocytosis. (See "Langerhans cell histiocytosis", section on 'Skin and oral mucosa'.)
- Sparse hair, particularly of the eyebrows and eyelashes, and hypohidrosis may suggest anhidrotic ectodermal dysplasia. (See "The genodermatoses", section on 'Ectodermal dysplasias'.)
- Patients with familial dysautonomia may have blotchy skin and multiple areas of skin trauma. (See "Hereditary sensory autonomic neuropathies", section on 'HSAN3 (Familial dysautonomia)'.)

Eyes — The eye examination may provide a number of potential diagnostic clues, including:

- Palpebral conjunctivitis: Infectious mononucleosis, Newcastle disease (a viral infection associated with exposure to chickens or other birds).
- Bulbar conjunctivitis: Leptospirosis, Kawasaki disease (picture 11).
- Phlyctenular conjunctivitis (with small, white, elevated lesions): Tuberculosis.
- Ischemic retinopathy with hemorrhages and retinal detachment, ischemic optic neuropathy: Polyarteritis nodosa [20,21].
- Absence of the pupillary constrictor response: Hypothalamic or autonomic dysfunction.
- Absent tears and corneal reflexes: Familial dysautonomia (Riley-Day syndrome).
- Abnormal funduscopic examination: Miliary TB (choroid tubercles) (picture 12), toxoplasmosis (raised yellow-white, cottony lesions in a nonvascular distribution) (picture 13), vasculitis (picture 14).

Sinuses — The sinuses should be palpated in patients with purulent or persistent nasal discharge; tenderness may suggest a diagnosis of sinusitis.

Oropharynx — Abnormalities of dentition and other lesions in the oropharynx may provide important clues to the underlying cause of fever. As examples:

- Pharyngeal hyperemia without exudate occasionally can be the only sign of infectious mononucleosis caused by EBV or CMV, toxoplasmosis, tularemia, or leptospirosis.
- Dental abscess and other oral or facial infections can cause persistent fever [22-25]. Oral infections also can be associated with other infections (eg, sinusitis, brain abscess, mediastinal abscess).
- Anomalous dentition (hypodontia, adontia, or conical "peg teeth") is a characteristic of anhidrotic ectodermal dysplasia. (See "The genodermatoses", section on 'Ectodermal dysplasias'.)
- A smooth tongue that lacks fungiform papillae or excessive salivation may suggest familial dysautonomia. (See "Hereditary sensory autonomic neuropathies", section on 'HSAN3 (Familial dysautonomia)'.)
- Patients with leukemia or Langerhans cell histiocytosis can have gingival hypertrophy or inflammation and loosening or loss of teeth. (See "Overview of the presentation and classification of acute lymphoblastic leukemia in children" and "Langerhans cell histiocytosis", section on 'Skin and oral mucosa'.)

Lymph nodes — May be enlarged and tender to palpation in a number of conditions, including Kikuchi-Fujimoto disease. (See "Causes of peripheral lymphadenopathy in children", section on 'Overview'.)

Chest — Examination of the chest may reveal findings consistent with pneumonia. The presence of a cardiac murmur, especially one of new onset, may suggest infective endocarditis. (See "Clinical features and diagnosis of community-acquired pneumonia in children" and "Infective endocarditis in children".)

Abdomen — Hepatic or splenic enlargement is common in infections of the reticuloendothelial system (salmonellosis, brucellosis, etc.), cat scratch disease, infective endocarditis, malaria, and many others. Tenderness on palpation of the liver edge may be noted in patients with liver abscess or cat scratch disease [26].

Musculoskeletal — The bones and muscles should be palpated for tenderness.

- Tenderness over a bone can indicate the presence of osteomyelitis, malignant invasion of the bone marrow, or infantile cortical hyperostosis. (See "Clinical features of hematogenous osteomyelitis in children" and "Overview of the presentation and classification of acute lymphoblastic leukemia in children" and "Differential diagnosis of the orthopedic manifestations of child abuse", section on 'Infantile cortical hyperostosis (Caffey disease)'.)
- Muscle tenderness can be found in trichinellosis, various arboviral infections, dermatomyositis, or polyarteritis. Tenderness over the trapezius muscle may indicate subdiaphragmatic abscess [12]. (See "Trichinellosis" and "Pathogenesis and clinical manifestations of juvenile dermatomyositis and polymyositis" and "Clinical manifestations and diagnosis of polyarteritis nodosa".)
- Hyperactive deep tendon reflexes may suggest hyperthyroidism. (See "Clinical manifestations and diagnosis of hyperthyroidism in children and adolescents".)
- Hypoactive deep tendon reflexes may suggest familial dysautonomia. (See "Hereditary sensory autonomic neuropathies", section on 'HSAN3 (Familial dysautonomia)'.)

Genitourinary — Patients with FUO should have a careful rectal, external genitalia, and pelvic examination (for sexually active female adolescents). The rectal examination is performed to evaluate the patient for perirectal tenderness or a mass, which can indicate a pelvic abscess or tumor. Stool should be examined for occult blood.

DIAGNOSTIC TESTING — The laboratory and imaging evaluations for FUO should be directed toward the likely causes of fever based upon the patient's age, duration of fever, and findings from the history and physical examination. In a review of 40 children with FUO referred to a pediatric rheumatology clinic (presumably after the more common causes of FUO had been ruled out), results of laboratory, radiologic, and pathologic studies were occasionally abnormal, but none of the tests resulted in a specific diagnosis [27].

The tempo of the evaluation is dictated by the appearance of the patient. The pace should be rapid if the child appears severely ill. It can be more deliberate if the child is less ill appearing. Sometimes the fever resolves without explanation before invasive diagnostic testing is undertaken.

Initial tests — We recommend the following tests for all children with FUO:

- Complete blood count (CBC) and careful examination of the peripheral smear
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Aerobic blood cultures
- Urinalysis and urine culture
- Chest radiograph
- Tuberculin skin testing
- Serum electrolytes, blood urea nitrogen (BUN), creatinine, and hepatic enzymes
- HIV serology

Additional tests may be indicated depending upon the presence of clues from the history, examination, or initial tests. (See 'Additional tests' below.)

- CBC, differential, and smear — The CBC and smear are to evaluate the child for anemia and thrombocytosis or thrombocytopenia. Anemia may be a clue to malaria, infective endocarditis, IBD, SLE, or tuberculosis [28]. Thrombocytosis is a nonspecific acute phase reactant, but it can be a clue to Kawasaki disease. (See "Kawasaki disease: Clinical features and diagnosis".)

  The total white blood cell count (WBC) and the differential generally are less helpful, although children with >10,000 polymorphonuclear leukocytes (PMN) or 500 nonsegmented neutrophils/mm3 had a greater risk of severe bacterial infection in some series [29,30]. If atypical lymphocytes are present, a viral infection is likely; bizarre or immature forms should prompt further evaluation for leukemia. (See "Overview of the presentation and classification of acute lymphoblastic leukemia in children".)

Eosinophilia may be a clue to parasitic, fungal, neoplastic, allergic, or immunodeficiency disorders. (See "Approach to the patient with eosinophilia" and "Drug fever".)

- ESR and CRP — The ESR and CRP are nonspecific acute phase reactants but serve as general indicators of inflammation. An elevated ESR or CRP makes factitious fever less likely. Following the course of an elevated ESR or CRP assists in monitoring disease progress. A normal ESR or CRP can slow the pace of more invasive investigation. However, ESR or CRP may be normal in noninflammatory conditions associated with FUO (eg, dysautonomia, ectodermal dysplasia, thalamic dysfunction, diabetes insipidus, drug fever) [18]. The ESR also may be lowered artifactually in conditions involving consumption of fibrinogen (such as disseminated intravascular coagulopathy), and may be raised in non-inflammatory disorders characterized by hypergammaglobulinemia.
- Blood cultures — Routine blood cultures should be obtained from all patients. Several sets of blood cultures should be obtained over 24 hours in patients in whom infective endocarditis is being considered. (See "Infective endocarditis in children".)

  The use of special media or environmental conditions or holding blood cultures in the laboratory for a longer-than-normal period of incubation is valuable in select cases. These techniques can facilitate the isolation of anaerobes, Brucella, Leptospira, and Spirillum.

- Urinalysis and urine culture — Urinalysis and urine culture are important diagnostic tests; UTI is among the most frequent causes of FUO in children [8,10,11]. In one series, the two most frequent laboratory errors were failure to perform a urinalysis and failure to adequately pursue the finding of pyuria [5]. Sterile pyuria can be a clue to Kawasaki disease or genitourinary tuberculosis. (See "Kawasaki disease: Clinical features and diagnosis" and "Renal disease in tuberculosis".)
- Chest radiograph — Patients with FUO should have a chest radiograph to evaluate for infiltrates and lymphadenopathy.
- PPD — All patients should have an intradermal intermediate-strength purified protein derivative (PPD) tuberculin skin test. Control skin testing is of limited value and is not recommended by most experts since patients with TB may have a positive control and negative PPD [31-34].
- Serum electrolytes, blood urea nitrogen (BUN), creatinine, and hepatic enzymes — Serum electrolytes, blood urea nitrogen (BUN), creatinine, and hepatic enzymes are obtained to evaluate renal and/or hepatic involvement. Hypernatremia may suggest diabetes insipidus; elevated hepatic enzymes may be a clue to a viral infection without distinctive features (eg, Epstein-Barr virus, cytomegalovirus), or brucellosis.
- HIV serology — HIV serology is suggested since the manifestations of primary HIV infection can be highly variable.

Additional tests — A number of other tests may be indicated in patients with clues from the history or physical, or abnormalities on general tests described above.

Laboratory tests

- Stool studies — Stool cultures or examination for ova and parasites may be warranted in patients with loose stools or recent travel.
- Bone marrow — Bone marrow examination in children is most useful in diagnosing cancer (especially leukemia), histiocytic disorders, and hemophagocytic disease [35]. It is not generally helpful in identifying infection.

  In one review of 414 bone marrow examinations for the evaluation of FUO in children, an organism (Salmonella group D) was recovered from the bone marrow but no other site in only one case [36]. By contrast, bone marrow results established noninfectious diagnoses in 8 percent of cases, including malignancy (6.7 percent), hemophagocytic syndromes (0.7 percent), histiocytosis (0.5 percent), and hypoplastic anemia (0.2 percent). Most of these disorders were suspected from clinical clues before the bone marrow examination was performed.

- Serologies — We suggest a targeted approach to serologic studies in children with FUO. As discussed above, we recommend HIV serology for all children with FUO since primary HIV has many

manifestations. Serologic testing for syphilis should be performed in neonates, young infants, and adolescents with FUO. Other serologies that may be warranted, depending upon the case, include brucellosis, tularemia, EBV, CMV, toxoplasmosis, bartonellosis, and certain fungal infections.

Serologies also can be useful for some parasitic infections such as extraintestinal amebiasis or strongyloidiasis and in other viral infections, such as lymphocytic choriomeningitis virus. Serology cannot be applied to most enteroviruses since there are too many different serotypes for general screening.

- Serum antinuclear antibody — Serum antinuclear antibody should be obtained for children older than five years of age with a strong family history of rheumatologic disease. A positive antinuclear antibody test suggests the presence of an underlying connective tissue disorder, particularly systemic lupus erythematosus [37]. (See "Measurement and clinical significance of antinuclear antibodies", section on 'Diseases associated with a positive ANA'.)
- Immunoglobulins — Serum concentrations of IgG, IgA, and IgM should be measured in children with evidence of recurrent or persistent infection and in those with persistent fever and a negative initial evaluation [12]. Low concentrations may indicate an immunodeficiency. Elevated levels also can be a clue, suggesting deficiency in another arm of the immune system, chronic infection, or an autoimmune disorder. (See "Approach to the child with recurrent infections" and "Primary humoral immune deficiencies: An overview", section on 'Hyperimmunoglobulin M syndromes'.)

  IgE levels are unlikely to be helpful unless there is evidence of allergy or infection, suggesting the hyperimmunoglobin E syndrome (eg, eosinophilia). (See "Hyperimmunoglobulin E syndrome".)

  Serum IgD levels should be obtained in patients with periodic or intermittent fever. Specific molecular genetic tests for other periodic disorders are available but should probably be obtained only after consultation with an expert in these conditions. (See "Hyperimmunoglobulin-D syndrome: Clinical manifestations and diagnosis" and "Periodic fever syndromes and other autoinflammatory diseases: An overview".)

- Molecular testing — In certain cases, molecular testing (eg, polymerase chain reaction) can be useful. Examples include EBV, CMV, parvovirus, and bartonella. (See appropriate topic reviews).

Imaging — One of the most difficult decisions is when to pursue additional imaging in patients with FUO. Diagnostic imaging of the nasal sinuses, mastoids, and gastrointestinal (GI) tract should be performed initially only for specific indications, but may be warranted in children in whom FUO persists without explanation for a long period.

- Abdominal imaging — Children with persistent fever, elevated ESR or CRP, anorexia, and weight loss should have studies to exclude inflammatory bowel disease, particularly if they also have abdominal complaints with or without anemia. However, imaging of the GI tract also should be pursued eventually in children whose fevers persist without other explanation and may be caused by conditions such as psoas abscess or cat scratch disease. Ultrasonography, computed tomographic (CT) scanning, and magnetic resonance imaging (MRI) can be useful in evaluating the abdomen [38]. These tests can detect abscesses, tumors, and lymphadenopathy.
- CNS imaging — Imaging of the CNS with or without an electroencephalogram generally is not helpful in the evaluation of children with FUO.
- WBC scans — Gallium and indium-111-labeled WBC scanning can highlight inflammatory lesions and tumors and provide noninvasive screening of the entire body [39]. However, these tests are not diagnostic, and follow-up with other imaging studies is required. One group found that radionuclide scans seldom revealed an unsuspected diagnosis in children with FUO [37]. Another found that gallium scanning can be helpful when there is suspicion of localized infection but is unlikely to be helpful in those with only systemic signs [40].
- Other imaging techniques — A number of other imaging techniques, including radiographic bone survey, technetium bone scan, and liver-spleen scan can be employed in selected cases when a thorough evaluation has failed to reveal the cause of FUO and suspicion for a source that could be revealed by these tests exists.
- PET scans — Positron emission tomography (PET) scanning is another technique that may be helpful in patients with persistent FUO who remain without a diagnosis after initial evaluation. In a review of

prospective studies, (18)F-FDG PET contributed to the diagnosis in 25 to 69 percent of cases of FUO [41]. (18)F-FDG PET was more sensitive than Ga-citrate SPECT in detecting tumors, infection, and inflammation.

Studies of PET scans in the evaluation of FUO in children are limited. One group studied PET in 11 children with FUO awaiting liver transplant [42]. The scans were positive in five, all of whom had positive bacterial cultures and/or histologic evidence of infection in the excised liver; other scanning procedures in these children had been negative. PET scans were negative in the other six children, none of whom had evidence of infection in the liver at the time of transplant.

- Immunoscintigraphy — Immunoscintigraphy is another technique that may be helpful in certain patients with persistent FUO who remain without a diagnosis after initial evaluation. In 30 neonates and infants with FUO, immunoscintigraphy with labeled antigranulocyte antibody had a sensitivity and specificity of 72 and 95 percent, respectively, for detection of infection (as verified by conventional radiography, MRI, CT, biopsy, blood culture, and clinical follow-up) [43].

Other evaluations

- Electrocardiography and echocardiography should be obtained in patients with positive blood cultures and suspicion for infective endocarditis. (See "Infective endocarditis in children".)
- Ophthalmologic examination by slit lamp is useful in some patients with FUO to evaluate the presence of uveitis or leukemic infiltration.
- Biopsy (eg, of lymph nodes or liver) should be reserved for children with evidence of involvement of specific organs.
- Sophisticated abdominal imaging procedures largely have eliminated the need for exploratory laparoscopy or laparotomy in the evaluation of children with FUO.

EMPIRICAL TREATMENT — Empirical treatment with antiinflammatory medications or antibiotics generally should be avoided as diagnostic measures in children with FUO. Exceptions include nonsteroidal agents in children with presumed JIA and antituberculous drugs in critically ill children with possible disseminated TB.

Antiinflammatory drugs do not help to distinguish fevers of infections from those of noninfectious causes. Empirical trials of broad-spectrum antibiotics can mask or delay the diagnosis of important infections, such as meningitis, parameningeal infection, infectious endocarditis, or osteomyelitis. Use of empirical antibiotics also can hamper the ability to isolate an organism from the blood or a specific site if further culturing is warranted as the evaluation proceeds.

OUTCOME — In contrast to adults, most children with FUO have treatable or self-limited diseases. The fever resolves over time in most cases, and a specific diagnosis eventually can be made in others [8,9,12,44].

Despite this fact, the overall prognosis is far from benign. In two series from the 1970s, mortality was 9 percent in one group of 100 children with FUO and 6 percent in another group of 54 children [4,6]. In more recent series, mortality is less frequent [8,9].

Curiously, the prognosis may be better when a diagnosis cannot be established after extensive evaluation [5,27,44]. Of those without a definitive diagnosis, many appear to do well, although episodes of fever may recur [5,44].

In long-term follow-up (median 3.5 years, range 1.2 to 5.3 years) of 19 children with FUO for at least two weeks and in whom no diagnosis was established, 16 of 19 (82 percent) were afebrile and completely well [44]. Two patients were subsequently diagnosed with JIA, one shortly after discharge and one 1.5 years later. One child, who had presented with abdominal pain and fever, had two episodes of intussusception (8 and 14 months after discharge), and the authors speculate that her initial episode might have been intussusception that spontaneously reduced.

Among 40 children who were referred for pediatric rheumatology evaluation with FUO of at least one month's duration and in whom no diagnosis was established, 37 were available for follow-up at a mean of 60.5 months

[27]. Two children developed inflammatory bowel disease IBD (one 7 months and one 3.5 years after initial evaluation); in both cases, fever resolved after initiation of appropriate therapy for IBD.

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: Fever in children (The Basics)")
- Beyond the Basics topics (see "Patient information: Fever in children")

SUMMARY AND RECOMMENDATIONS

- The diagnosis of fever of unknown origin (FUO) should be reserved for children with fever of at least eight days' duration in whom no diagnosis is apparent after initial evaluation either in the hospital or as an outpatient. (See 'Definitions' above.)
- Infections are the most common causes of FUO in children, followed by connective tissue disorders and neoplasms. However, in many cases, a definitive diagnosis is never established. (See 'Etiology' above.)
- A careful history and detailed physical examination are essential for all patients. These should be repeated on several occasions. (See 'Diagnostic approach' above.)
- The history should include details about the fever, associated complaints, and exposures (eg, to ill contacts, animals, insects, travel, drugs). (See 'History' above.)
- The patient should be examined while febrile. Important aspects of the examination include vital signs, the skin, scalp, eyes, sinuses, oropharynx, chest, abdominal, and musculoskeletal and genitourinary systems. (See 'Examination' above.)
- We suggest the following tests as part of the initial evaluation (see 'Initial tests' above):

- Complete blood count (CBC) and peripheral smear
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Blood cultures
- Urinalysis and urine culture
- Chest radiograph
- Tuberculin skin testing
- Serum electrolytes, blood urea nitrogen (BUN), creatinine, and hepatic enzymes
- HIV serology

- Additional tests and imaging studies should be based upon the findings of the history, examination, and initial tests. Diagnostic imaging of the nasal sinuses, mastoids, and gastrointestinal tract may be warranted eventually in children in whom FUO persists without explanation. (See 'Additional tests' above and 'Other evaluations' above.)
- Empiric treatment with antiinflammatory medications or antibiotics generally should be avoided as diagnostic measures in children with FUO. (See 'Empirical treatment' above.)

Strategies for the evaluation of fever in neonates and infants

(less than three months of age)

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INTRODUCTION — Fever is a prominent symptom of many different disease processes. Neonates and young infants may manifest fever as the only sign of significant underlying infection. Clinically distinguishing those with a serious febrile illness from those who are mildly ill may be difficult [1]. This has led to an aggressive approach to fever in this age group, usually including diagnostic tests, empiric antibiotics and, often, hospital admission.

A systematic approach to evaluating infants with fever without a source in this age group would ideally identify the patient with a serious bacterial illness (SBI) and minimize the testing and treatment of the patient with a mild illness. Several strategies for identifying the infant with fever who has an SBI have been proposed and tested. The strengths and limitations of these protocols, as well as the utilization of proposed guidelines are discussed here.

The definition, immunologic vulnerability, and etiology of fever in infants less than three months of age, as well as the evaluation and management of fever in these patients, are discussed elsewhere. (See "Definition and etiology of fever in neonates and infants (less than three months of age)" and "Evaluation and management of fever in the neonate and young infant (less than three months of age)".)

TRADITIONAL STRATEGIES — Several studies have attempted to identify patients who can be managed safely as outpatients with or without empiric antibiotic treatment [2]. There is some variation among them regarding inclusion criteria, inpatient or outpatient population, and whether or not antibiotics were given expectantly. This has led to confusion in the literature and a lack of consensus regarding the optimal approach to young infants with fever. Furthermore, even when guidelines have been proposed, they have not been consistently followed by many practitioners in the community [3-5]. (See 'Problems with these approaches' below.)

Nevertheless, these studies established the safety of treating a select population of young infants as outpatients. The sum of these studies suggests that the incidence of serious bacterial infection (SBI) among infants categorized as low risk after a full evaluation is 2.2 percent (range, 0 to 6.3 percent) [2]. When limited to studies that prospectively identified infants at low risk of SBI (figure 1) and performed outpatient observation with no antibiotics, the frequency of SBI varied from 0.5 to 1.1 percent in studies that either did or did not include lumbar puncture as part of the initial evaluation, respectively [6]. (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)", section on 'Evaluation and management'.)

Data from some of the largest studies led to the development of the "Boston," "Rochester," and "Philadelphia" criteria for identifying young infants with fever who are at low risk of SBI [7-10].

Boston protocol — The Boston group prospectively evaluated 503 28- to 89-day-old infants with rectal temperature greater than 38ºC (100.4ºF) who met the following criteria and were managed as outpatients [9]:

- No immunizations or antimicrobials within the preceding 48 hours
- No evidence of dehydration, ear, soft tissue, or bone infection
- Overall well appearance
- Caretaker available by telephone

The laboratory criteria defining low-risk patients included:

- Peripheral white blood cell (WBC) count less than 20,000/microL
- CSF with WBC <10/microL
- UA <10 WBC per high-powered field
- No infiltrate on chest radiograph if one was obtained

Infants in the study group received 50 mg/kg ceftriaxone intramuscularly and were sent home with scheduled follow-up visit 24 hours later.

The categorization of infants with a WBC count between 15,000 and 20,000/microL as low risk was more liberal than in other studies, and 27 patients (5.4 percent) had an SBI identified during follow-up. Nevertheless, there were no adverse outcomes; all infants with SBIs received an appropriate course of antimicrobial therapy and were well at follow-up.

Philadelphia protocol — Another group described an eight-year experience with 747 infants 29- to 60-days of age with a rectal temperature ≥38.2ºC (100.8ºF) [8]. Low-risk criteria included patients who were well-appearing with:

- WBC <15,000/microL
- Band-neutrophil ratio <0.2
- UA <10 WBC/hpf and a negative urine Gram stain
- CSF <8 WBC/microL and a negative CSF Gram stain
- Chest radiograph lacking an infiltrate if one was obtained
- Stool without blood and few or no WBCs on the smear in infants with diarrhea

All high-risk patients were hospitalized and treated with empiric antibiotics. Low-risk patients (19 percent of the study population) were discharged if follow-up was assured within 24 hours. In contrast to the Boston group, low-risk patients were not treated with empiric antibiotics.

The sensitivity for identifying patients with SBI was 98 percent (95% CI 92-100 percent); the specificity was 42 percent (95% CI 38-46 percent); the positive predictive value was 14 percent (95% CI 11-17 percent); and the negative predictive value was 99.7 percent (95% CI 98-100 percent), suggesting that these criteria did not miss many infants with SBI. However, many well infants underwent excessive laboratory testing, and many were managed as inpatients.

Rochester protocol — Another group attempted to identify low-risk febrile infants (defined as a rectal temperature greater than or equal to 38.0ºC or 100.4ºF) younger than 60 days [10]. This schema utilized the following criteria:

- ≥37 weeks gestation, and hospitalized no longer than the mother
- Infant was previously healthy
- Infant was well-appearing, with no ear, soft tissue, or bone infections

Laboratory criteria were as follows:

- WBC 5,000 to 15,000/microL with an absolute band count <1,500/microL
- Urinalysis with <10 WBC/hpf and no bacteria seen
- Stool with <5 WBC/hpf if obtained

High-risk infants were hospitalized with empiric antibiotics, and low-risk patients were sent home without antibiotics but with reliable follow-up.

Of the 931 well-appearing infants, 437 (47 percent) were classified as low risk. Only five low-risk infants had an SBI with a negative predictive value of 98.9 percent (95% CI 97-100 percent). Although there was no consistent empiric treatment with antibiotics, there were no adverse outcomes, lending support to the consideration of less aggressive therapy in low-risk infants [11].

Limitations in neonates — Studies that have assessed the applicability of the various strategies to neonates ages 1 to 28 days have found an increased number of SBIs missed in this age group and high prevalence of SBI when compared with infants one to three months of age [12-16]. As an example, one study from an urban pediatric emergency department evaluated 254 neonates ages 3 to 28 days of age with a temperature of 38ºC or higher, 32 of whom had an SBI [14]. When the Philadelphia criteria were applied to all 254 neonates, 109 (43 percent) were identified as low risk, five of whom actually had an SBI (two with bacteremia, two with bacterial urinary tract infection, and one with bacterial gastroenteritis). These findings suggest that neonates should be considered high risk, and a complete sepsis evaluation with hospital admission are warranted regardless of clinical picture and laboratory results.

CLINICAL GUIDELINES — In addition to the protocols described above, a number of groups have developed clinical guidelines in an effort to unify the approach to febrile young infants. However, like the protocols, the guidelines suffer from lack of uniformity, extensive laboratory testing, and lack of compliance in the community. (See 'Problems with these approaches' below.)

Expert panel — In 1993, an expert panel developed guidelines for the approach to infants and children 36 months of age and younger with fever without a source [17]. They were published simultaneously in the journals, Pediatrics and Annals of Emergency Medicine, but not endorsed by either the American Academy of Pediatrics or the American College of Emergency Physicians. These guidelines were updated in 2000. Recommendations were made for infants 28 to 90 days of age, although some of the studies included infants only up to 60 days (figure 1) [6]. (See 'Problems with these approaches' below.)

American College of Emergency Physicians — A clinical policy regarding children under three years presenting to the emergency department with fever was published in 2003 [18].

The policy is similar to the previous guidelines and emphasizes the following key points:

- Febrile infants 1 to 28 days of age are distinguished from older children regarding the possibility of serious bacterial infection (SBI).
- A chest radiograph is indicated in children less than three months with evidence of acute respiratory illness.
- A urinary tract infection (UTI) is an important source of fever for all children less than one year of age and for girls under two years.
- A negative urine dipstick or urinalysis does not exclude a UTI in neonates and young infants under two years of age. If a UTI is suspected, a culture should be sent.

The accompanying editorial is supportive of the policy, adding that empiric treatment with acyclovir pending PCR results for herpes simplex virus should be considered in some patients less than 28 days of age [19]. The author also suggests that children who are treated with antibiotics should have CSF obtained for culture. (See "Neonatal herpes simplex virus infection: Management and prevention".)

PROBLEMS WITH THESE APPROACHES — Studies of patients evaluated and treated according to the protocols and guidelines described above have established the safety of treating well-appearing infants, who have been carefully screened with laboratory testing, as outpatients. However, each of the strategies studied has its limitations. In addition, these strategies have not been uniformly utilized in community settings.

Limitations of protocols — Criticism of these strategies for identifying low-risk infants and sending them home with follow-up, either with or without a dose of ceftriaxone, include the following:

- While the Philadelphia and Rochester protocols have been promoted because of their high negative predictive value (ability to remove patients with SBI from the low-risk group), each suffers from a relatively low positive predictive value (14 and 12 percent, respectively), attributable to the large numbers of patients considered high risk and therefore hospitalized for antibiotics [8,10].
- All of these approaches require extensive laboratory testing, increasing both patient discomfort and expense.
- The Boston protocol results in the administration of broad-spectrum antibiotics to a number of infants who do not have SBIs, unnecessarily exposing them to the risks of parenteral antibiotics, although only

for one to two doses. The effect of the use of broad-spectrum antibiotics on the development of antimicrobial resistance also must be considered.

- While these approaches generally have been applied to infants up to the age of three months, there are no data to suggest that the difference between 60 days and 90 days is clinically important. These arbitrary age categories represent the inclusion criteria of various study cohorts.
- The studies on which these approaches were based generally were conducted in urban emergency departments. It is not clear how the results apply to community primary care physicians.

Utilization of guidelines — Several studies suggest that the promoted guidelines have not been widely adopted in community settings [5,20,21].

As an example, a study from the Pediatric Research in Office Settings (PROS) network followed the management strategies, illness frequency, and clinical outcomes in 3066 infants ages three months and younger, seen in office practices, who had a temperature of 38ºC or higher either at home or in the clinician's office [5]. The infants had no other major comorbidities and had been discharged from the hospital as newborns. Laboratory testing was performed at the discretion of the clinician according to his or her usual and customary practice. The following results were noted:

- The incidence of SBI was similar in this study of outpatient offices to the incidence found in studies conducted in emergency departments.
- Only 4 of 1056 infants (0.4 percent) who were well-appearing, aged 25 days or older, and who had a fever of less than 38.6ºC, had bacteremia and/or bacterial meningitis.
- There were no episodes of bacterial meningitis diagnosed in more than 1000 infants ages two to three months, and only 14 infants overall (0.5 percent) had bacterial meningitis.
- Factors associated with a high risk of bacteremia/bacterial meningitis included age ≤30 days, higher temperatures (≥38.6ºC), ill appearance, abnormal cry, and abnormal white blood cell (WBC) count, defined in this study as <5000 or ≥15,000/microL.
- UTIs were common (19 percent of uncircumcised boys and 13 percent of girls), but only around 50 percent of infants had a urine test.

The PROS clinicians hospitalized 36 percent of infants, performed laboratory testing in 75 percent, and initially treated 57 percent with antibiotics. Sixty-one of 63 infants (97 percent) with bacteremia/bacterial meningitis were treated with antibiotics at the initial visit. Practitioners followed current guidelines in only 42 percent of episodes.

On the other hand, 96 percent of infants had more than one contact with their clinician during the illness (either by phone or office visit). The importance of reliable follow-up is crucial when a practitioner decides to forego invasive studies in a well-appearing young infant.

The discrepancy between office practice, as described in the PROS study, and current practice guidelines is noteworthy. Although the relatively small numbers of patients seen in an office practice, in comparison to the numbers of patients seen in a busy urban emergency department, make it unlikely that an individual practitioner will miss the diagnosis of an occult SBI over the course of his or her career, a single missed case of sepsis or meningitis would be devastating for the patient, the family, and the practitioner [22]. Clinicians must remember that low risk does not mean no risk, and acceptable risk must be considered for each individual patient.

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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 topic (see "Patient information: Fever in children (The Basics)")
- Beyond the Basics topic (see "Patient information: Fever in children")

SUMMARY — The ideal strategy for evaluating a febrile neonate or infant less than three months of age would involve identifying the patients with a serious bacterial illness (SBI) and minimizing testing and treatment of those with a mild illness. Traditional strategies and clinical guidelines have used the following clinical and laboratory characteristics to determine which infants are at low risk to have an SBI (see 'Traditional strategies' above):

- Well appearance, lack of significant medical history, and lack of obvious focus of infection on examination
- Peripheral white blood cell (WBC) count <15,000/microL
- Urinalysis with <10 WBC/hpf and a negative urine Gram stain
- Cerebrospinal fluid with <8 to 10 WBC/microL and a negative CSF Gram stain, when obtained
- Chest radiograph (CXR) lacking an infiltrate if CXR is obtained
- Stool without blood and/or few or no WBCs on the smear, when obtained

Strategies using clinical and laboratory characteristics to determine the risk of SBI in neonates and young infants are not ideal, however, and have the following limitations:

- Neonates (≤28 days) with significant bacterial infections can appear to be at low risk. (See 'Limitations in neonates' above.)
- The specificity of these strategies for identifying patients with SBI is poor. Therefore, large numbers of infants who do not have an SBI are considered high risk, receive broad-spectrum antibiotics, and may be hospitalized.
- All of these approaches require extensive laboratory testing, increasing both patient discomfort and expense.
- The strategies were developed and tested in urban emergency departments. It is not clear how they apply in community primary care settings.
- Clinical guidelines have not been widely adopted in community settings.

Definition and etiology of fever in neonates and infants (less than three months of age)

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INTRODUCTION — Fever is a prominent symptom of many different disease processes. Neonates and young infants may manifest fever as the only sign of significant underlying infection. The incidence of serious bacterial infection (SBI) is higher in infants less than three months of age, particularly those under 28 days, than at any other time in childhood. In addition, these young patients can experience significant morbidity from some viral infections.

This topic will review the definition and etiology of fever in the neonate and young infant less than three months of age. Strategies that have been developed to evaluate febrile children in this age group, as well as the evaluation and management of fever in neonates and infants less than three months of age and in infants and children age three to 36 months are discussed separately. (See "Strategies for the evaluation of fever in neonates and infants (less than three months of age)" and "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Fever without a source in children 3 to 36 months of age".)

DEFINITION OF FEVER — Rectal temperatures are the standard for detecting fever in infants less than three months of age. A rectal temperature of 38ºC (100.4ºF) generally is regarded as fever in the neonate 0 to 28 days

of age. The definition of fever in the one- to three-month-old varies from 38 to 38.2ºC (100.4 to 100.7ºF) depending on the study cited and on local custom [1-3]. Axillary and tympanic membrane temperatures are unreliable in young children [4].

Caregiver report of fever — It is not uncommon for caregivers to report an elevated temperature in an infant who is afebrile at the time of evaluation. A history of objective fever by rectal temperature requires evaluation even if the infant is afebrile at the time of presentation. On the other hand, an afebrile infant with a reported history of subjective fever only who has not had antipyretic therapy and who looks well and has no suspicious findings on history or physical examination may avoid laboratory testing. However, this should only occur when reliable follow-up can be arranged, rectal temperature can be monitored at home, and parents understand indications to seek medical consultation.

As an example, in a study of 292 infants younger than two months of age with a history of fever who were admitted to the hospital for possible sepsis, caretakers reported fever by rectal thermometer in 244 infants and tactile fever in 48 infants [5]. The following were findings in a retrospective review of outcomes of these children:

- Of 244 infants with reported fever per rectum, 224 (92 percent) had fever on presentation or during the subsequent 48 hours of hospitalization. In contrast, 22 of 48 infants (46 percent) with reported tactile fever had fever on presentation or during the subsequent 48 hours of hospitalization.
- Of 26 infants with tactile fever who were afebrile on presentation, none had subsequent fever during hospitalization, and one had a serious bacterial infection (urinary tract infection).
- Of 40 infants with reported fever per rectum who were afebrile on presentation, eight (20 percent) had subsequent fever during hospitalization, and four (10 percent) had serious bacterial infection. (See 'Serious bacterial infection' below.)
- Among the 19 infants with serious bacterial infection (five of whom were afebrile on presentation), all exhibited abnormal clinical and/or laboratory features on evaluation that were suggestive of underlying serious infection.

This study was conducted shortly after the licensing of Haemophilus influenzae type b vaccine and prior to the introduction of the heptavalent pneumococcal vaccine. The fact that these patients differ with respect to current immunization practice and the possible benefit derived from herd immunity limits interpretation of these findings in a modern-day population where the etiologies of SBI and the invasiveness of the related pathogens have shifted significantly. This uncertainty increases the importance of the clinical assessment and assurance of reliable follow-up.

However, in a study of infants seen in community settings, cases of bacteremia and/or bacterial meningitis, although rare, were documented among infants with normal temperatures in the office but fever at home by rectal thermometer [6].

Bundling — Bundling of infants in clothing or blankets generally causes an elevation in skin temperature rather than rectal temperature [7]. However, in a study of newborns who were bundled and had rectal temperatures measured over the next 2.5 hours, 2 of 12 infants reached a temperature of 38ºC [8]. Nevertheless, a minimally elevated rectal temperature should rarely, if ever, be attributed to bundling. In addition, a fever >38.5ºC (101ºF) should not be attributed to bundling regardless of the manner taken.

When overbundling is "suspect" as a cause for an elevated temperature, the child may be unbundled and the temperature retaken rectally in 15 to 30 minutes. The infant can be considered afebrile if the repeat temperature is normal and the infant remains well-appearing and has not received antipyretic therapy [7]. Parental education and follow-up with the primary care provider are essential in this circumstance.

IMMUNOLOGY — The immunologic competence of the neonate and young infant improves steadily in the first three months of life. The developing fetus has T and B lymphocytes at an early gestational age, but the development of immunologic function must be modulated to coexist with the mother's immune system. The newborn's immunologic task switches abruptly at birth from this coexistent state (graft preservation) to protection from invading pathogens.

At birth, T and B lymphocytes are present in numbers similar to or exceeding adult levels. However, the function of these cells in the newborn is diminished in areas such as mitogen-induced proliferation (T cells) and ability to induce immunoglobulin synthesis (B cells). Levels of the infant's own IgG increase steadily in the first few months of life as maternal levels decrease. (See "The humoral immune response" and "Immunity of the newborn".) Neutrophils also are present at early stages of gestation but differ in functional capacity from adult neutrophils [9].

This immune system development explains the vulnerability to different types of infectious diseases at varying ages within the first three months of life. Very young infants are more susceptible to serious bacterial infection than older infants. This susceptibility is related to the decline of maternal antibody at a time when the infant's antibody production is beginning to increase and the child has not yet been immunized against pneumococcus and Haemophilus influenzae type b (see 'Bacterial pathogens' below). A more detailed discussion of newborn immunology is found separately. (See "The development of immune cells in the fetus and neonate" and "Immunity of the newborn".)

PATHOPHYSIOLOGY OF FEVER — The pathophysiology, adaptive value, and treatment of fever are discussed separately. (See "Pathophysiology and management of fever in infants and children".)

ETIOLOGY — The ability to generalize data from prior studies is limited in that many of these prospective and retrospective studies were conducted in an era where numerous vaccines that are now included in routine childhood immunizations were unavailable (eg, pneumococcal conjugate vaccine, Haemophilus influenza type b vaccine, varicella vaccine, rotavirus vaccine). Additionally, the Advisory Committee on Immunization Practices recommends influenza vaccine administration for all children ≥6 months [10]. While vaccination for influenza does not directly impact the youngest infants, older children serve as the most effective vectors of disease transmission in the community. Consequently, the epidemiology of influenza in the youngest infants is likely to be changed by the vaccination of older children.

Viral infection — Viral infection is the most common cause of fever in this age group. In a study of infants 28 days or younger, a subgroup of 960 neonates with fever 17 percent had identifiable viral infections and 14 percent had a SBI [11]. In contrast, a prospective study of 1779 febrile infants 1 to 90 days of life identified viral pathogens in 35 percent of the cohort versus bacterial pathogens in 10 percent [12].

The neonate acquires infection through vertical transmission and postnatally from sources such as family members and hospital personnel. Neonates and young infants are more likely than older infants to experience morbidity from a viral infection, in part because of a decreased responsiveness of T cell-mediated immunity. (See 'Immunology' above.)

Viruses that can cause serious illness in this age group include:

- Herpes simplex (see "Overview of TORCH infections")
- Varicella (see "Varicella-zoster infection in the newborn")
- Enteroviruses (see "Clinical manifestations and diagnosis of enterovirus infections")
- Influenza virus (see "Clinical features and diagnosis of influenza in children")
- Some adenoviruses (see "Epidemiology and clinical manifestations of adenovirus infection")
- Respiratory syncytial virus (see "Respiratory syncytial virus infection: Clinical features and diagnosis")

Serious bacterial infection

Definition — Many of the studies of fever in the neonate and young infant define outcomes by the occurrence of serious bacterial infection (SBI). In most studies, SBIs are defined as bacteremia, bacterial meningitis, bacterial pneumonia, skin and soft tissue infections, osteomyelitis, bacterial gastroenteritis, septic arthritis, or urinary tract infection. Although not classically described in the literature of the early 1990s, the attention to community-acquired Staphylococcus aureus has made pustulosis a relevant disease entity to be considered in skin and soft tissue infections in neonates [13].

Incidence — The incidence of SBI in the neonate and young infant is difficult to quantify due to the variability in definitions of fever provided in the literature. Nevertheless, a meta-analysis of studies published between 1974 and 1990 found that 7 percent of all febrile infants (>39ºC or 102.2ºF) under three months of age had an SBI,

and bacteremia or bacterial meningitis occurred in 2.5 percent [14]. A higher incidence of these illnesses occurred in infants in the first month of life (8.7 and 3.7 percent, respectively).

Two studies performed after the introduction of vaccination against Hemophilus influenza, type B found a higher prevalence of SBI (12 to 13 percent) in febrile neonates under 29 days of age [15,16].

An observational study during the time period after introduction of routine vaccination with heptavalent pneumococcal vaccine demonstrates a rate of 12.8 percent in infants 1-90 days with fever (18.8 percent in children ≤28 days and 11.3 percent in infants >28 days) [17]. That the introduction of the heptavalent pneumococcal vaccine has decreased the rates of bacteremia is evident in an observational cohort study that identified children 3 years of age or younger and included 50 immunized and 67 unimmunized children 0-90 days of age. In this cohort, the rates of SBI were significantly higher among unimmunized children. Moreover, there were no cases of pneumococcal bacteremia in any of the infants who had received at least one dose of heptavalent pneumococcal vaccine [18].

Hyperpyrexia is rare among febrile infants younger than 3 months. However, one observational study found that the 98 infants (under 3 months of age) with temperature ≥40º C had a 29 percent absolute increase in prevalence of SBI (38 versus 9 percent) [19].

Bacterial pathogens — Unique pathogens must be considered as a cause for bacteremia and bacterial meningitis in neonates, including Group B streptococcus and gram-negative enteric organisms such as Escherichia coli, both acquired from the maternal genital tract [14]. (See "Group B streptococcal infection in neonates and young infants", section on 'Clinical manifestations'.) One study found that the incidence of E. coli bacteremia was inversely related to age (21, 13, and 4 percent in infants 0 to 1 month, 1.1 to 2 months, and 2.1 to 3 months, respectively) [20]. Although of much lower prevalence, Listeria monocytogenes also is often included among the top three bacterial pathogens in neonates. (See "Clinical features and diagnosis of bacterial meningitis in the neonate" and "Clinical manifestations and diagnosis of Listeria monocytogenes infection".)

In a study conducted in a single center on a cohort of 1298 febrile infants age 1-90 days, the most common pathogens identified in infants with SBI included Gram positives: Staphylococcus aureus, Group B streptococcus, Enterococcus species, and Gram negatives: Escherichia coli, Klebsiella sp, Enterobacter cloacae, Salmonella sp [21].

Sources of infection — UTI accounts for most SBI in infants under 90 days of age; being seen in up to 73 percent of febrile infants with SBI in one series [22]. Bacteremia, cellulitis, meningitis, and pneumonia comprise other important sources of infection (table 1) [12,22].

A study from the Pediatric Research in Office Settings (PROS) network described rates of SBI among 3066 infants ages three months and younger, who were evaluated in the primary care office setting rather than the emergency department [6]. The incidence of both bacteremia and bacterial meningitis decreased with increasing age:

- 3 and 1.1 percent, respectively, in infants zero to one month of age
- 1.4 and 0.4 percent in infants greater than one to two months of age
- 0.7 and 0 percent in infants greater than two to three months of age

Urinary tract infection (UTI) was common in the cohort overall, occurring in 19 percent of uncircumcised boys, 13 percent of girls, and 17 percent of infants of either gender with prolonged illness. These numbers are likely underestimates, as only slightly more than 50 percent of infants had a urine test.

The significance of the urinary tract as a source of SBI in febrile young infants was further substantiated in a large prospective study of 1025 infants ≤60 days of age, who were evaluated for fever ≥38ºC in eight pediatric emergency departments [23]. The following findings were noted:

- Among infants with fever ≥39ºC, 16 percent had a UTI, in comparison to 7 percent of other infants.
- UTI was diagnosed in 21 percent of uncircumcised males and in 9 percent of infants overall.

The risk of UTI in uncircumcised male infants is discussed in detail elsewhere. (See "Epidemiology and risk factors for urinary tract infections in children", section on 'Host factors'.)

Salmonella is a consideration in young infants with fever, particularly in those who also have diarrhea or blood in the stool. A relatively small percent of these infants will have associated bacteremia [24]. Salmonella meningitis occurs rarely in young infants.

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- Basics topics (see "Patient information: Fever in children (The Basics)")
- Beyond the Basics topic (see "Patient information: Fever in children")

SUMMARY — Fever may be the only sign of significant underlying infection in neonates and young infants. The following points regarding the definition and etiology of fever in this age group are important to consider:

- Fever in neonates and infants less than three months of age is defined as a rectal temperature ≥38ºC (100.4ºF) (see 'Definition of fever' above).
- A reliable caretaker report of fever should be carefully evaluated, even if the infant is afebrile at presentation. We suggest that a thorough history and physical examination be performed in all such infants. The temperature should be repeated after a brief period of observation (see 'Caregiver report of fever' above).
- Bundling can cause a minimal elevation in rectal temperature. Fever may be attributed to bundling in the infant with no history of fever, who appears well, has a normal physical examination, and whose rectal temperature is <38.4ºC after unbundling (see 'Bundling' above).
- Viral infections are the most common cause of fever in neonates and young infants.
- Viruses that can cause significant infection include herpes simplex (see "Overview of TORCH infections"), varicella (see "Varicella-zoster infection in the newborn"), enteroviruses (see "Clinical manifestations and diagnosis of enterovirus infections"), influenza virus (see "Clinical features and diagnosis of influenza in children"), some adenoviruses (see "Epidemiology and clinical manifestations of adenovirus infection"), and respiratory syncytial virus (see "Respiratory syncytial virus infection: Clinical features and diagnosis").
- Bacterial pathogens that cause significant infection in the neonate (≤28 days of age) are Group B streptococcus, gram-negative enteric organisms such as Escherichia coli, and Listeria monocytogenes. (See "Group B streptococcal infection in neonates and young infants", section on 'Clinical manifestations' and "Clinical manifestations and diagnosis of Listeria monocytogenes infection".)
- Sources of serious bacterial infection (SBI) among neonates and infants less than three months of age are urinary tract infections, bacteremia, bacterial gastroenteritis, bacterial meningitis, and skin/soft tissue infections (see 'Sources of infection' above).

Pathophysiology and management of fever in infants and children

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INTRODUCTION — Fever is an abnormal elevation of body temperature that occurs as part of a specific biologic response that is mediated and controlled by the central nervous system.

The pathophysiology and treatment of fever in infants and children will be reviewed here. Other causes of elevated body temperature in children and the evaluation and management of fever in specific populations of infants and children are discussed separately:

- (See "Heat stroke in children" and "Heat illness (other than heat stroke) in children".)
- (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Fever without a source in children 3 to 36 months of age".)
- (See "Management of fever in sickle cell disease".)
- (See "Etiologies of fever of unknown origin in children" and "Approach to the child with fever of unknown origin".)
- (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Management of fever in children with non-chemotherapy-induced neutropenia".)
- (See "Fever in children with chemotherapy-induced neutropenia".)
- (See "Fever in human immunodeficiency virus-infected infants and children".)

TEMPERATURE MEASUREMENT — The most common sites of temperature measurement in clinical practice are the rectum, mouth, and axilla; in addition, parents and caregivers may measure temperature at the tympanic membrane or forehead (temporal artery). Each of these sites has its own range of normal values [1].

Opinions differ about the best site of temperature measurement for young children who cannot cooperate with oral thermometry. The Bright Futures Guidelines for Health Supervision suggest rectal thermometry for children younger than four years of age, whereas the National Institute for Clinical Excellence recommends axillary or tympanic membrane thermometry for young children [2,3].

Rectal thermometry is generally considered the gold standard for measurement of core body temperature [4]. Rectal thermometry is usually performed in infants and young children if the result has clinical implications. Rectal thermometry is contraindicated in patients with neutropenia.

Oral thermometry generally is preferred in children who are old enough to cooperate. Oral temperature is typically 0.6ºC (1.0ºF) lower than rectal temperature because of mouth breathing, which is particularly important in patients with tachypnea. Oral temperatures also may be affected by recent ingestion of hot or cold liquids [1,5].

Axillary temperature is consistently lower than rectal temperature, but the absolute difference varies too widely for a standard conversion [6]. Axillary temperatures may be measured in neutropenic patients who are unable to use an oral thermometer.

Infrared tympanic membrane (TM) thermometers measure the amount of heat produced by the tympanic membrane. Temperature readings are close to core temperature, although the infrared TM reflective devices commonly used in homes, hospitals, and offices are considerably less accurate than TM thermistors used in research and by anesthesiologists [4,7-15]. Individual studies comparing TM and rectal temperatures in children have had contradictory results. A systematic review concluded that TM thermometry shows insufficient agreement with established methods of core temperature measurement to be used in situations where detection of fever has clinical implications (eg, laboratory evaluation of the febrile neonate or young infant) [16].

Infrared skin thermometers measure the amount of heat produced by the temporal arteries. The accuracy of such measurements may be affected by sweating or vascular changes [1]. As with tympanic temperature measurement, studies comparing temporal and rectal temperatures have contradictory results, and temporal temperatures should not be used to make clinical decisions [4,17-24].

Converting between Fahrenheit and Celsius — Fahrenheit and Celsius temperature equivalents are provided in the table (table 1).

- To convert a temperature measured in Fahrenheit to Celsius:
- (Temperature in °F – 32) x (5/9) = Temperature in °C
- To convert a temperature measured in Celsius to Fahrenheit:
- [(9/5) x Temperature in °C] + 32 = Temperature in °F

TEMPERATURE HOMEOSTASIS — Body temperature is controlled by the thermoregulatory center of the hypothalamus. The thermoregulatory center balances heat production, derived primarily from metabolic activity in muscle and the liver, with heat dissipation from the skin and lungs. The thermoregulatory center is able to maintain a fairly steady body temperature in normal temperature environments. However, at environmental temperatures higher than approximately 35°C [95°F]), the body's ability to dissipate heat is overwhelmed, and core temperature rises. (See "Heat stroke in children", section on 'Pathophysiology'.)

NORMAL BODY TEMPERATURE — The mean normal temperature is generally considered to be 37ºC (98.6ºF) [25]. This value usually is attributed to studies dating to the 19th century. In a more recent study of young adults, the upper limit of normal body temperature was 37.2ºC (98.9ºF) in the morning and 37.7ºC (99.9ºF) overall [26]. Normal body temperature varies with age, time of the day, level of activity, and phase of the menstrual cycle, among other factors [1,5].

Infants and young children generally have higher temperatures than older children and adults. This relates to the greater surface-area-to-body-weight ratio and the higher metabolic rate of infants and small children. In the newborn period (age 0 to 28 days), the mean normal temperature is 37.5°C, with an upper limit of normal (ie, two standard deviations above the mean) of 38ºC (100.4ºF) [27].

Normal temperature varies daily, with a morning nadir and late afternoon/early evening peak. The mean amplitude of variation is 0.5ºC (0.9ºF) [26]. During a febrile illness, daily low and high temperature readings are maintained, but at higher-than-normal levels. Daily variation can be as high as 1ºC in some individuals recovering from a febrile illness.

ELEVATED BODY TEMPERATURE — Elevated body temperature may result from fever (increased body temperature with elevated hypothalamic set-point) or hyperthermia (increased body temperature with normal hypothalamic set-point) (figure 1). It is important to differentiate between these conditions because they have different clinical implications and management strategies. (See 'Management of fever' below and "Heat stroke in children", section on 'Hospital management'.)

Fever — Fever is an abnormal elevation of body temperature that occurs as part of a specific biologic response that is mediated and controlled by the central nervous system. (See 'Pathogenesis' below.)

The temperature elevation that is considered "abnormal" depends upon the age of the child and the site of measurement. The temperature elevation that may prompt clinical investigation for infection depends upon the age of the child and the clinical circumstances (eg, immune deficiency, sickle cell disease, ill-appearance, etc.) [28-31].

- In the neonate (0 to 28-30 days of age), fever generally is defined by rectal temperature ≥38.0ºC (100.4ºF). In the one- to three-month-old, fever generally is defined by rectal temperature ≥38.0 to 38.2ºC (100.4 to 100.7ºF). (See "Definition and etiology of fever in neonates and infants (less than three months of age)", section on 'Definition of fever'.)

- In children 3 to 36 months, fever generally is defined by rectal temperatures ranging from ≥38.1 to 39.0ºC (100.6 to 102.2ºF) and high fever by temperatures >39.0ºC (102.2ºF). (See "Fever without a source in children 3 to 36 months of age", section on 'Fever of concern'.)
- In older children and adults, fever may be defined by oral temperatures ranging from ≥37.8 to 39.4ºC (100.0 to 103.0ºF), and high fever by temperatures ≥39.5ºC (103.1ºF).
- The temperature thresholds of concern for children with underlying conditions (eg, sickle cell disease, neutropenia, HIV) are discussed separately. (See appropriate topic reviews.)

Pathogenesis — Fever is the result of a highly coordinated series of events that begins peripherally with the synthesis and release of interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), interferon (IFN)-alpha, and other endogenous pyrogenic cytokines by phagocytic cells in the blood or tissues (figure 2) [32]. These cytokines enter the blood and are carried to the anterior hypothalamus, where they induce an abrupt increase in the synthesis of prostaglandins, especially prostaglandin E2 (PGE2). The induction of PGE2 in the brain raises the hypothalamic set-point for body temperature (figure 1).

After the set-point is raised, the thermoregulatory center recognizes current body temperature to be too low and initiates a series of events to raise body temperature to the new set-point. This involves augmentation of heat production by increased metabolic rate and increased muscle tone and activity, and decreased heat loss through diminished perfusion of the skin. Body temperature rises until a new equilibrium is achieved at the elevated set-point. The upper limit of temperature due to fever appears to be 42ºC (107.6ºF), but it is unusual for temperature to exceed 41ºC (106ºF) without some element of concomitant hyperthermia [1,33,34].

In addition to causing fever, pyrogenic cytokines increase the synthesis of acute-phase proteins by the liver, decrease serum iron and zinc levels, provoke leukocytosis, and accelerate skeletal muscle proteolysis. IL-1 also induces slow-wave sleep, perhaps explaining the somnolence frequently associated with febrile illnesses. The increase in peripheral PGE2 may account for the myalgias and arthralgias that often accompany fever. Increased heart rate is a normal physiologic response to fever.

Benefits and harms — Whether fever is beneficial or harmful is disputed [34]. Fever is an integral part of the inflammatory response and, as such, may have a role in fighting infection. However, defense mechanisms can go awry. Even if fever does have a role in defending the host against infection, it may still be that, in some circumstances, fever does more harm than good [35,36].

- Potential benefits — Potential benefits of fever include retardation of the growth and reproduction of some bacteria and viruses (perhaps related to decreased serum iron) and enhanced immunologic function at moderately elevated temperatures (although some of the benefits are reversed at temperatures approaching 40ºC (104ºF) [34,37-42]. Some animal studies have demonstrated enhanced survival with fever [43,44]. However, as with immune function, the benefits may be diminished or even reversed as temperature increases [44,45]. Whether these findings apply to humans is not known.

  Indirect evidence of the benefit of fever has been suggested by the adverse effects of treating fever with antipyretics (eg, prolonged symptoms in children with varicella treated with acetaminophen and prolonged shedding of rhinovirus in young adults with the common cold treated with aspirin) [38,46,47]. However, it is not clear whether the observed effects were due to suppression of fever or some other direct physiologic effect of the antipyretic (eg, suppression of the inflammatory response).
- Potential harms — Fever can make patients uncomfortable. It is associated with increased metabolic rate, oxygen consumption, carbon dioxide production, and demands on the cardiovascular and pulmonary systems. For the normal child, these stresses are of little or no consequence. However, for the child in shock or for the child with a pulmonary or cardiac abnormality, the increased demands can be detrimental and may offset any immunologic benefit from the fever.

  In experimental studies, fever has been associated with impaired immunologic responses (eg, phagocytosis of staphylococci and lymphocyte transformation in response to mitogens) and cerebral injury (including edema and hemorrhage) [48-50]. Whether these findings apply to humans is not known.

  There is no evidence to suggest that fever ≥40ºC (104ºF) is associated with increased risk of adverse outcome (eg, brain damage) although this belief is held by many caregivers and clinicians [37,51,52].

Hyperthermia — Hyperthermia is an abnormal elevation of body temperature that occurs without a change in the thermoregulatory set point in the hypothalamus (figure 1). This failure of normal homeostasis results in heat production that exceeds the body's capacity for dissipation [37].

Characteristic clinical features of hyperthermia include a history of environmental heat exposure or use of drugs that interfere with normal thermoregulation (eg, anticholinergics); hot, dry skin; and central nervous system dysfunction (eg, delirium, convulsions, coma). Hyperthermia can be rapidly fatal; adverse physiologic effects begin to occur at temperatures >41°C (105.8°F). (See "Heat stroke in children", section on 'Clinical features' and "Heat illness (other than heat stroke) in children", section on 'Evaluation and management'.)

EVALUATION OF FEVER — Fever is a sign of underlying disease, the cause of which should be determined, particularly if the child is ill-appearing or the fever persists. In most cases, the child has additional symptoms and signs of an acute infection, which can be managed as indicated. However, in some children, particularly children with underlying disease, fever may be a sign of a more serious or even life-threatening process. The evaluation of fever in specific populations of children is discussed separately:

- (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Fever without a source in children 3 to 36 months of age".)
- (See "Etiologies of fever of unknown origin in children" and "Approach to the child with fever of unknown origin".)
- (See "Management of fever in sickle cell disease".)
- (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Management of fever in children with non-chemotherapy-induced neutropenia".)
- (See "Fever in children with chemotherapy-induced neutropenia".)
- (See "Fever in human immunodeficiency virus-infected infants and children".)

MANAGEMENT OF FEVER — Fever is an important clinical sign. The first step in the management of fever is to determine its cause. (See 'Evaluation of fever' above.) Once the cause is known, the main reason to treat fever is to improve the child's comfort [37].

Anticipatory guidance — Patients, parents, and other caregivers frequently make the decision to treat fever without consulting a healthcare provider. Many patients and caregivers believe that fever is harmful and that temperature elevation requires treatment regardless of its cause or effects [51,53]. Education of patients, parents, and caregivers is required to counter these beliefs [5,34,37]. Such education should be provided at health supervision visits and reinforced during acute visits for acute febrile illnesses.

Important components of the anticipatory guidance for fever include [1,3,5,34,37]:

- Fever is not an illness, but a physiologic response.
- In otherwise healthy children, most fevers are self-limiting and benign, provided that the cause is known and fluid loss is replaced; fever does not cause brain damage.
- There is no evidence that fever makes the illness worse.
- Initial measures to reduce the child's temperature include provision of extra fluids, lighter clothing, and reduced activity.
- Fever may require treatment with an antipyretic agent if the child is uncomfortable (as indicated by decreased activity level, decreased fluid intake, etc.) or if there are signs of serious illness (in which case a healthcare provider should be consulted).
- Children who require treatment for fever do not need to be awakened to receive the antipyretic agent.
- Children who are receiving antipyretic medications should not be given combination cough and cold preparations.
- Antipyretic medications should be dosed according to weight, rather than age. The healthcare provider should provide written dosing instructions and a measuring device, such as a properly marked syringe (for liquid formulations); the dosing directions and measuring devices that are included with over-the-counter medications are variable and inconsistent [54]. The instructions should include which formulation (or which concentration of a liquid formulation); how to measure the appropriate volume (for liquid formulation); how often to administer; how to monitor the response; when to discontinue; and when to contact the healthcare provider.
- Instructions for safe storage of antipyretic medications.

Antipyretic agents — Antipyretic agents treat fever by restoring the thermoregulatory set-point to normal. The most commonly used antipyretic agents in children and adolescents are acetaminophen and ibuprofen. Aspirin should not be used because of its association with Reye syndrome [37].

Indications — Routine treatment of fever in otherwise normal children is not warranted [1]. Decisions regarding the treatment of fever in children should be made on a case-by-case basis depending upon the clinical circumstances (eg, underlying disease, level of discomfort, desire to monitor fever curve, etc.) [1].

There is no evidence that reducing fever reduces the morbidity or mortality from a febrile illness (with the possible exception of children with underlying conditions that limit the ability to tolerate increased metabolic demands) or that antipyretic therapy decreases the recurrence of febrile seizures [37]. (See "Febrile seizures", section on 'Antipyresis'.)

Potential benefits of treating fever with antipyretics include improvement of discomfort and decrease in insensible water loss, which may decrease the risk of dehydration [37]. Antipyretic agents also have analgesic effects, which may enhance their overall effect. Potential downsides of treating fever include delayed identification of an underlying illness and drug toxicity; it is uncertain whether treating fever increases the risk or complications of certain types of infections. (See 'Benefits and harms' above.)

Indications for the short-term treatment of fever may include [1,34]:

- Shock
- Underlying neurologic or cardiopulmonary disease, or other condition with increased metabolic rate (eg, burn, postoperative state)
- Alteration in fluid and electrolyte balance
- High fever (ie, ≥40ºC [104ºF])
- Discomfort

Children with temperature elevation and the possibility of hyperthermia also require treatment, but the treatment of hyperthermia differs from that of fever. Antipyretic medications are ineffective in children with heat stroke and may exacerbate concomitant liver injury or coagulopathy. (See "Heat stroke in children", section on 'Hospital management' and "Heat illness (other than heat stroke) in children", section on 'Evaluation and management'.)

Suggested approach — The choice of antipyretic agent for children with underlying medical conditions may be influenced by the underlying medical conditions (eg, avoidance of acetaminophen in children with liver failure) or desire to avoid drug interactions with chronic medications (eg, selective serotonin reuptake inhibitors may enhance the antiplatelet effect of ibuprofen).

For children without underlying medical conditions, or with underlying medical conditions that do not influence the choice of antipyretic, we suggest beginning treatment with acetaminophen because of its long track record of safety [1,3]. Ibuprofen is an alternative to acetaminophen, particularly if antiinflammatory effect is desired in addition to antipyresis. Patient/parent preference is a major factor in the choice of antipyretic because patients/parents frequently make the decision to treat fever without consulting a healthcare provider. (See 'Acetaminophen' below and 'Ibuprofen' below.)

If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, it is reasonable to switch from acetaminophen to ibuprofen or ibuprofen to acetaminophen [1,3]. (See 'Treatment response' below.)

We do not suggest combining or alternating acetaminophen with ibuprofen because of the potential for dosing confusion, increased toxicity, and contribution to fever phobia [3,37,55]. (See 'Combining or alternating therapy' below.)

The height of the fever is an important determinant of the efficacy of antipyretic therapy; efficacy is increased at lower temperatures [56]. In randomized trials, acetaminophen and ibuprofen are more effective in reducing temperature than placebo; ibuprofen is slightly more effective and longer-lasting than acetaminophen [56-61]. Randomized trials comparing combining or alternating acetaminophen and ibuprofen with single-agent therapy

have inconsistent results [55,62-67]. It is not clear that the difference in temperature reduction with the different regimens is clinically important. Few trials have evaluated improvement in the child's comfort, which is a more relevant outcome than magnitude of temperature reduction [37].

Ibuprofen has generalized antiinflammatory effects, whereas acetaminophen does not. In an individual case, antiinflammatory effects may be an advantage or a disadvantage. On one hand, inflammation is a major cause of tissue injury and patient discomfort. On the other hand, inflammation is part of the immunologic response.

Given the relatively small difference in efficacy of acetaminophen and ibuprofen, the choice of agent is based upon the potential toxicity with therapeutic dosing. Appropriate therapeutic doses of acetaminophen and ibuprofen are remarkably free of side effects [3,61,68-70]. However, acetaminophen has a longer track record of safety than ibuprofen [1,3].

Antipyretic regimens

Acetaminophen — For most children with fever who require treatment with an antipyretic agent, we suggest acetaminophen because of its long track record of safety at therapeutic doses [1,3].

Acetaminophen generally is not recommended for infants younger than three months of age unless they have been examined by a healthcare provider. Fever may be the only sign of serious infection in such infants. (See "Definition and etiology of fever in neonates and infants (less than three months of age)", section on 'Serious bacterial infection'.)

The dose of acetaminophen is 10 to 15 mg/kg per dose (maximum dose 800 mg to 1 g) every four to six hours (with no more than five doses in a 24-hour period) with a maximum daily dose of 90 mg/kg per day up to 4 g/day [37]. Some sources suggest that acetaminophen should not be administered more than five times per day. We do not recommend a "loading dose" (eg, an initial dose of 30 mg/kg) of acetaminophen for routine clinical care because it may increase the risk of dosing confusion [37].

Approximately 80 percent of febrile children who are treated with acetaminophen have a reduction in temperature of 1 to 2°C (1.8 to 3.6°F) [37,71]. Acetaminophen begins to work in 30 to 60 minutes and has its peak effect in three to four hours. The duration of action is four to six hours.

When administered at appropriate doses, acetaminophen is remarkably free of side effects [61,68]. An association between acetaminophen and asthma has been described, but causality has not been demonstrated. (See "Risk factors for asthma", section on 'Acetaminophen'.)

Overdose of acetaminophen may be lethal. Overdose may occur if acetaminophen is administered simultaneously with combination cough and cold remedies that contain acetaminophen, with unsupervised ingestion, and unclear instruction for administration [37]. (See "Acetaminophen (paracetamol) poisoning in children and adolescents", section on 'Unintentional ingestions'.)

Ibuprofen — We suggest ibuprofen as the initial antipyretic agent when antipyretic and antiinflammatory activity are desired (eg, in children with juvenile arthritis) [1].

The dose of ibuprofen is 10 mg/kg per dose (maximum dose 600 mg) every six hours with a maximum daily dose of 40 mg/kg up to 2.4 g/day [37]. Ibuprofen begins to work in <60 minutes and has its peak effect (decline in temperature of 1 to 2°C (1.8 to 3.6°F)) in three to four hours. The duration of action is six to eight hours [37,71].

Ibuprofen generally is not recommended for infants younger than six months [37]. Such infants have limited renal function relative to older infants and children and potentially are at increased risk for renal toxicity [37].

Adverse effects of ibuprofen may include gastritis and gastrointestinal bleeding [72]. However, when administered at appropriate doses, ibuprofen is safe [61,69]. Anecdotal reports have linked nonsteroidal antiinflammatory drugs with the development or more rapid progression of necrotizing fasciitis due to group A streptococci in children with varicella [73,74]. However, a review of the literature, including five prospective studies, did not demonstrate a correlation [70].

Overdose may occur if ibuprofen is administered simultaneously with combination cough and cold remedies that contain ibuprofen, with unsupervised ingestion, and unclear instruction for administration [37]. Overdose of ibuprofen appears more easily managed than overdose of acetaminophen [75]. (See "Management of ibuprofen poisoning in children and adolescents", section on 'Epidemiology' and "Management of ibuprofen poisoning in children and adolescents", section on 'Clinical features of acute overdose'.)

Combining or alternating therapy — We do not suggest combining or alternating therapy with acetaminophen and ibuprofen to treat fever in children [3,37,55]. Although alternating acetaminophen and ibuprofen is a common practice [34,76-78], the evidence is insufficient to support or refute its efficacy and safety. Until additional information is available, the practice of combining or alternating acetaminophen and ibuprofen should be undertaken with caution [62].

The American Academy of Pediatrics clinical report on fever and antipyretic use in children suggests that combined treatment with acetaminophen and ibuprofen may increase the possibility of inaccurate dosing and may contribute to "fever phobia" [37]. The National Institute for Health and Clinical Excellence advises against the use of combination acetaminophen and ibuprofen [3]. If the decision is made to use combined therapy, dosing instructions and intervals must be thoroughly explained. (See 'Anticipatory guidance' above.)

Parents report alternating therapy at intervals ranging from two to six hours [37]. Published studies evaluating the efficacy of combined therapy with acetaminophen and ibuprofen have used different thresholds for fever, sites of temperature measurement (eg, rectal, axillary), dosing regimens, and periods of observation for outcome assessment [55,62-67]. Two trials found no difference between combination therapy and single-agent therapy [62,65]. Four found combining or alternating antipyretics to be associated with more rapid reduction of fever, lower mean temperature, and/or longer duration of antipyresis than single-agent therapy with acetaminophen [63,66,67] or ibuprofen [63,64]. However, the dosing intervals in one of the trials were longer, and the doses lower, than those that are typically used for single-agent therapy [63]. In addition, the observations may not be clinically significant; in one of the trials that demonstrated a temperature reduction benefit, the parents did not perceive a difference in the effectiveness of therapy [66].

There are few data about the safety of combined therapy with acetaminophen and ibuprofen, but there are several theoretical risks (especially that of renal injury), particularly in children with volume depletion [79,80]. No major adverse events were reported in any of the randomized trials [55]. In one of the trials, mild elevation in liver enzymes occurred in eight children (1.7 percent), and mildly abnormal renal function was observed in 14 children (3 percent); the abnormalities resolved by 14 days [63].

Duration — The duration of administration of antipyretic therapy depends upon the child's response; the end-point is the child's comfort [37]. Prolonged use of antipyretic agents generally is not necessary because most febrile illnesses in children are self-limited viral infections.

Treatment response — Treatment with antipyretic agents should make the febrile child more comfortable. It is more important for caregivers to monitor the child's general appearance (for signs of serious illness such as lethargy, stiff neck, altered mental status, petechial or purpuric rash, etc.), activity level, and fluid intake than to monitor the temperature curve. With either acetaminophen or ibuprofen, a response should be seen within 60 minutes; the response peaks in three to four hours [37]. If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, some experts would suggest switching from acetaminophen to ibuprofen or ibuprofen to acetaminophen [1,3]. There are no published studies to evaluate the safety or efficacy of this practice; however, in theory, some fevers may respond better to one antipyretic agent than another.

Persistence of a febrile illness beyond four or five days, a marked increase in the height of the maximum fever during the course of the illness, or the development of new localizing symptoms should raise concerns about alternative diagnoses or bacterial superinfection, which should be evaluated by a healthcare provider (or re-evaluated by a healthcare provider if the child was seen at the onset of illness) [37].

Use in young infants — The American Academy of Pediatrics clinical report on fever and antipyretic use in children suggests that acetaminophen not be administered to infants younger than three months and that ibuprofen not be administered to children younger than six months without evaluation by a clinician [37]. Fever may be the only sign of serious infection in a young infant, and such infections should be excluded before

symptomatic treatment of fever is initiated. (See "Definition and etiology of fever in neonates and infants (less than three months of age)", section on 'Serious bacterial infection'.)

Decisions regarding the use of acetaminophen in infants younger than three months after serious infection has been excluded should be made on a case-by-case basis. The safety of acetaminophen in young infants can be extrapolated from its use as an analgesic in this population. (See "Prevention and treatment of neonatal pain", section on 'Acetaminophen'.) However, there is little information about its efficacy as an antipyretic.

External cooling — External cooling is the treatment of choice for heat stroke and other forms of heat illness in which rapid cooling is necessary to prevent end-organ damage. (See "Heat stroke in children", section on 'Rapid cooling' and "Heat illness (other than heat stroke) in children", section on 'Evaluation and management'.)

We do not routinely suggest external cooling for temperature reduction in previously well infants and children with a febrile illness [3]. In randomized trials comparing the combination of tepid sponging and antipyretic therapy to antipyretic therapy alone, the added benefit of tepid sponging in temperature reduction was short-lived, and sponging was associated with increased discomfort [81-83].

However, external cooling may be the only available method of temperature reduction in children in whom antipyretic agents are contraindicated (eg, hypersensitivity to antipyretic agents, severe liver disease). In addition, external cooling may be used as an adjunct to antipyretic therapy for children in whom more rapid and greater reduction of body temperature is necessary than can be achieved with antipyretic agents alone. In such cases, antipyretic agents should be administered at least 30 minutes before external cooling [5]. Antipyretic agents are necessary to reset the thermoregulatory set-point, without which external cooling will result in an increase in heat production [1].

Possible indications for concomitant antipyretic administration and mechanical cooling in children with fever include:

- Uncertainty about the cause of elevated temperature (heat illness versus fever) (see 'Hyperthermia' above)
- Fever combined with a component of heat illness (eg, from over-wrapping, hypovolemia, or drugs such as atropine)
- Underlying neurologic disorder, in which the child may have abnormal temperature control and poor response to antipyretic agents

When mechanical cooling is necessary to treat fever, we suggest sponging with comfortably warm or tepid water (generally around 30ºC [85ºF]). Sponging is more effective than immersion because evaporation from the skin augments heat loss. Although temperature reduction may be faster with cold water, sponging with cold water is also more uncomfortable. Alcohol should not be used, because its fumes are absorbed across the alveolar membrane and possibly across the skin, resulting in central nervous system toxicity [84].

Cooling blankets can be useful in hospitalized children who are critically ill or who have problems with temperature control (eg, children with acute head injury).

Alternative therapies — Practitioners of complementary and alternative therapy may suggest a number of remedies for fever in infants and children (eg, calcium lactate). These remedies have not been studied in clinical trials, and there is little to no information about their efficacy or safety. We do not recommend their use.

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: Fever in children")

SUMMARY AND RECOMMENDATIONS

- Fever is an abnormal increase in body temperature that results from elevation of the hypothalamic set-point (figure 2). The magnitude of temperature increase that prompts evaluation depends upon the age of the child and the clinical circumstances. (See above.)
- The cause of fever should be determined, particularly in infants younger than three months of age and infants and children with underlying medical conditions that increase the risk of serious infection (eg, sickle cell disease, neutropenia, human immunodeficiency virus infection). (See above.)
- Decisions regarding the treatment of fever in children should be made on a case-by-case basis. Indications for the treatment of fever may include shock; underlying medical conditions that would be exacerbated by increased metabolic demand; fluid or electrolyte imbalance; temperature ≥40ºC (104ºF); and discomfort. (See above.)
- The choice of antipyretic agent for children with underlying medical conditions may be influenced by the underlying medical condition and chronic medications. (See above.)
- When the decision is made to use an antipyretic agent in a child without an underlying medical condition, or with an underlying medical condition that does not influence the choice of antipyretic, we suggest beginning treatment with acetaminophen (Grade 2B). The dose is 10 to 15 mg/kg per dose (maximum dose 800 mg to 1 g) every four to six hours (with no more than five doses in a 24-hour period); maximum daily dose: 90 mg/kg per day up to 4 g/day). (See above.)

  Ibuprofen is an alternative to acetaminophen, particularly if antiinflammatory effect is desired. The dose of ibuprofen is 10 mg/kg per dose (maximum dose 600 mg) every six hours (maximum daily dose: 40 mg/kg up to 2.4 g/day). (See above.)
- If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, some experts would suggest switching from acetaminophen to ibuprofen or ibuprofen to acetaminophen. (See 'Treatment response' above.)
- We do not suggest combining or alternating acetaminophen with ibuprofen (Grade 2B). (See above.)
- Prolonged use of antipyretic agents generally is not necessary. Persistence of fever beyond four or five days, a marked increase in the height of the fever during the course of illness, or the development of new localizing symptoms should raise concerns about alternative diagnoses or bacterial superinfection, which should be evaluated. (See above.)
- We do not routinely suggest external cooling for temperature reduction in previously well infants and children with a febrile illness (Grade 2A). (See above.)

Strategies for the evaluation of fever in neonates and infants (less than three months of age)

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INTRODUCTION — Fever is a prominent symptom of many different disease processes. Neonates and young infants may manifest fever as the only sign of significant underlying infection. Clinically distinguishing those with a serious febrile illness from those who are mildly ill may be difficult [1]. This has led to an aggressive approach to fever in this age group, usually including diagnostic tests, empiric antibiotics and, often, hospital admission.

A systematic approach to evaluating infants with fever without a source in this age group would ideally identify the patient with a serious bacterial illness (SBI) and minimize the testing and treatment of the patient with a mild illness. Several strategies for identifying the infant with fever who has an SBI have been proposed and tested. The strengths and limitations of these protocols, as well as the utilization of proposed guidelines are discussed here.

The definition, immunologic vulnerability, and etiology of fever in infants less than three months of age, as well as the evaluation and management of fever in these patients, are discussed elsewhere. (See "Definition and etiology of fever in neonates and infants (less than three months of age)" and "Evaluation and management of fever in the neonate and young infant (less than three months of age)".)

TRADITIONAL STRATEGIES — Several studies have attempted to identify patients who can be managed safely as outpatients with or without empiric antibiotic treatment [2]. There is some variation among them regarding inclusion criteria, inpatient or outpatient population, and whether or not antibiotics were given expectantly. This has led to confusion in the literature and a lack of consensus regarding the optimal approach to young infants with fever. Furthermore, even when guidelines have been proposed, they have not been consistently followed by many practitioners in the community [3-5]. (See 'Problems with these approaches' below.)

Nevertheless, these studies established the safety of treating a select population of young infants as outpatients. The sum of these studies suggests that the incidence of serious bacterial infection (SBI) among infants categorized as low risk after a full evaluation is 2.2 percent (range, 0 to 6.3 percent) [2]. When limited to studies that prospectively identified infants at low risk of SBI (figure 1) and performed outpatient observation with no antibiotics, the frequency of SBI varied from 0.5 to 1.1 percent in studies that either did or did not include lumbar puncture as part of the initial evaluation, respectively [6]. (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)", section on 'Evaluation and management'.)

Data from some of the largest studies led to the development of the "Boston," "Rochester," and "Philadelphia" criteria for identifying young infants with fever who are at low risk of SBI [7-10].

Boston protocol — The Boston group prospectively evaluated 503 28- to 89-day-old infants with rectal temperature greater than 38ºC (100.4ºF) who met the following criteria and were managed as outpatients [9]:

- No immunizations or antimicrobials within the preceding 48 hours
- No evidence of dehydration, ear, soft tissue, or bone infection
- Overall well appearance
- Caretaker available by telephone

The laboratory criteria defining low-risk patients included:

- Peripheral white blood cell (WBC) count less than 20,000/microL
- CSF with WBC <10/microL
- UA <10 WBC per high-powered field
- No infiltrate on chest radiograph if one was obtained

Infants in the study group received 50 mg/kg ceftriaxone intramuscularly and were sent home with scheduled follow-up visit 24 hours later.

The categorization of infants with a WBC count between 15,000 and 20,000/microL as low risk was more liberal than in other studies, and 27 patients (5.4 percent) had an SBI identified during follow-up. Nevertheless, there were no adverse outcomes; all infants with SBIs received an appropriate course of antimicrobial therapy and were well at follow-up.

Philadelphia protocol — Another group described an eight-year experience with 747 infants 29- to 60-days of age with a rectal temperature ≥38.2ºC (100.8ºF) [8]. Low-risk criteria included patients who were well-appearing with:

- WBC <15,000/microL
- Band-neutrophil ratio <0.2
- UA <10 WBC/hpf and a negative urine Gram stain
- CSF <8 WBC/microL and a negative CSF Gram stain
- Chest radiograph lacking an infiltrate if one was obtained
- Stool without blood and few or no WBCs on the smear in infants with diarrhea

All high-risk patients were hospitalized and treated with empiric antibiotics. Low-risk patients (19 percent of the study population) were discharged if follow-up was assured within 24 hours. In contrast to the Boston group, low-risk patients were not treated with empiric antibiotics.

The sensitivity for identifying patients with SBI was 98 percent (95% CI 92-100 percent); the specificity was 42 percent (95% CI 38-46 percent); the positive predictive value was 14 percent (95% CI 11-17 percent); and the negative predictive value was 99.7 percent (95% CI 98-100 percent), suggesting that these criteria did not miss many infants with SBI. However, many well infants underwent excessive laboratory testing, and many were managed as inpatients.

Rochester protocol — Another group attempted to identify low-risk febrile infants (defined as a rectal temperature greater than or equal to 38.0ºC or 100.4ºF) younger than 60 days [10]. This schema utilized the following criteria:

- ≥37 weeks gestation, and hospitalized no longer than the mother
- Infant was previously healthy
- Infant was well-appearing, with no ear, soft tissue, or bone infections

Laboratory criteria were as follows:

- WBC 5,000 to 15,000/microL with an absolute band count <1,500/microL
- Urinalysis with <10 WBC/hpf and no bacteria seen
- Stool with <5 WBC/hpf if obtained

High-risk infants were hospitalized with empiric antibiotics, and low-risk patients were sent home without antibiotics but with reliable follow-up.

Of the 931 well-appearing infants, 437 (47 percent) were classified as low risk. Only five low-risk infants had an SBI with a negative predictive value of 98.9 percent (95% CI 97-100 percent). Although there was no consistent empiric treatment with antibiotics, there were no adverse outcomes, lending support to the consideration of less aggressive therapy in low-risk infants [11].

Limitations in neonates — Studies that have assessed the applicability of the various strategies to neonates ages 1 to 28 days have found an increased number of SBIs missed in this age group and high prevalence of SBI when compared with infants one to three months of age [12-16]. As an example, one study from an urban pediatric emergency department evaluated 254 neonates ages 3 to 28 days of age with a temperature of 38ºC or higher, 32 of whom had an SBI [14]. When the Philadelphia criteria were applied to all 254 neonates, 109 (43 percent) were identified as low risk, five of whom actually had an SBI (two with bacteremia, two with bacterial urinary tract infection, and one with bacterial gastroenteritis). These findings suggest that neonates should be considered high risk, and a complete sepsis evaluation with hospital admission are warranted regardless of clinical picture and laboratory results.

CLINICAL GUIDELINES — In addition to the protocols described above, a number of groups have developed clinical guidelines in an effort to unify the approach to febrile young infants. However, like the protocols, the guidelines suffer from lack of uniformity, extensive laboratory testing, and lack of compliance in the community. (See 'Problems with these approaches' below.)

Expert panel — In 1993, an expert panel developed guidelines for the approach to infants and children 36 months of age and younger with fever without a source [17]. They were published simultaneously in the journals, Pediatrics and Annals of Emergency Medicine, but not endorsed by either the American Academy of Pediatrics or the American College of Emergency Physicians. These guidelines were updated in 2000. Recommendations were made for infants 28 to 90 days of age, although some of the studies included infants only up to 60 days (figure 1) [6]. (See 'Problems with these approaches' below.)

American College of Emergency Physicians — A clinical policy regarding children under three years presenting to the emergency department with fever was published in 2003 [18].

The policy is similar to the previous guidelines and emphasizes the following key points:

- Febrile infants 1 to 28 days of age are distinguished from older children regarding the possibility of serious bacterial infection (SBI).
- A chest radiograph is indicated in children less than three months with evidence of acute respiratory illness.
- A urinary tract infection (UTI) is an important source of fever for all children less than one year of age and for girls under two years.
- A negative urine dipstick or urinalysis does not exclude a UTI in neonates and young infants under two years of age. If a UTI is suspected, a culture should be sent.

The accompanying editorial is supportive of the policy, adding that empiric treatment with acyclovir pending PCR results for herpes simplex virus should be considered in some patients less than 28 days of age [19]. The author also suggests that children who are treated with antibiotics should have CSF obtained for culture. (See "Neonatal herpes simplex virus infection: Management and prevention".)

PROBLEMS WITH THESE APPROACHES — Studies of patients evaluated and treated according to the protocols and guidelines described above have established the safety of treating well-appearing infants, who have been carefully screened with laboratory testing, as outpatients. However, each of the strategies studied has its limitations. In addition, these strategies have not been uniformly utilized in community settings.

Limitations of protocols — Criticism of these strategies for identifying low-risk infants and sending them home with follow-up, either with or without a dose of ceftriaxone, include the following:

- While the Philadelphia and Rochester protocols have been promoted because of their high negative predictive value (ability to remove patients with SBI from the low-risk group), each suffers from a relatively low positive predictive value (14 and 12 percent, respectively), attributable to the large numbers of patients considered high risk and therefore hospitalized for antibiotics [8,10].
- All of these approaches require extensive laboratory testing, increasing both patient discomfort and expense.
- The Boston protocol results in the administration of broad-spectrum antibiotics to a number of infants who do not have SBIs, unnecessarily exposing them to the risks of parenteral antibiotics, although only

for one to two doses. The effect of the use of broad-spectrum antibiotics on the development of antimicrobial resistance also must be considered.

- While these approaches generally have been applied to infants up to the age of three months, there are no data to suggest that the difference between 60 days and 90 days is clinically important. These arbitrary age categories represent the inclusion criteria of various study cohorts.
- The studies on which these approaches were based generally were conducted in urban emergency departments. It is not clear how the results apply to community primary care physicians.

Utilization of guidelines — Several studies suggest that the promoted guidelines have not been widely adopted in community settings [5,20,21].

As an example, a study from the Pediatric Research in Office Settings (PROS) network followed the management strategies, illness frequency, and clinical outcomes in 3066 infants ages three months and younger, seen in office practices, who had a temperature of 38ºC or higher either at home or in the clinician's office [5]. The infants had no other major comorbidities and had been discharged from the hospital as newborns. Laboratory testing was performed at the discretion of the clinician according to his or her usual and customary practice. The following results were noted:

- The incidence of SBI was similar in this study of outpatient offices to the incidence found in studies conducted in emergency departments.
- Only 4 of 1056 infants (0.4 percent) who were well-appearing, aged 25 days or older, and who had a fever of less than 38.6ºC, had bacteremia and/or bacterial meningitis.
- There were no episodes of bacterial meningitis diagnosed in more than 1000 infants ages two to three months, and only 14 infants overall (0.5 percent) had bacterial meningitis.
- Factors associated with a high risk of bacteremia/bacterial meningitis included age ≤30 days, higher temperatures (≥38.6ºC), ill appearance, abnormal cry, and abnormal white blood cell (WBC) count, defined in this study as <5000 or ≥15,000/microL.
- UTIs were common (19 percent of uncircumcised boys and 13 percent of girls), but only around 50 percent of infants had a urine test.

The PROS clinicians hospitalized 36 percent of infants, performed laboratory testing in 75 percent, and initially treated 57 percent with antibiotics. Sixty-one of 63 infants (97 percent) with bacteremia/bacterial meningitis were treated with antibiotics at the initial visit. Practitioners followed current guidelines in only 42 percent of episodes.

On the other hand, 96 percent of infants had more than one contact with their clinician during the illness (either by phone or office visit). The importance of reliable follow-up is crucial when a practitioner decides to forego invasive studies in a well-appearing young infant.

The discrepancy between office practice, as described in the PROS study, and current practice guidelines is noteworthy. Although the relatively small numbers of patients seen in an office practice, in comparison to the numbers of patients seen in a busy urban emergency department, make it unlikely that an individual practitioner will miss the diagnosis of an occult SBI over the course of his or her career, a single missed case of sepsis or meningitis would be devastating for the patient, the family, and the practitioner [22]. Clinicians must remember that low risk does not mean no risk, and acceptable risk must be considered for each individual patient.

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 topic (see "Patient information: Fever in children (The Basics)")
- Beyond the Basics topic (see "Patient information: Fever in children")

SUMMARY — The ideal strategy for evaluating a febrile neonate or infant less than three months of age would involve identifying the patients with a serious bacterial illness (SBI) and minimizing testing and treatment of those with a mild illness. Traditional strategies and clinical guidelines have used the following clinical and laboratory characteristics to determine which infants are at low risk to have an SBI (see 'Traditional strategies' above):

- Well appearance, lack of significant medical history, and lack of obvious focus of infection on examination
- Peripheral white blood cell (WBC) count <15,000/microL
- Urinalysis with <10 WBC/hpf and a negative urine Gram stain
- Cerebrospinal fluid with <8 to 10 WBC/microL and a negative CSF Gram stain, when obtained
- Chest radiograph (CXR) lacking an infiltrate if CXR is obtained
- Stool without blood and/or few or no WBCs on the smear, when obtained

Strategies using clinical and laboratory characteristics to determine the risk of SBI in neonates and young infants are not ideal, however, and have the following limitations:

- Neonates (≤28 days) with significant bacterial infections can appear to be at low risk. (See 'Limitations in neonates' above.)
- The specificity of these strategies for identifying patients with SBI is poor. Therefore, large numbers of infants who do not have an SBI are considered high risk, receive broad-spectrum antibiotics, and may be hospitalized.
- All of these approaches require extensive laboratory testing, increasing both patient discomfort and expense.
- The strategies were developed and tested in urban emergency departments. It is not clear how they apply in community primary care settings.
- Clinical guidelines have not been widely adopted in community settings.

Fever without a source in children 3 to 36 months of age

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INTRODUCTION — Fever is a common symptom among children seeking medical care. Most children undergo evaluation for a febrile illness before their third birthday, and nearly one-third of pediatric outpatient visits are for fever [1-3].

When the history and physical examination cannot identify a specific source of fever in an acutely ill, nontoxic-appearing child less than three years of age, the illness is often called fever without a source (FWS). Alternative terms are fever without localizing signs (FWLS) or fever without a focus.

This topic will review the etiology, evaluation, and management of the child 3 to 36 months of age with fever of less than seven days duration. Fever in newborns, infants younger than three months, and fever of unknown origin (≥7 days) are reviewed separately. (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)" and "Approach to the child with fever of unknown origin" and "Etiologies of fever of unknown origin in children".)

BACKGROUND

Fever of concern — In children 3 to 36 months of age, the diagnosis of fever is based upon core temperature, which is measured most accurately rectally. The history of an elevated temperature recorded at home should be considered equivalent to that taken in a medical facility. Fever 39ºC (102.2ºF) or higher is the threshold above which evaluation for a source of occult infection, including urinary tract infection (UTI), may be warranted [4]. (See 'Occult sources of infection' below.)

The majority of children with fever have either a self-limited viral infection or a recognizable source of bacterial infection. However, research in the 1970s identified a population of well-appearing febrile young children who had occult bacteremia [5,6]. Subsequent studies demonstrated that some of these children went on to develop serious focal bacterial infections, such as pneumonia and meningitis [7,8]. Although laboratory testing identified a group of children at an increased risk for occult bacteremia, many who were not bacteremic received presumptive treatment with broad spectrum antibiotics while awaiting definitive blood culture results.

The introduction of vaccines to prevent Haemophilus influenzae type b (Hib) and pneumococcal disease has dramatically lowered the incidence of occult bacteremia and, as a result, changed the issues facing the clinician who is evaluating a young child with fever. (See 'Impact of vaccines' below.)

Population of interest — This topic will focus on the evaluation and management of well-appearing, immunocompetent children 3 to 36 months of age with fever ≥39ºC (102.2ºF) of less than seven days duration and no focus of infection identified by a complete physical examination. The evaluation of the febrile infant younger than three months is discussed separately. (See "Evaluation and management of fever in the neonate and young infant (less than three months of age)".)

Immunization status — The approach to the child who has fever without a source is greatly determined by immunization status.

Complete immunization — In the discussion that follows, a completely immunized child has received the primary booster series of three immunizations with conjugate vaccines for Haemophilus influenzae, type b (Hib) and Streptococcus pneumoniae (PCV7 or PCV13) and remains on schedule. Patients who have not received the booster 12 to 15 months after the third Hib and either PCV7 or PCV13 are also considered to be at much lower risk of bacteremia. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Abbreviated or alternative schedule'.)

Incomplete immunization — In the discussion that follows, an incompletely immunized child has not received the primary booster series of three vaccinations with both Hib and either PCV7 or PCV13. Based on these criteria, any child under six months of age is incompletely immunized.

CAUSES OF FEVER — Fever can be caused by infectious and noninfectious processes. The vast majority of young children with fever have an infectious etiology. Noninfectious etiologies include drug fever, immunization reactions, central nervous system dysfunction, malignancy (eg, leukemia), and chronic inflammatory conditions (ie, inflammatory bowel disease and juvenile idiopathic arthritis).

Although caretakers may sometimes attribute fever to teething, fever >38.5ºC is unlikely to be caused by teething [9]. (See "Anatomy and development of the teeth", section on 'Primary teeth eruption'.)

The source of fever may be a recognizable bacterial or viral illness. In a study of a large cohort of children 3 to 36 months of age presenting to a primary care provider with a febrile illness, a readily identifiable presumed bacterial illness was diagnosed at the initial encounter in 56 percent of children, almost 90 percent of whom had otitis media [1]. A specific viral infection (eg, croup, bronchiolitis, varicella, roseola) was identified in an additional 4 percent of children [1]. Similarly, 6 percent of 21,216 children 3 to 36 months of age with fever ≥39ºC seen in the emergency department of an urban tertiary care children's hospital had a recognizable viral syndrome, 47 percent had FWS, and 47 percent had a specific bacterial infection requiring antibiotics or chronic illness (eg, immunocompromised state, central line) that affected the fever evaluation [10].

Serious bacterial infectious syndromes that occur in children 3 to 36 months of age include meningitis, pneumonia, and cellulitis. In one series (prior to the introduction of Hib and pneumococcal conjugate vaccines)

of 996 febrile children less than 36 months of age, <1 percent had meningitis, 10 percent had focal soft tissue infections, and 30 percent had pneumonia [11]. These diagnoses are discussed in detail elsewhere. (See "Clinical features and diagnosis of acute bacterial meningitis in children older than one month of age" and "Cellulitis and erysipelas" and "Clinical features and diagnosis of community-acquired pneumonia in children".)

OCCULT SOURCES OF INFECTION — The goal of the evaluation of a young child with fever is to identify sources of infection that require further evaluation and definitive treatment. Such infections are usually bacterial, although the majority of children who are well-appearing and have no identifiable source of infection have a nonspecific self-limited viral illness [1,12]. The remainder of this discussion will focus on occult bacterial infections.

Pneumonia — Most children with fever and pneumonia have some abnormality on physical examination: usually tachypnea, abnormal auscultation, or nasal flaring, suggesting respiratory tract disease [13-15]. However, a reliable physical examination in a young child can be a challenge. In an observational study, radiographic pneumonia was found in 20 to 30 percent of highly febrile young children (<5 years) without clinical evidence of pneumonia, but with a white blood cell count (WBC) ≥20,000/mm3 [16]. Similarly, another observational study demonstrated that 41 percent of children between 3 and 36 months of age with a WBC >25,000/mm3 had lobar or segmental pneumonia on chest radiograph [17]. This association between leukocytosis and pneumonia remains strong, even in the post-conjugate pneumococcal vaccine era [18]. (See "Clinical features and diagnosis of community-acquired pneumonia in children".)

Urinary tract infection — The urinary tract is the most common site of bacterial infection among febrile infants and young children. This finding was demonstrated in two large prospective studies [19,20]. The prevalence of UTI in these reports was significantly influenced by demographic factors, such as sex, age, race, and circumcision status (table 1). (See "Epidemiology and risk factors for urinary tract infections in children", section on 'Host factors'.)

- The prevalence of UTI is highest among girls and warrants urinalysis and urine culture in all females age 3 to 24 months with fever ≥39ºC (102.2ºF) and no source (table 1).
- Among boys, UTI is increased in uncircumcised compared with circumcised male infants with fever, with the greatest incidence in infants younger than three months of age (table 1). The low incidence of UTI among circumcised boys supports the practice of not routinely obtaining a catheterized urine specimen for culture in febrile, circumcised boys over six months of age.
- Among highly febrile boys (ie, temperature ≥39ºC, or 102.2ºF) who are 3 to 24 months with no source of infection, the probability of UTI is 10 to 25 percent in uncircumcised and 2 to 4 percent in circumcised [20]. The highest prevalence is found in younger boys. Furthermore, bladder catheterization is a painful, invasive procedure that many parents might prefer to avoid if their child's probability of disease is less than 5 percent. Thus, our practice is to evaluate for UTI in uncircumcised males ≤12 months and circumcised males ≤6 months. Some investigators suggest that high fever (ie, ≥39ºC, or 102.2ºF) without a source is sufficient justification for urine studies on the first visit in all highly febrile boys between the age of 3 and 24 months [21]. (See 'Initial approach' below and "Epidemiology and risk factors for urinary tract infections in children".)

Bacteremia — Bacteremia that occurs in a seriously ill patient with a focal infection, such as meningitis, septic arthritis, or cellulitis, is usually readily identified. The risk of sepsis in a child who is ill-appearing, febrile, and without an obvious source of infection is also apparent. This discussion will focus on the young febrile child who looks well and may have unsuspected, or occult, bacteremia.

Before routine immunization with Hib and either PCV7 or PCV13, the prevalence of occult bacteremia was 5 percent in well-appearing febrile children [5,6]. The predominant pathogens were S. pneumoniae (80 percent) and Hib (20 percent). Neisseria meningitidis represented a small number of cases.

Predictors — Factors associated with an increased the risk of occult bacteremia in unimmunized children to over 10 percent included [22-24]:

- Age 3 to 36 months
- Fever ≥39ºC
- WBC ≥15,000/microL

Neither response to antipyretics nor clinical appearance predicted bacteremia [25-27].

Some children with bacteremia went on to have serious bacterial infections (SBI), including meningitis [7,28]. When children at risk for bacteremia were treated empirically with antibiotics until the results of blood cultures were known, they were less likely to develop these complications [22,23,29].

Impact of vaccines — The initiation of routine immunization of infants with the conjugate vaccines for Hib and S. pneumoniae has dramatically altered the prevalence of invasive disease due to these organisms. The incidence of occult bacteremia in well-appearing febrile children has fallen from 5 to below 1 percent, while the rate of isolation of a contaminant from blood cultures has remained constant at 1.8 percent [15,30-36]. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Invasive disease' and "Prevention of Haemophilus influenzae infection", section on 'Efficacy/effectiveness'.)

Since the routine immunization of children with PCV7 or PCV13 vaccine, pathogens other than S. pneumoniae are the cause of the majority of cases of unsuspected bacteremia [32]. E. coli and Staphylococcus aureus are frequently isolated organisms. Most reports of occult bacteremia also include cases caused by N. meningitidis, Group A streptococcus, and Salmonella species [32,37]. Laboratory parameters (ie, WBC >15,000/microL) may be less reliable predictors of bacteremia with these pathogens. (See 'WBC and ANC counts' below.)

In addition, the impact of PCV7 or PCV13 on variables, such as the role of nonvaccine serotypes in invasive pneumococcal disease and the duration and durability of protection after vaccination, continues to evolve. (See "Impact of universal infant immunization with pneumococcal (Streptococcus pneumoniae) conjugate vaccines in the United States" and "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Invasive disease'.)

Given the decreased prevalence of occult bacteremia in the post-conjugate vaccine era, a less aggressive approach to the management of completely immunized, well-appearing, febrile (≥39ºC) children 3 to 36 months of age who do not have a focal source of infection appears reasonable [34,38]. (See 'Initial approach' below.)

A cost-effectiveness decision analysis of evaluation and management strategies for FWS in the post-conjugate vaccine era considered negative aspects of diagnostic testing and treatment and used cases of meningitis and lives saved as outcome measures [39]. The management strategies evaluated were no work-up, clinical judgment, blood culture, blood culture plus antibiotics, WBC plus blood culture and antibiotics, and WBC plus selective blood culture and antibiotics. The following observations were noted:

- Assuming a rate of pneumococcal bacteremia of >1.5 percent, WBC plus selective blood culture and antibiotics was the most cost-effective approach.
- With a rate of pneumococcal bacteremia <0.5 percent, strategies that utilized empiric testing and treatment were no longer cost-effective.
- At low rates of bacteremia, clinical judgment became more useful in selecting a high-risk population that might benefit from selective testing and treatment.

EVALUATION — The goal of the evaluation of the young, well-appearing, febrile child without an apparent source of infection is to identify a subtle bacterial infection and/or the risk of a more serious occult bacterial infection, both of which require further investigation and antibiotic therapy.

History — Historical features of a febrile illness that suggest an occult source of infection may be subtle and not immediately obvious to the caretakers. Therefore, a thorough history must include information about the child's functional status, including oral intake, presence of irritability or lethargy, and associated symptoms. The duration of fever appears to be a poor predictor of unsuspected bacteremia [40].

Specific questions regarding cough, vomiting, or change in activity should be included. As an example, children with pneumonia may have cough or tachypnea noted by a caretaker. Signs or symptoms of UTI (eg, dysuria, frequency, abdominal pain, back pain, new onset incontinence), should be specifically sought. Likewise, vomiting, with or without diarrhea, can occur in young children with UTI, and caretakers occasionally note that the urine is foul-smelling, although these symptoms are nonspecific. Finally, a young child with a deep soft tissue or bone infection may protect the affected area.

A careful history must identify any known underlying medical condition that increases the child's risk for serious infection, such as sickle cell disease or urinary tract reflux. In addition, the immunization history will greatly influence the subsequent evaluation, since the child who is incompletely immunized is at greater risk for occult bacteremia than the one who is completely immunized. (See 'Immunization status' above and 'Incomplete immunization' above.)

Physical examination — The child who is being evaluated for a subtle infection or fever without a source should be well-appearing. Febrile children who are acutely ill with symptoms, such as lethargy, poor perfusion, hypoventilation or hyperventilation, and cyanosis are said to appear toxic or septic. They are considered to have a significant bacterial infection until proven otherwise. Cultures of blood, urine, and CSF, when meningitis is suspected, should be obtained, intravenous fluid provided, antibiotic therapy initiated, and admission to the hospital arranged. (See 'Ill-appearing' below.)

Attention to abnormal vital signs and a thorough physical examination may identify a source of infection. Specific features to note include the following:

- Tachycardia, tachypnea, or pulse oximetry ≤95 percent
- Lesions in the oropharynx that may identify a recognizable viral illness, such as herpes gingivostomatitis (anterior ulcers) or Coxsackie virus (pharyngeal vesicles) (see "Soft tissue lesions of the oral cavity in children" and "Clinical manifestations and diagnosis of enterovirus infections" and "Herpetic gingivostomatitis in young children", section on 'Clinical features')
- Increased work of breathing indicated by nasal flaring, retractions or use of accessory muscle, or focal lung findings, such as rales or decreased breath sounds
- Abdominal tenderness
- Pain with bone palpation or passive joint range of motion
- Skin findings, such as petechiae, cellulitis, or viral exanthem

Laboratory testing — Testing in febrile children 3 to 36 months of age has been used to screen for the risk of bacterial infection as well as to diagnose specific infections. The decision to perform laboratory tests depends upon a variety of factors including age, immunization status, and obvious findings of infection (eg, otitis media, bronchiolitis, croup).

Recommendations regarding when to obtain specific tests are provided below. (See 'Initial approach' below.)

WBC and ANC counts — Several studies have identified an increased risk of occult pneumococcal bacteremia among unimmunized children with WBC ≥15,000/microL and absolute neutrophil count (ANC) ≥10,000/microL [32,41-43]:

- A single center, prospective observational study of 1911 children, 3 to 36 months of age, who had fever without a source ≥39ºC (102.2ºF) and performed after introduction of Hib found that a WBC ≥15,000/microL had a sensitivity of 86 percent and a specificity of 77 percent for occult bacteremia [41]. The frequency of bacteremia in these patients was 1.5 percent (149/1911).
- A multicenter, prospective observational study of 6579 children, 3 to 36 months of age, who had fever without a source ≥39ºC (102.2ºF) and performed after introduction of Hib found that a WBC ≥15,000/microL had a sensitivity of 80 percent and a specificity of 69 percent for occult bacteremia, and an ANC ≥10,000/microL had a sensitivity of 76 percent with a specificity of 78 percent [42]. In multivariate logistic regression analysis, ANC was an independent predictor of bacteremia with adjusted OR 1.15 (95% CI 1.06-1.25) for each 1000 cells/mm3 increase in the ANC. The frequency of bacteremia in this sample was 2.5 percent.
- A multicenter retrospective observational study of 41,948 children, age 3 to 36 months, who had blood cultures performed after introduction of Hib and PCV7, found that a WBC ≤15,000/microL had a negative predictive value of 99.5 percent [32]. In this study, the frequency of bacteremia (1.6 percent) was less than blood culture contamination (1.8 percent).

Taken together, these studies suggest that a WBC >15,000/microL, while not ideal in screening for occult bacteremia, is helpful in determining which incompletely immunized children deserve blood culture and treatment in the post-conjugate vaccine era. However, these reports and others also have demonstrated that an

elevated WBC, by itself, has both limited sensitivity and specificity as an indicator of SBI, particularly as other pathogens, such as S. aureus become more prominent isolates in children with bacteremia [32,44].

Urine tests — Multiple studies and two meta-analyses have evaluated screening tests for UTI [45,46]. In general, urine screening tests markedly improve the ability to detect UTI, but a urine culture should be sent in all young children in whom a catheterized urine is obtained. The usefulness of various urine screening tests (dipstick, Gram stain, and microscopy) is summarized in the table and discussed elsewhere (table 2). (See "Clinical features and diagnosis of urinary tract infections in children", section on 'Rapidly available tests'.)

Cultures — The diagnosis of a SBI is often made with cultures, although the inherent delay between the initial evaluation of the patient and the availability of culture results complicates decisions regarding empiric antibiotic therapy.

- Blood — Continuously monitored blood culture systems have decreased the length of time for a blood culture to turn positive. The mean time to positive blood cultures for pathogens is approximately 15 hours, compared with 31 hours for contaminants [47].
- Urine — For the diapered child, urine for culture should be collected by catheterization, or in exceptional cases (eg, tight phimosis), suprapubic aspiration. Bag specimens should not be sent for culture because they are frequently contaminated. A clean catch is the preferred method of urine collection for culture in the child who is toilet-trained. The culture definition of UTI is discussed elsewhere. (See "Urine collection techniques in children" and "Clinical features and diagnosis of urinary tract infections in children", section on 'Diagnosis of UTI'.)
- CSF — Children who are being evaluated for fever without a source should be well-appearing and, therefore, not require lumbar puncture. That being said, CSF should be obtained from any patient with suspected meningitis. (See "Clinical features and diagnosis of acute bacterial meningitis in children older than one month of age", section on 'Course'.)

Chest radiograph — A chest radiograph should be obtained in patients with tachypnea, respiratory distress, or oxygen saturation ≤95 percent. In addition, chest radiograph is suggested in children with WBC >20,000/microL even in the absence of these findings. (See 'Pneumonia' above.)

Inflammatory mediators — Preliminary evidence suggests that elevations in levels of inflammatory mediators (ie, C-reactive protein and procalcitonin) may be better markers of SBI than WBC and ANC in children at significant risk for bacterial infection, although the usefulness of these tests in practice is uncertain.

- C-reactive protein (CRP) is an acute phase reactant released by the liver following inflammation or tissue damage. Observational studies that have evaluated CRP as a screening tool for occult bacterial infection report a wide range of sensitivity and specificity that vary by cutoff levels used to identify infants and children with SBI [48-52]. In addition, CRP concentrations generally do not increase until 12 hours after the onset of fever and can rise in both viral and bacterial infections [50].
- Procalcitonin (PCT) levels rise in response to bacterial infections more rapidly than those of CRP. Limited preliminary data suggest that PCT levels may be more sensitive and specific markers for severe invasive bacterial infection in infants and children than WBC, ANC, and CRP [52-57]. However, in most clinical settings, PCT has limited availability.
- A previously derived "Lab-score" that assigns points for procalcitonin levels ≥0.5 ng/mL (2 points) or 2 ng/mL (4 points), C-reactive protein 40 to 99 mg/L (2 points) or ≥100 mg/L (4 points), and a positive urine dipstick (1 point) was validated in 408 children with a 23 percent prevalence of serious bacterial illness, most commonly pyelonephritis, but including bacteremia, meningitis, and septic arthritis [58]. The Lab-score had better diagnostic accuracy (sensitivity 86 percent, specificity 83 percent) than any single inflammatory marker, including a white blood cell count ≥15,000 cells/mm3 (sensitivity 52 percent, specificity 75 percent). A Lab-score >3 was associated with an increase in the probability of serious bacterial illness from 23 percent pretest to 60 percent posttest. However, the children in this region only had an immunization rate of 40 percent for Streptococcus pneumoniae. Thus, these findings may not apply to regions were more children are completely immunized.

INITIAL APPROACH — The evaluation and management of the febrile child 3 to 36 months of age without a source of infection must balance the consequences of not diagnosing a SBI with the decreasing prevalence of occult infection and the potential adverse effects of excessive testing and treatment. Burdens of testing and

expectant antibiotic therapy include false-positive results, adverse reactions to antibiotics, and, possibly, the effect of widespread antibiotic use on patterns of antibiotic resistance. The likelihood of SBI varies significantly by clinical appearance, age, and immunization status. (See 'Occult sources of infection' above.)

Well-appearing children 3 to 36 months of age, with fever ≥39ºC (102.2ºF), who have no underlying medical condition that would alter susceptibility to infection, and no focus of infection identified by a complete physical examination, are hereafter referred to as children with FWS.

Ill-appearing — Children who are ill-appearing or have unstable vital signs should be fully evaluated for serious infection with cultures of blood, urine, and, when meningitis is suspected, CSF. Those with tachypnea or leukocytosis (>20,000/microL) should have a chest radiograph. These patients should receive parenteral antibiotic therapy targeting the likely pathogens in this age group (S. pneumoniae, S. aureus, N. meningitidis, H. influenzae type b) and be admitted to the hospital.

Well-appearing

Immunization incomplete — The risk of occult bacteremia in incompletely immunized children is estimated to be as high as 5 percent (ie, what it was during the preconjugate vaccine era); the actual risk is probably somewhat lower because of "herd immunity." (see 'Immunization status' above and 'Impact of vaccines' above).

Strategies for the evaluation and management of these children reflect the increased risk of bacteremia compared with completely immunized children and are drawn from experience and guidelines developed during the preconjugate vaccine era [4,29,30,32,41,47,59,60].

We suggest the following approach to evaluation of these children:

- CBC with differential.
- Blood culture should be obtained if the WBC is ≥15,000/microL. As a practical matter, the blood culture may be drawn with the CBC and sent if the WBC is ≥15,000/microL. Recognizing that WBC is not an ideal screening tool, some clinicians may prefer to always send a blood culture in these patients [32,37,39].
- Urinalysis, and urine culture by bladder catheterization or in exceptional cases (eg, tight phimosis), suprapubic aspiration.
- Chest radiograph in children with WBC ≥20,000/microL.

Children with an abnormal urinalysis should be treated for a urinary tract infection, although in questionable cases awaiting results of urine culture represents a reasonable alternative. (See "Acute management, imaging, and prognosis of urinary tract infections in children".)

We recommend that children with FWS who are incompletely immunized who have a WBC ≥15,000/microL receive parenteral antibiotic therapy pending blood and urine cultures [4,39]. Ceftriaxone (50 mg/kg, intramuscularly) is preferred because of its antimicrobial spectrum and prolonged duration of action. Clindamycin (10 mg/kg, intravenously followed by oral clindamycin eight hours later) is one alternative for patients allergic to cephalosporins. Outpatient follow-up should occur within 24 hours. Patients in whom outpatient follow-up is uncertain should be admitted.

This strategy of selective treatment of high-risk children with FWS and WBC ≥15,000/microL is in agreement with the practice guidelines of the American Academy of Pediatrics and the American College of Emergency Physicians for children with FWS [4,61,62].

Support for treating patients 3 to 36 months of age with FWS and significant risk of bacteremia with empiric parenteral antibiotics is derived from meta-analyses and randomized trials performed before the routine availability of Hib, PCV7, and PCV13 conjugate vaccines [22,23,29].

- A meta-analysis of four randomized controlled trials of 7899 children, age 3 to 36 months, who had a fever ≥39 ºC (102.2ºF), found that treatment of occult bacteremia with IM ceftriaxone reduced the

chance of serious bacterial infections by approximately 75 percent (Number needed to treat (NNT) 17; OR 0.25; 95% CI 0.07-0.89) and that oral antibiotics were not effective [63].

- A meta-analysis of prospective and retrospective studies of children age 3 to 36 months with fever without a source and bacteremia found that the mean probability of subsequent meningitis was 8.2 percent (all H. influenzae, type b) in patients treated with oral antibiotics and 0.3 percent in patients treated with parenteral antibiotics versus 9.8 percent in untreated children. No child treated with ceftriaxone developed culture-positive meningitis (0.3 percent; 95% CI 0.0-1.5 percent). The authors concluded that antibiotic therapy is effective in preventing meningitis [8].
- A randomized, double blind, placebo controlled trial of 955 children between the ages of 3 to 36 months with fever ≥39ºC (102.2ºF) demonstrated no difference in major infectious morbidity between bacteremic children receiving oral amoxicillin (2 of 19) or placebo (1 of 8). The incidence of diarrhea was 15 percent in children receiving amoxicillin versus 11 percent in the placebo group (p = 0.10) [23]. The overall rate of bacteremia was 2.8 percent in this study.
- An unblinded, randomized controlled trial of 6733 children between the ages of 3 to 36 months with fever ≥39ºC (102.2ºF) also described an overall rate of bacteremia of 2.8 percent (195 of 6733) [29]. Five definitive focal infections (three meningitis, one pneumonia, and one sepsis) developed in the 3347 children receiving amoxicillin versus none in those treated with IM ceftriaxone (OR 0.0, 95% CI 0.0-0.5).
- An unblinded, randomized trial of 96 children, between 6 and 24 months of age with a temperature >40ºC (104ºF), found that 4.3 percent of untreated patients (2 of 46) developed pneumococcal meningitis versus none of the 50 children treated with intramuscular aqueous penicillin G at the initial visit followed by oral penicillin for 10 days. Bacteremia was identified in 10.4 percent of all children [22].

Possible dermatologic adverse reactions were more commonly seen in the ceftriaxone group (8.7 versus 4.9 percent), but gastrointestinal complaints, such as diarrhea, were not different (14.5 versus 15.0 percent). No anaphylaxis was seen in either group.

Taken together, these studies indicate that unimmunized children with FWS avoid progression of bacteremia to focal infections, especially meningitis, when treated with parenteral antibiotics. Given the increasing prevalence of penicillin resistant S. pneumoniae, intramuscular ceftriaxone remains a preferred parenteral agent.

Immunization complete — A child with FWS who is completely immunized has a risk of bacteremia that is <1 percent. Decision analysis suggests that at this low risk, laboratory evaluation and empiric antibiotic therapy do not significantly alter the likelihood of progression to focal bacterial infection and are not indicated [39,64]. (See 'Immunization status' above and 'Impact of vaccines' above.)

However, the risk of UTI as an occult source of infection remains substantial in fully immunized children, depending on age, gender, and circumcision status. This risk guides recommendations for evaluation and treatment in these patients [63].

- For children over six months of age with FWS who are completely immunized, we suggest that girls less than 24 months of age and uncircumcised boys less than 12 months receive a urinalysis and urine culture. Urine for culture should be collected by catheterization or, in exceptional cases (eg, tight phimosis or severe labial adhesions), suprapubic aspiration. Bag specimens should not be sent for culture because they are frequently contaminated. (See "Urine collection techniques in children" and 'Urinary tract infection' above.)
- For girls >24 months of age, uncircumcised boys >12 months of age and circumcised boys >6 months of age, all of whom have been completely immunized, we do not suggest routine laboratory evaluation or presumptive treatment with antibiotics. However, urinalysis and urine culture should be obtained in those with signs or symptoms of UTI, which must be specifically sought (eg, dysuria, frequency, abdominal pain, back pain, new onset incontinence). In addition, children with a prior history of UTI, urogenital anomalies, or prolonged fever (>48 hours) warrant urinalysis and urine culture. (See "Clinical features and diagnosis of urinary tract infections in children" and 'Urinary tract infection' above.)
- Children with FWS who are completely immunized against Hib and either PCV7 or PCV13, meet criteria for urine testing, and have an abnormal urinalysis should be treated for UTI. Appropriate follow-up should be arranged. (See "Acute management, imaging, and prognosis of urinary tract infections in children".)

FOLLOW-UP — Follow-up should be arranged within 24 hours for those children with FWS who have received parenteral antibiotics. Patients who are not treated with antibiotics should be instructed to seek medical attention within 48 hours if they have persistent fever.

Careful instructions should be given to caretakers to return immediately if fever becomes higher, the patient looks sicker, or local symptoms or signs develop (eg, cough, diarrhea, cellulitis).

Positive blood cultures — An organism may not be identified definitively for 24 to 48 hours after the blood culture becomes positive, making management decisions difficult. The clinical appearance of the child and the Gram stain of the organism can be useful in deciding whether or not the child should be admitted to the hospital. Consultation with the microbiology laboratory personnel and/or an infectious disease consultant may be helpful in narrowing the list of potential organisms and the likelihood that the findings represent a pathogen. Patients with a positive culture that is felt to be a pathogen should be reevaluated and managed according to appearance, persistence of fever, and specific isolate (algorithm 1).

The main goal is to identify and avoid progression to serious bacterial infection, especially meningitis:

S. pneumoniae

- Febrile — In a retrospective observational study prior to PCV7 availability, 548 children with a blood culture positive for S. pneumoniae had outcomes examined. Children who were well, but persistently febrile at the revisit and did not receive antibiotics at the initial visit had a 33 to 42 percent chance of infection (primarily persistent bacteremia) and a 4.4 percent chance of meningitis [60]. Meningitis developed despite initial oral antibiotic therapy in 2 of 49 children (4 percent). Because of this high risk of SBI, patients with a blood culture positive for S. pneumoniae who are febrile on revisit should undergo a full sepsis evaluation (including lumbar puncture). They should also receive parenteral antibiotics tailored to the isolate's susceptibility or to the community susceptibility pattern for S. pneumoniae if the culture susceptibility is not yet available.

  These children may receive continued antibiotic therapy as an outpatient for 7 to 10 days with close follow-up if CSF findings show no evidence of meningitis. Antibiotic regimens should provide coverage for resistant S. pneumoniae. Possibilities include high dose oral amoxicillin (30 mg/kg per dose, three times daily; maximum dose: 3 grams daily), oral amoxicillin-clavulanate 45 mg/kg per dose twice daily (maximum dose of amoxicillin: 3 grams daily), or clindamycin 10 mg/kg per dose three times daily in penicillin allergic patients.
- Afebrile — Well-appearing, afebrile children who did not receive antibiotics at the initial visit and who have a blood culture positive for S. pneumoniae have an approximately 9 percent risk of persistent bacteremia [60]. These patients can be managed with antibiotics as an outpatient with close follow-up. Another blood culture should be drawn before further antibiotic therapy is initiated. Antibiotic regimens should provide coverage for resistant S. pneumoniae. Possibilities include high dose oral amoxicillin (30 mg/kg per dose, three times daily; maximum dose: 2 to 3 grams daily), oral amoxicillin-clavulanate (45 mg/kg per dose, twice daily; maximum dose: 3 grams total daily dose of amoxicillin), or clindamycin (10 mg/kg per dose, three times daily) in penicillin allergic patients.

Other pathogens — The limited data for bacteremia caused by organisms other than S. pneumoniae suggests that outpatient therapy with oral antibiotics does not prevent serious bacterial infection, even in well-appearing, afebrile children. In addition, the risk of meningitis is presumed to be high for patients with N. meningitidis bacteremia.

For these reasons, hospital admission and parenteral antibiotic therapy is suggested for children with a blood culture that is positive for N. meningitidis, H. influenzae type b, S. aureus, gram negative rods, or other pathogens. A lumbar puncture should be performed if meningitis is clinically suspected. CSF evaluation is also recommended for patients with blood culture positive for N. meningitidis and for young infants (three to six months of age) with Group B Streptococcus bacteremia. Well children over three months of age with a blood culture positive for E. coli or S. aureus do not need a lumbar puncture.

Probable blood culture contaminant — With the decline in the prevalence of occult bacteremia, it is now more likely that a blood culture will be positive for a contaminant than for a pathogen [30-32,47]. Microbiologic features, such as Gram stain, showing gram-positive rods, gram-positive cocci that are coagulase negative, and

slow growth suggest a contaminant. Consultation with the microbiology laboratory and/or an infectious disease specialist may be useful when preliminary results are unclear.

The child who is well on follow-up, afebrile, and has an isolate from blood culture that is a likely contaminant can be followed without antibiotic treatment, pending the final identification of the organism.

Children who are not well on follow-up or continue to have fever should be reevaluated and the assumption that the positive blood culture represents a contaminant should be reevaluated (algorithm 1). (See 'Positive blood cultures' above.)

Positive urine culture — Children with a positive urine culture should be treated for UTI. (See "Acute management, imaging, and prognosis of urinary tract infections in children".)

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: Fever in children (The Basics)")
- Beyond the Basics topics (see "Patient information: Fever in children")

SUMMARY AND RECOMMENDATIONS

General issues

- The following recommendations apply to well-appearing children 3 to 36 months of age, with fever ≥39ºC (102.2ºF), who have no underlying medical condition that would alter susceptibility to infection, and no focus of infection identified by a complete physical examination, hereafter referred to as children with FWS. (See 'Background' above.)
- The majority of children with fever have either a self-limited viral infection or a recognizable source of bacterial infection. (See 'Occult sources of infection' above.)

- Serious bacterial infections that occur in children 3 to 36 months of age include meningitis, pneumonia, and focal skin infections.
- Subtle sources of infection, such as pneumonia or osteomyelitis, can sometimes be identified with a careful history and physical examination.
- Relatively common occult sources of infection include pneumonia and urinary tract infections (UTIs), with occasional cases of bacteremia.

- A thorough history, including immunization status and complete physical examination, should be performed in all febrile children to identify obvious and subtle focuses of infection. (See 'History' above and 'Physical examination' above.)

Ill-appearing child

- Children who are ill-appearing or have unstable vital signs require full evaluation for serious infection with cultures of blood, urine, and when meningitis is suspected, CSF. A chest radiograph should be obtained in patients who have tachypnea or respiratory distress and is warranted for those with WBC ≥20,000/microL, even in the absence of physical findings of pneumonia. (See 'Ill-appearing' above.)

- Children who are ill-appearing or have unstable vital signs should receive parenteral antibiotic therapy targeting the likely pathogens in this age group (S. pneumoniae, S. aureus, N. meningitidis, H. influenzae type b) and be admitted to the hospital. (See 'Ill-appearing' above.)

Well-appearing child

Incompletely immunized

- For children with FWS who have not been completely immunized, we suggest the following tests:

- CBC with differential: A blood culture should be sent for those with WBC ≥15,000/microL. Some clinicians may choose to send a blood culture for all patients. (See 'Immunization incomplete' above.)
- Urinalysis and urine culture by bladder catheterization or, in exceptional cases (eg, tight phimosis or severe labial adhesions), suprapubic aspiration. (See 'Urine tests' above and 'Immunization incomplete' above.)
- Chest radiograph when WBC ≥20,000/microL. (See 'Immunization incomplete' above.)

- We recommend that incompletely immunized children with FWS and WBC ≥15,000/microL receive parenteral antibiotic therapy pending culture results (Grade 1B). A single dose of intramuscular ceftriaxone (50 mg/kg) is preferred because of its antimicrobial spectrum and duration of action. (See 'Immunization incomplete' above.)
- These patients should be seen for follow-up by their primary care provider within 24 hours. An alternative is to follow-up in the emergency department if a regular source of primary care is unavailable. (See 'Follow-up' above.)

Completely immunized

- For children >6 months of age with FWS who are completely immunized, we suggest that girls <24 months of age and uncircumcised boys <12 months receive a urinalysis and urine culture. Urine for culture should be collected by catheterization or, in exceptional cases (eg, tight phimosis or severe labial adhesions), suprapubic aspiration. Bag specimens should not be sent for culture because they are frequently contaminated. (See 'Urinary tract infection' above and "Urine collection techniques in children".)
- For girls >24 months of age, uncircumcised boys >12 months of age and circumcised boys >6 months of age with FWS, all of whom have been completely immunized, we do not suggest routine laboratory evaluation. In addition, these children should not receive presumptive treatment with antibiotics (Grade 1B). However, urinalysis and urine culture should be obtained in those with history of prior UTI, urogenital anomalies, prolonged fever (>48 hours), or physical findings of UTI. (See 'Urine tests' above and 'Immunization complete' above.)
- Completely immunized children with fever ≥39ºC (102.2ºF) and an abnormal urinalysis should be treated for a urinary tract infection. (See "Acute management, imaging, and prognosis of urinary tract infections in children" and 'Immunization complete' above.)

Clinical follow-up

- We recommend that children with fever that persists for more than 48 hours or with a deterioration in clinical condition undergo repeat medical evaluation.

Culture follow-up

Urine cultures

- Patients with a positive urine culture require treatment tailored to the identified organism and their clinical status. (See "Acute management, imaging, and prognosis of urinary tract infections in children".)

Blood cultures

- Children of 3 to 36 months of age with a positive blood culture for a presumed pathogen require reevaluation and management based on their appearance, persistence of fever, and specific isolate (algorithm 1). (See 'Positive blood cultures' above.)
- We suggest that the child who is well on follow-up, afebrile, and has an isolate from a preliminary report of a blood culture that is a likely contaminant be followed on a daily basis as an outpatient without antibiotic treatment, pending the final identification of the organism (Grade 2C). (See 'Probable blood culture contaminant' above.)

Drug fever

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INTRODUCTION — Clinicians are universally aware of the common occurrence of fever caused by drugs, although reliable data on incidence are not available. Fever can be the sole manifestation of an adverse drug reaction in 3 to 5 percent of cases [1,2]. The risk of developing drug fever increases with the number of drugs prescribed, especially in elderly patients. Individuals with active HIV infection also appear to have an increased susceptibility to drug reactions of all types, including fever [3-5].

The recognition of drug fever is clinically important. Failure to recognize the etiologic relationship between a drug and fever often has undesired consequences including extra testing, unnecessary therapy, and longer hospital stays.

DEFINITION — For the purpose of this discussion, drug fever will be defined as "a disorder characterized by fever coinciding with administration of a drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident after a careful physical examination and laboratory investigation [6]." Others have applied definitions such as "the febrile response to a drug without cutaneous manifestations [7]," but, in our view, such a definition is overly restrictive. Data on drug fever are largely derived from hundreds of single case reports and a few small series. There are no controlled trials on this subject, and reporting bias may significantly distort our view.

MECHANISMS — The mechanisms of drug fever are multiple and, in many cases, are poorly or incompletely understood. However, most authorities classify drug-related fevers into five broad categories [1,2,7-9].

- Hypersensitivity reactions
- Altered thermoregulatory mechanisms
- Reactions that are directly related to administration of the drug
- Reactions that are direct extensions of the pharmacologic action of the drug
- Idiosyncratic reactions

Fever associated with hypersensitivity — Hypersensitivity is the most common cause of drug fever [1-3,6-8]. Various mechanisms can cause fever, including the formation of circulating antibody-antigen complexes and/or a T-cell immune response provoked by a drug or its metabolites. Any one episode may involve multiple antigenic determinants and mechanisms. Fever is occasionally recognized when certain drugs are used in combination, such as methotrexate and azathioprine in the treatment of refractory rheumatoid arthritis [10].

Many clinicians are reluctant to diagnose a drug fever due to hypersensitivity if the patient has been on the drug for a period of time. However, the timing of the onset of fever due to hypersensitivity is often not a reliable diagnostic clue [7,11]. In most cases, fever appears several days to three weeks after the drug has been started, but the lag time can be as long as several years. On the other hand, fever can arise within hours of a rechallenge, intentional or otherwise, in a previously sensitized patient.

Fever may the sole manifestation of a hypersensitivity reaction. However, rash, urticaria, hepatic or renal dysfunction, pulmonary involvement, mucosal ulceration, and hematologic abnormalities are not uncommon accompanying events.

Withdrawal of the offending drug usually results in defervescence within 72 to 96 hours, which helps to confirm the diagnosis, but delays of five to seven days have been observed. The issue of rechallenge is discussed below.

Febrile drug reactions, often associated with a rash, are common in patients with active HIV infection [3,12-14]. Mechanisms are probably multifactorial, involving both hypersensitivity and direct toxicity of drug metabolites. The febrile reaction to some antiretroviral drugs, such as abacavir, may be genetically determined and prevented with pharmacogenetic testing prior to commencement of treatment [15]. The new onset of drug reactions in a previously healthy person may even lead a clinician to suspect the diagnosis of HIV [4]. (See "Fever and rash in HIV-infected patients".)

An unusually high incidence of drug fever is also seen in patients with cystic fibrosis. The parenteral beta-lactams, piperacillin, and imipenem/cilastatin seem to be particularly likely to cause fever in this patient population [16].

Although virtually any drug is capable of causing fever via a hypersensitivity mechanism, five drugs or drug-classes deserve special mention:

Anticonvulsants — Aromatic anticonvulsants such as carbamazepine and phenytoin, phenobarbital and primidone are important causes of drug fever [17-21]. The estimated incidence is 1 reaction per 5000 treated patients [22]. Fever usually begins five to six days after commencement of the drug and may be accompanied by an illness resembling infectious mononucleosis or even a pseudolymphoma syndrome. When the drug is discontinued, there may be slow resolution of fever and lymphadenopathy, taking from two to six weeks.

Skin reactions often accompany fever. Most patients have a morbilliform skin rash, but some develop severe skin reactions including Steven Johnson syndrome or toxic epidermal necrolysis, which can be fatal [22]. Some patients develop concurrent hepatitis and/or interstitial nephritis, but virtually any organ of the body may be damaged in patients with the anticonvulsant hypersensitivity syndrome.

A family history of a drug hypersensitivity reaction should alert physicians to the possibility of familial inheritance of abnormal drug detoxification pathways [23]. Clinicians also need to be aware that cross-sensitivity may occur between drugs in this class.

Minocycline — Minocycline is a widely used antimicrobial agent, especially for the treatment of acne. Long term minocycline therapy is also sometimes used for patients with osteomyelitis or prosthetic-related infection due to methicillin-resistant staphylococci. Various febrile reactions have been reported, some associated with joint, lung, liver, and skin involvement, and often accompanied by eosinophilia [24-27]. In most of these reports, patients were taking minocycline for many months to years before the reaction occurred; this may result in the drug being overlooked as the cause of the fever.

Other antimicrobial agents — Antimicrobials, along with antipyretics, are the most common drugs to be prescribed for febrile illnesses; antimicrobial agents are also the most common cause of drug fever, accounting for approximately one-third of episodes [11]. This especially applies to beta-lactams, sulfonamides and nitrofurantoin [11]. Drug fever due to an antimicrobial agent can cause clinical confusion because the return of a fever in an infected patient who has defervesced on antimicrobial treatment may be misinterpreted as relapse of the original infection. Unless drug fever is considered, further investigations usually follow; the drug is changed or other antimicrobials added; and treatment is unnecessarily prolonged or complicated.

Allopurinol — Allopurinol is an uncommon but important cause of drug fever. It is usually prescribed for the prevention of gout but is also used to diminish tumor lysis syndrome in patients receiving chemotherapy for malignancy. Allopurinol-induced fever is often accompanied by hepatotoxicity, deterioration of renal function, severe rash, and eosinophilia (60 percent) [28].

Allopurinol should always be considered in the differential diagnosis of fever in patients taking this drug. There is probably a genetic predisposition and the reaction is more likely to occur in the presence of drug accumulation, especially when there is renal impairment and/or concurrent use of thiazide diuretics [28].

Heparin — Heparin is a rare cause of drug fever [29]. Heparin-induced fever can be particularly difficult to diagnose in critically ill or postoperative patients who often receive the drug for prophylaxis against thromboembolism. To date, low molecular weight heparins do not appear to cause drug fever.

Fever due to altered thermoregulation — A wide array of drugs can cause fever by disrupting the normal thermoregulatory mechanisms of the body. Body temperature is primarily regulated by the anterior hypothalamus, balancing heat loss via the periphery against heat production by the tissues. Normally, the body's "thermostat" is set at just below 37ºC with a diurnal variation of about 1ºC.

Hyperthermia occurs when metabolic production of heat exceeds heat dissipation. Fever, which is a regulated response, occurs when the thermoregulatory center is reset at a higher temperature by "endogenous pyrogens" including the cytokines interleukin (IL)-1 alpha and -1 beta, tumor necrosis factor (TNF)-alpha and -beta, and interferon alpha [30]. In response to infection, inflammation, injury, or antigenic challenge, specific host cells produce these pyrogenic polypeptides. Cyclooxygenase and local prostaglandin E2 levels in turn mediate the temperature resetting mechanism, which includes muscle activity (shivering), vasomotor tone of the skin, and sweating.

Determinants of body temperature include the time of day, age, severe debility, thyroid function, and treatment with glucocorticoid and antiprostaglandin agents. Raised body temperature is most commonly due to the febrile response, but other mechanisms include abnormal hypothalamic function, decreased heat dissipation, and increased heat production [31].

Drugs can alter or modify all of the mechanisms described above in the following ways:

- Exogenous thyroid hormone can increase the metabolic rate and directly increase heat production.
- Drugs with anticholinergic activity, such as tricyclic antidepressants, atropine, antihistamines, phenothiazines, and butyrophenone tranquilizers can cause fever by disturbing central hypothalamic function and the peripheral effector mechanisms detailed above. Marked hyperthermia can ensue when these drugs are taken in combination [2,7,8]. Oligohydrosis and hyperthermia has also been reported with the antiepileptic drug, zonisamide [32].
- Sympathomimetic agents such as amphetamines, cocaine, and related agents disturb both central hypothalamic function and peripheral effector mechanisms by causing peripheral vasoconstriction. In addition, drug induced psychomotor agitation may in turn lead to increased muscle activity and secondary heat production [33]. 3,4-methylene dioxymethamphetamine (MDMA or "ecstasy") is a recreational drug with sympathomimetic properties which can cause a potentially fatal acute syndrome characterized by hyperthermia, seizures, rhabdomyolysis, acute renal failure, and coagulopathy, especially when taken prior to vigorous exercise such as dancing. It is likely that this reaction is also related to the serotonin syndrome (see below) [34,35].

Fever associated with drug administration — The parenteral administration of a wide variety of drugs can directly lead to fever. Solutions containing drugs can become contaminated with endotoxin or other exogenous pyrogens. Fever can also accompany a chemical phlebitis caused by drug administration, and local inflammation and/or sterile abscesses can occur at sites of injection. Fever sometimes follows injections with paraldehyde, pentazocine, and other drugs. Many routine vaccinations are associated with low-grade fever for 48 hours or less.

Pyrogenic contaminants in intravenous fluids are occasionally responsible for dramatic febrile episodes with rigors and hypotension that usually occur shortly after the infusion has commenced. This may cause considerable confusion during the perioperative period [11]. Some drugs, such as amphotericin B and bleomycin, have intrinsic but poorly understood pyrogenic properties. (See "Pharmacology of amphotericin B".)

In the past fever sometimes resulted from drug impurities; this was a particular problem with earlier, less highly purified formulations of vancomycin [36].

Fever as an extension of the pharmacologic effect of a drug — The most common example of fever as an extension of the pharmacologic effect of the drug is the fever observed following chemotherapy for various solid tumors, lymphomas, and leukemias. Cell necrosis and lysis release various pyrogenic substances from damaged cells; the resulting inflammatory response is also accompanied by cytokine activation of the febrile response. Fever commences two to three days after chemotherapy and may last for one week or more. This early febrile response usually can be distinguished from febrile neutropenia which rarely develops before the second week after chemotherapy.

Jarisch-Herxheimer reaction — The parallel situation in antimicrobial chemotherapy is the Jarisch-Herxheimer reaction. Fever and transient exacerbation of constitutional symptoms are thought to result from the sudden release of bacterial products from injured and/or killed bacteria [37]. Classically, this reaction was described following treatment for secondary and tertiary syphilis, brucellosis, and enteric fever. It can also occur with treatment of schistosomiasis and trypanosomiasis.

Severe reactions of this type have been observed following treatment of borreliosis, particularly Borrelia recurrentis, with a mortality rate of approximately 5 percent. (See "Clinical features and management of relapsing fever".) In one study of 49 patients with proven louse-borne relapsing fever, pretreatment with anti-TNF-alpha antibodies reduced the incidence of rigors from 90 percent in placebo recipients to 50 percent, and the mean increase in temperature from 1.5ºC to only 0.8ºC [38].

Fever due to an idiosyncratic reaction — Febrile idiosyncratic drug reactions are a heterogeneous category of drug-induced fevers. These reactions include unpredictable syndromes and genetic disorders, and there is some overlap with hypersensitivity phenomena. Despite these difficulties, several conditions are notable.

Malignant hyperthermia — Malignant hyperthermia is a rare but dramatic event characterized by the sudden appearance of fever over 40ºC, muscle rigidity, metabolic acidosis, and hemodynamic instability during general anesthesia [39,40]. The condition is inherited as an autosomal dominant trait in 50 percent of cases and thought to be present in 1 in 15,000 to 1 in 40,000 of the general population. Fifty percent of clinical cases occur in children. The primary defect is a mutation in the gene for the skeletal muscle ryanodine receptor (RyR1), which is a calcium channel found in the sarcoplasmic reticulum. (See "Severe hyperthermia (heat stroke) in adults".)

Most episodes of malignant hyperthermia have been triggered by muscle depolarizing agents, such as succinylcholine, and inhaled anesthetic agents, such as halothane. It is critical to recognize this syndrome in patients under general anesthesia because early intervention and treatment with dantrolene may be life-saving.

Neuroleptic malignant syndrome — The neuroleptic malignant syndrome (NMS) is characterized by high fever, muscle rigidity, altered and fluctuating mental state, and dysautonomias [40-42]. More than 25 different drugs have been incriminated, most prominently the major tranquilizers such as haloperidol; all of the implicated drugs are central nervous system (CNS) dopamine depleting agents. The probability of developing NMS is directly related to the antidopaminergic potency of the neuroleptic agent. Abrupt withdrawal of dopaminergic agents also can precipitate NMS. Hyperthermia results from increased myocyte metabolic activity and altered hypothalamic thermoregulation. (See "Neuroleptic malignant syndrome".)

NMS is associated with significant mortality unless it is recognized and the drug withdrawn. Treatment regimens include cooling, dantrolene, bromocriptine, and muscular paralysis with ventilation.

The atypical antipsychotic clozapine may also cause fever, but the mechanism is unclear [43].

Serotonin syndrome — The serotonin syndrome may be confused with neuroleptic malignant syndrome, but it is a distinct entity [39,44]. Serotonin syndrome is a predictable consequence of excess agonistic activity on central and peripheral serotonin receptors [33]. Features include agitation, confusion, hyperthermia, and autonomic hyperactivity such as diaphoresis, tachycardia, and neuromuscular disturbances, including rigidity, clonus, and tremors. The mechanism is related to excessive stimulation of the 5-HT1A and 5-HT2A receptors resulting in increased serotonin concentrations in the CNS and peripherally. Serotonin syndrome is increasingly common because of the widespread use of serotonin reuptake inhibitors (SSRIs) in the treatment of various psychiatric disorders [45]. It may also be precipitated alone or in combination by L-tryptophan, linezolid [46,47], lysergic acid diethylamide (LSD), lithium, L-dopa, dextromethorphan, tramadol, meperidine, and the monoamine oxidase inhibitors. (See "Serotonin syndrome".)

Glucose-6-phosphate dehydrogenase deficiency — Fever may occur when patients with glucose-6-phosphate deficiency are prescribed drugs such as primaquine, quinine sulfate, or sulfonamides. Fever, however, is a minor complication compared to the hemolytic anemia induced by these drugs.

Uncoupling oxidative phosphorylation — Toxic concentrations of salicylates and the wood preservative pentachlorophenol can short circuit the normal oxidative phosphorylation process in mitochondria and result in excess heat production and hyperthermia. Hyperthermia in patients with salicylate toxicity is a late and serious finding requiring aggressive treatment such as hemodialysis [33]. (See "Aspirin poisoning in adults".)

GENERAL CLINICAL ISSUES — Drug fever is usually a diagnosis of exclusion. The first assumption of most clinicians is that fever is due to infection, which may not always be easy to exclude. Connective tissue diseases and malignancy, which are other causes of fever of unknown origin, are also often difficult to exclude (see "Etiologies of fever of unknown origin in adults"). Thus, in hospitalized patients, undiagnosed drug fever may prolong the hospitalization and result in extensive and expensive investigation. In one large study, hospital stay was prolonged by a mean of 8.7 days per episode, generating an average of five blood cultures and 2.85 radiologic studies [11].

Presence of rash — Rash, when present, may be a valuable clue to the presence of drug fever, but its absence should not deter the clinician from suspecting the diagnosis. In one series of 51 episodes of drug fever, rash occurred in only 18 percent of cases and was rarely urticarial [6].

Fever patterns — As mentioned above, the timing of the onset of fever in relation to beginning the drug and the pattern of fever are frequently not helpful in making a diagnosis. The median time to onset is about eight days [11], but varies from less than 24 hours to many months. Similarly, the pattern of fever may vary from a low-grade fever without other associated symptoms [7] to a "hectic" pattern with chills and rigors. The latter pattern was observed in approximately 40 percent of hospitalized patients in one report [6]. The spiking pattern of fever in such patients can be exacerbated by regular treatment with antipyretics.

Some patients with drug fever look severely ill, as if they were profoundly septic [48]; others look and feel surprisingly well while febrile. Relative bradycardia, in which there is a large dissociation between the temperature and pulse rate, can occasionally be a useful clue to the presence of drug fever but occurs in only about 10 percent of cases [6].

Laboratory investigations — The white blood cell count can be elevated with accompanying eosinophilia in drug fever, but these findings occur in less than 20 percent of cases [6]. The erythrocyte sedimentation rate is usually increased, but this is a nonspecific finding. Unexplained disturbance of liver function and/or renal impairment can provide clues to the diagnosis. If urine microscopy reveals pyuria, a stain for eosinophils can be performed and may be positive, especially in interstitial nephritis caused by beta-lactam antibiotics. (See "Clinical manifestations and diagnosis of acute interstitial nephritis".)

Radiology — A chest radiograph may show another cause of fever, such as pneumonia, but has no positive predictive value in most patients with drug fever.

Cessation of the drug(s) — In the majority of patients, the only way to know if a patient has a drug fever is by stopping the drug(s). The usual approach is to discontinue the most probable offending drug first, followed sequentially by cessation of other drugs if fever persists. Discontinuing all medications at once may eliminate the fever but may also put the patient at some risk from the underlying disease and prevent identification of the causative drug. In most, but not all cases, resolution of drug fever will occur within 72 to 96 hours of discontinuing the offending drug.

Rechallenge — Rechallenge with the putative offending agent can confirm the diagnosis if fever recurs. Rechallenge is usually safe [6], particularly when the initial febrile illness is mild, but untoward events can arise [11]. In clinical practice, rechallenge is not often performed.

SUMMARY

- Clinicians are universally aware of the common occurrence of fever caused by drugs, although reliable data on incidence are not available. Fever can be the sole manifestation of an adverse drug reaction in 3

to 5 percent of cases. The risk of developing drug fever increases with the number of drugs prescribed, especially in elderly patients. Patients with HIV infection also appear to have an increased susceptibility to drug reactions of all types, including fever. Failure to recognize the etiologic relationship between a drug and fever often has undesired consequences including extra testing, unnecessary therapy, and longer hospital stays.(See 'Introduction' above.)

- Drug fever can be defined as "a disorder characterized by fever coinciding with administration of a drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident after a careful physical examination and laboratory investigation." (See 'Definition' above.)
- The mechanisms of drug fever are multiple and, in many cases, are poorly or incompletely understood. However, most authorities classify drug-related fevers into five broad categories:

- Hypersensitivity reactions
- Altered thermoregulatory mechanisms
- Reactions that are directly related to administration of the drug
- Reactions that are direct extensions of the pharmacologic action of the drug
- Idiosyncratic reactions (See 'Mechanisms' above.)

- Drug fever is usually a diagnosis of exclusion. The first assumption of most clinicians is that fever is due to infection, which may not always be easy to exclude. Connective tissue diseases or malignancy, which are other causes of fever of unknown origin, are also often difficult to exclude. (See 'General clinical issues' above.)
- Rash, when present, may be a valuable clue to the presence of drug fever, but its absence should not deter the clinician from suspecting the diagnosis. (See 'Presence of rash' above.)
- The timing of the onset of fever in relation to beginning the drug and the pattern of fever are frequently not helpful in making a diagnosis. The median time to onset is about eight days, but varies from less than 24 hours to many months. Similarly, the pattern of fever may vary from a low-grade fever without other associated symptoms to a "hectic" pattern with chills and rigors. (See 'Fever patterns' above.)
- The white blood cell count can be elevated with accompanying eosinophilia in drug fever, but these findings occur in less than 20 percent of cases. The erythrocyte sedimentation rate is usually increased, but this is a nonspecific finding. Unexplained disturbance of liver function and/or renal impairment can provide clues to the diagnosis. If urine microscopy reveals pyuria, a stain for eosinophils can be performed and may be positive, especially in interstitial nephritis caused by beta-lactam antibiotics. (See 'Laboratory investigations' above.)
- In the majority of patients, the only way to know if a patient has a drug fever is by stopping the drug(s). The usual approach is to discontinue the most probable offending drug first, followed sequentially by cessation of other drugs if fever persists. Discontinuing all medications at once may eliminate the fever but may also put the patient at some risk from the underlying disease and prevent identification of the causative drug. In most, but not all cases, resolution of drug fever will occur within 72 to 96 hours of discontinuing the offending drug. (See 'Cessation of the drug(s)' above.)

Fever in human immunodeficiency virus-infected infants and children

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INTRODUCTION — An approach to the evaluation of fever in HIV-infected infants and children is reviewed here. The natural history, classification, and epidemiology of pediatric HIV are discussed separately. (See "Natural history and classification of pediatric HIV infection" and "Epidemiology of pediatric HIV infection".)

OVERVIEW — Fever is a common reason for unscheduled outpatient clinic visits and hospital admission of HIV-infected children. Febrile children with human immunodeficiency virus (HIV) infection are diverse in their clinical presentations, necessitating a thoughtful and varied diagnostic approach. Febrile episodes may be acute (arbitrarily defined here as lasting for five or fewer consecutive days) or prolonged.

Some acutely febrile HIV-infected children have fever alone (fever without a source (FWS)); others have focal infections, such as otitis media, pneumonia, or herpes simplex virus (HSV) stomatitis. Similarly, prolonged fever may be associated with a discernible cause, or a cause may not be evident after careful physical examination and initial laboratory testing (fever of unknown origin (FUO)). Such fevers can be caused by HIV-associated opportunistic infections or malignancy. (See "Fever without a source in children 3 to 36 months of age" and "Etiologies of fever of unknown origin in children" and "Approach to the child with fever of unknown origin".)

Acutely febrile children with HIV infection often have illness that is mild and self-limited. Not all of these patients require diagnostic testing or antibiotic therapy. However, a few of these children have more serious infectious diseases. Differentiating these seriously ill patients from the larger group of mildly ill children can be difficult. HIV-infected children with prolonged fever often have complicating medical conditions, and the diagnostic evaluation can be complex.

Most of the available information on the management of febrile HIV-infected children is anecdotal. Prospective studies of diagnosis and treatment are lacking. Additional information is needed in many areas, including the incidence of various infectious and noninfectious causes of fever, the indications for expectant antibiotic therapy in HIV-infected children with FWS, and the outcome of occult bacteremia with and without expectant therapy.

ETIOLOGY OF FEVER — Acutely febrile HIV-infected children may have focal infection, fever without a source, FUO, HIV-associated opportunistic infection, or malignancy.

Serious bacterial and opportunistic infections — Fevers in HIV-infected children frequently are caused by infection. Multiple serious bacterial infections are acquired immunodeficiency syndrome (AIDS)-defining conditions in children along with the opportunistic infections and malignancies that define this disease in adults. (See "Natural history and classification of pediatric HIV infection".)

Before the widespread use of antiretroviral therapy, serious bacterial infections occurred commonly in HIV-infected children [1-5]. Even after single- and double-agent antiretroviral therapy became widely available in the United States for the treatment of HIV-infected children, serious bacterial infections remained common. In an analysis of the records of 3331 HIV-infected children enrolled in 13 separate trials of antiretroviral therapy (not including highly active antiretroviral therapy (HAART)), serious bacterial infections occurred at a rate of 15.1 per 100 patient-years, far exceeding the rates observed for herpes zoster, Pneumocystis carinii pneumonia (PCP, officially renamed Pneumocystis jirovecii pneumonia), esophageal candidiasis, cytomegalovirus (CMV) disease, tuberculosis (TB), toxoplasmosis, and other opportunistic infections [6].

The rate of serious bacterial infections in HIV-infected children in the era of HAART is unknown.

Streptococcus pneumoniae, Salmonella species, Staphylococcus aureus, and Haemophilus influenzae type b (Hib) are the bacterial organisms isolated most frequently from children with HIV infection. Risk factors for bacterial infection in HIV-infected children have not been defined precisely, but young children with vertically

acquired HIV appear to be at particularly high risk. At least in one study, the risk was lower in children younger than 12 months, which might suggest a protective role for maternal antibody [1].

FWS and FUO — The etiology of febrile illness among HIV-infected children is poorly defined. In a review of 68 inpatient admissions among HIV-infected children at Texas Children's Hospital, we found that 14 (21 percent) were attributable to FWS or FUO (unpublished data).

In the Texas Children's Hospital experience, most HIV-infected children with FWS have illness that is mild and self-limited; many appear to be caused by viruses. However, like immunologically normal children, some HIV-infected children with FWS have bacteremia or other serious complicating illnesses. The incidence of these complicating conditions probably is higher among HIV-infected children than among otherwise normal children with FWS [7]. The clinical or laboratory features, if any, that can be used to differentiate these few children with serious febrile illness from the larger group of febrile children with mild and self-limited illness are unknown. (See "Fever without a source in children 3 to 36 months of age".)

Like FWS, FUO is common among HIV-infected children. The term FUO is reserved for prolonged fevers, just as in immunocompetent hosts. Before the availability of HAART, at least 35 of 118 known HIV-infected children treated at Baylor College of Medicine had one or more episodes of unexplained fever lasting one month or longer (unpublished data). (See "Approach to the child with fever of unknown origin" and "Etiologies of fever of unknown origin in children".)

DIAGNOSTIC EVALUATION — Febrile HIV-infected children should be evaluated initially with a thorough medical history and physical examination. The character and duration of symptoms, HIV disease status, and history of recent exposures to ill contacts are of particular relevance. The physical examination should include a careful search for signs of focal infection or inflammation, and the patient should be assessed generally for illness severity or "toxicity."

A broad array of possible etiologies must be considered in the febrile child with advanced HIV disease, whereas the child with HIV disease well controlled by HAART often can be approached diagnostically much like a child without underlying illness.

One approach to the diagnostic evaluation of acutely febrile HIV-infected children is shown in the figure (figure 1).

Focal infection — The clinical features of focal infection in HIV-infected children are similar to the features observed in immunologically normal children. Fever and local signs of inflammation often are present. It is desirable, but not always feasible, to obtain cultures from the site of infection for accurate bacteriologic diagnosis and exclusion of other etiologic agents (eg, fungi).

Bacteremia should be suspected when certain serious focal infections (eg, pneumonia, cellulitis, or osteomyelitis) are present. Bacteremia also should be suspected in the child who appears toxic or septic. Routine bacterial blood cultures should be obtained from all such children.

Children with FWS — The HIV-infected child with FWS and no evidence of toxicity poses more diagnostic dilemmas. A substantial percentage of these children are bacteremic despite appearing well. An individualized approach is necessary to determine who warrants diagnostic laboratory studies. The extensive literature on identifying occult bacteremia in immunologically normal children with FWS may not be applicable to HIV-infected children.

For background purposes, a number of studies in immunocompetent children from 2 to 36 months of age after the introduction of Hib and pneumococcal conjugate vaccines document a frequency of occult bacteremia of less than 1 percent. Decision and cost-effectiveness analyses suggest that observation alone or screening with a complete blood count (CBC) followed by obtaining blood cultures and treating selected patients are the most reasonable approaches. (See "Fever without a source in children 3 to 36 months of age", section on 'Impact of vaccines'.)

Features to identify immunocompetent children at increased risk for occult bacteremia include: age between six and 24 months, body temperature greater than 39.4ºC (103ºF), and white blood cell count (WBC) of

15,000/microL or greater [8]. Conflicting data exist on the utility of C-reactive protein for this purpose. (See "Fever without a source in children 3 to 36 months of age", section on 'Predictors'.)

The predictive value of the above features in identifying febrile HIV-infected children who are at high risk for bacteremia has not been evaluated extensively. However, a retrospective study of HIV-infected children younger than 18 years identified 54 episodes of pneumococcal bacteremia, 26 of which were occult [7]. The sensitivity of elevated WBC in predicting bacteremia was low (40 percent for WBC >15,000/microL and 75 percent for WBC>10,000/microL). Thus, we recommend interpreting WBC in HIV-infected febrile children in relation to the patient's baseline values, rather than adhering to a fixed arbitrary threshold.

Several other diagnostic studies may be warranted in children with HIV infection and FWS:

- We obtain a blood culture if the rectal temperature is greater than 39.4ºC or if there are other findings, such as an elevated WBC, suggestive of bacteremia. (See "Fever without a source in children 3 to 36 months of age", section on 'Predictors'.)
- Young infants with bacterial meningitis may fail to manifest obvious signs of meningeal irritation (eg, nuchal rigidity), and a lumbar puncture (LP) may be necessary in some cases to exclude the diagnosis. Clinicians should apply clinical judgment in deciding when to perform an LP using the same considerations that apply in HIV-negative children. (See "Clinical features and diagnosis of acute bacterial meningitis in children older than one month of age", section on 'CSF examination' and "Lumbar puncture: Indications, contraindications, technique, and complications in children".)
- Because febrile infants frequently are tachypneic even without pulmonary disease and because pneumonia does not always produce obvious auscultatory physical findings, a chest radiograph may be necessary to exclude a diagnosis of pneumonia. (See "Clinical features and diagnosis of community-acquired pneumonia in children".)
- Urinalysis and urine culture may be indicated in some febrile infants to exclude occult urinary tract infection. (See "Clinical features and diagnosis of urinary tract infections in children".)

Children with FUO — FUO in HIV-infected children is associated with a broad spectrum of potential infectious and noninfectious causes. Some of the more important causes of FUO in HIV-infected children are listed in the table (table 1).

The broad spectrum of potential infectious and noninfectious causes for FUO necessitates meticulous physical examination and often extensive diagnostic testing. Such studies may include:

- Chest and sinus radiographs
- Blood cultures for routine bacteria, mycobacteria, and fungi
- Cultures of throat and nasopharynx, urine, and blood for viruses (especially CMV)
- Cryptococcal and other fungal antigen tests
- Epstein-Barr virus (EBV) antibody tests
- Liver enzyme measurements
- Ophthalmologic examination for chorioretinitis

Cerebrospinal fluid (CSF) can be obtained by LP for routine cell counts; protein and glucose concentrations; bacterial, mycobacterial, fungal, and viral studies; cryptococcal antigen tests and cytology.

Bone marrow aspiration and biopsy sometimes are useful diagnostically. Specimens should be obtained for Gram stain and bacterial culture, fungal stains and culture, stains for acid-fast bacteria, mycobacterial culture, viral culture, histopathology, and cytology.

High-resolution abdominal ultrasonography also may be warranted. FUO has been associated with microabscesses in the liver or spleen of HIV-infected patients in some studies. Etiologies include tuberculosis, visceral leishmaniasis, disseminated Mycobacterium avium, Pneumocystis carinii (jirovecii), Bartonella henselae, and others [9].

The breadth and pace of the diagnostic evaluation for FUO generally is determined by the pace of the illness. In the case of a child who appears only mildly ill, diagnostic studies are prioritized and conducted in a stepwise manner with common causes of disease excluded first. A patient with more fulminant illness may require

immediate and extensive testing to address the full range of diagnostic possibilities. (See "Approach to the child with fever of unknown origin" and "Etiologies of fever of unknown origin in children".)

EMPIRIC AND EXPECTANT ANTIBIOTIC THERAPY — As with the diagnostic evaluation, an individualized approach to the therapy of HIV-infected children with fever is necessary (figure 1). The selection of antibiotics for empiric or expectant therapy is influenced by several factors, including the nature of the infection (eg, presumed bacterial meningitis, pneumonia), the clinical scenario (eg, community-acquired versus hospital-acquired infection), the child's HIV disease status, and how ill the child appears.

The goal of empiric/expectant antibiotic therapy is to provide coverage against likely pathogens (ie, S. pneumoniae, Salmonella species, S. aureus, and Hib); it is not feasible to include coverage for every conceivable pathogen. Empiric therapy usually is directed only against potential bacterial pathogens. Unless there is convincing clinical or laboratory evidence of serious opportunistic fungal or viral infection, expectant or empiric therapy for these organisms is not indicated. Similarly, if PCP is suspected, laboratory confirmation of the diagnosis should be pursued before therapy is instituted.

Asymptomatic/mildly symptomatic HIV disease — In general, empiric antibiotic therapy for asymptomatic or mildly symptomatic HIV-infected children with fever should be similar to the routine coverage provided to immunologically normal children with comparable clinical presentations or focal infection.

We typically choose ceftriaxone (50 mg/kg IM or IV every 24 hours; maximum 2 g per day) or an oral antibiotic, such as amoxicillin-clavulanate (45 mg/kg per day of the amoxicillin component divided into two doses per day; maximum 3 g per day) or cefuroxime (30 mg/kg per day in two divided doses; maximum 2 g per day), for children who are less ill and can be managed as outpatients. Oral antibiotic therapy is possible for many well-appearing children with HIV infection and focal infection.

Other children, because of ill appearance or the nature of the focal infection, will require hospitalization and parenteral antibiotic therapy.

Advanced HIV disease — Children with more advanced HIV disease and debilitation may require broader initial antibiotic coverage. We generally include coverage for penicillin-resistant pneumococci in such patients. Because these organisms also may be resistant to cephalosporins, we usually add vancomycin (10 mg/kg per dose given every six hours; maximum 4 g per day) to cefotaxime (50 mg/kg IV every eight hours; maximum 12 g per day) or ceftriaxone (50 mg/kg IV every 24 hours; maximum 2 g per day).

Neutropenia — Children with neutropenia resulting from either HIV infection or various medications (eg, zidovudine) should be given antibiotics similar to those prescribed for other immunocompromised neutropenic children. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Management of fever in children with non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia", section on 'Empiric antimicrobial therapy'.)

Nosocomial infection — Nosocomial infection often requires very broad initial antibiotic therapy because of the wide variety of bacterial pathogens observed in that setting. Such treatment should be chosen with knowledge of prevailing pathogens and antimicrobial susceptibility patterns in the institution.

Fever without a source — Therapeutic decisions regarding the expectant therapy for HIV-infected children with FWS are influenced by the degree of elevation of the body temperature, the observed clinical appearance of the patient, and the WBC.

Because of the high incidence of bacteremia among febrile HIV-infected children, it probably is reasonable to administer expectant therapy more liberally to this group of patients than to a comparable group of otherwise healthy children with FWS. This was illustrated in a retrospective series of 54 HIV-infected children with pneumococcal bacteremia in which 0 of 19 patients who were treated with expectant antibiotics had persistent bacteremia on a follow-up visit within 72 hours compared to two of five patients who were released without antibiotics [7]. None of the 26 patients with occult bacteremia in this series died or developed meningitis or other complicating sequelae of pneumococcal infection.

Specific antibiotic options are similar to those used for immunocompetent children. Expectant therapy generally should be administered for 48 hours while awaiting the results of blood cultures. (See "Fever without a source in children 3 to 36 months of age", section on 'Initial approach'.)

Fever of unknown origin — As in immunologically normal children, expectant antibiotic therapy rarely is indicated in HIV-infected children with FUO, and such therapy often confounds the diagnostic evaluation. Therefore, all relevant diagnostic studies ideally should be obtained before the institution of specific therapeutic options.

SPECIFIC THERAPY — If a bacterial pathogen is isolated and other etiologic agents are excluded, antibiotic therapy can be targeted more narrowly.

DURATION OF TREATMENT — The duration of antibiotic therapy generally is similar to that for comparable infections in immunologically normal children.

SUMMARY AND RECOMMENDATIONS

Overview

- Acutely febrile HIV-infected children may have focal infection, fever without a source (FWS), fever of unknown origin (FUO), HIV-associated opportunistic infection, or malignancy. (See 'Etiology of fever' above.)
- The incidence of focal bacterial infection and bacteremia is increased among HIV-infected children. Streptococcus pneumoniae, Salmonella species, Staphylococcus aureus, and Haemophilus influenzae type b are the bacterial organisms isolated most frequently from children with HIV infection. (See 'Serious bacterial and opportunistic infections' above.)

Evaluation

- The diagnostic evaluation begins with a thorough medical history and physical examination. The character and duration of symptoms, HIV disease status, history of recent exposures to ill contacts, signs of focal infection/inflammation, and assessment of illness severity are of particular relevance (figure 1). (See 'Diagnostic evaluation' above.)
- Among children with focal infection, bacteriologic diagnosis by culture is desirable whenever it is possible. Blood cultures should be obtained in children with serious focal infections (eg, pneumonia, cellulitis, or osteomyelitis), and those who appear toxic or septic. (See 'Focal infection' above.)
- Among HIV-infected children with FWS, we obtain a blood culture if the rectal temperature is >39.4ºC or the WBC is elevated (compared to the patient's baseline). In addition, lumbar puncture, chest radiograph, urinalysis, and urine culture may be warranted to exclude serious bacterial infection. (See 'Children with FWS' above.)
- FUO in HIV-infected children is associated with a broad spectrum of potential infectious and noninfectious causes (table 1). Meticulous physical examination and diagnostic testing are necessary for specific diagnosis. (See 'Children with FUO' above.)

Treatment

- For most febrile children with or without HIV infection, empiric and expectant antibiotic therapy considerations are similar. However, children with advanced HIV disease, neutropenia, or nosocomial infection usually require broader initial antibiotic coverage. If a bacterial pathogen is isolated and other etiologic agents are excluded, empiric/expectant antibiotic therapy can be targeted more narrowly. The duration of antibiotic therapy generally is similar to that for comparable infections in immunologically normal children. (See 'Empiric and expectant antibiotic therapy' above.)
- Expectant antibiotic therapy rarely is indicated in HIV-infected children with FUO; if expectant antibiotic therapy is planned, relevant diagnostic studies ideally should be obtained before its institution. (See 'Fever of unknown origin' above.)

Fever in children with chemotherapy-induced neutropenia

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INTRODUCTION — Infection is a major cause of morbidity and mortality in cancer patients [1]. Fever may be the first manifestation of a life-threatening infection, particularly during periods of neutropenia. Febrile episodes occur in approximately one-third of neutropenic episodes in children with chemotherapy-induced neutropenia or after hematopoietic stem cell transplantation [2]. The approximate rate of occurrence is 0.76 episodes per every 30 days of neutropenia.

The demonstration of markedly reduced infection-related morbidity and mortality with the empiric use of broad-spectrum antibiotics during periods of febrile neutropenia was a major advance in the field of oncology in the 1970s [3,4]. Subsequent studies identified factors associated with a higher risk of bacterial infection and facilitated a more tailored approach to empiric therapy.

Because of important differences between oncology and hematology patients with neutropenia, fever in the pediatric cancer patient during periods of therapy-induced neutropenia are reviewed here. The types of infections and management of fever in the child with other forms of neutropenia are discussed separately. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Management of fever in children with non-chemotherapy-induced neutropenia".)

DEFINITIONS

Neutropenia — Neutropenia is strictly defined as an absolute neutrophil count (ANC) <1500 cells/microL. The ANC is calculated using the following formula:

ANC = total white blood cell count (cells/microL) x (percent neutrophils + percent bands) ÷ 100

For purposes of management of the febrile pediatric cancer patient, neutropenia is defined as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL during the next 48 hours [5,6].

The relative risk of infection is related to both the degree and duration of neutropenia. An increased risk becomes apparent at an ANC <1000 cells/microL, is greater at an ANC ≤500 cells/microL and greatest at an ANC ≤100 cells/microL (profound neutropenia) [2,7]. Patients with neutropenia projected to last for more than seven days also are at a higher risk of infection than are those with neutropenia of shorter duration [8].

Patients with hematologic malignancies that impair phagocytosis and killing of pathogens also are at increased risk of infection even if their ANC is normal (“functional neutropenia”) [6]. Other factors that predispose to infection in association with chemotherapy include breakdown of skin and mucosal barriers, such as mucositis following methotrexate treatment, and altered humoral and cellular immunity [9].

Infections in pediatric cancer patients are more common during periods of chemotherapy-induced neutropenia, but they also can occur in the absence of neutropenia. For example, 90 percent of pediatric oncology patients have central venous catheters, which may be a source of infection whether or not the child is neutropenic. Because children are not always able to convey localized complaints, children with cancer who develop fever must be evaluated for infections regardless of the ANC.

Fever — Fever generally is defined as a single oral temperature ≥38.3ºC (101ºF) in neutropenic patients [10]. A temperature ≥38ºC (100.4ºF) for longer than one hour or two elevations >38ºC (100.4ºF) during a 12-hour period are additional definitions of fever that may be used [6,11].

Oral temperature measurements are preferred, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Rectal temperature measurement should be avoided in neutropenic patients because of associated risks of mucosal trauma and bacteremia.

Fever often is the sole sign of occult infection in the neutropenic host [6]. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

Risk category — Patients with fever and neutropenia can be divided into high- and low-risk categories based upon presenting signs and symptoms, counts, underlying cancer, type of therapy and the anticipated length of neutropenia, and medical comorbidities [6]. However, there is no currently agreed-upon risk stratification specifically for children.

High-risk — High-risk patients have an increased risk of severe infection. The 2010 IDSA guidelines define patients with any of the following as high-risk [6]:

- Profound neutropenia (ANC ≤100 cells/microL) anticipated to last >7 days
- Evidence of hepatic insufficiency (aminotransferase levels >5 times normal values) or renal insufficiency (creatine clearance <30 mL/min)
- Comorbid medical problems including, but not limited to:

- Hemodynamic instability
- Oral or gastrointestinal mucositis that interferes with swallowing or causes diarrhea
- Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, or diarrhea
- New-onset neurologic or mental status changes
- Intravascular catheter infection (especially catheter tunnel infection)
- New pulmonary infiltrate or hypoxemia or underlying chronic lung disease

The Multiple Association for Supportive Care in Cancer (MASCC) score may be used to formally assess risk of infection [12]. Patients with MASCC score <21 are at high risk. However, the utility of the MASCC Risk-Index score in pediatric patients is questionable since it was derived from persons older than 16 years and is influenced by chronic medical conditions, such as chronic obstructive pulmonary disease, diabetes, and congestive heart failure that are uncommon in children.

High-risk patients should be admitted to the hospital for empiric antimicrobial therapy (algorithm 1).

Low-risk — Low-risk patients are those with [6]:

- Neutropenia expected to resolve within seven days
- Stable and adequate hepatic and renal function
- No active comorbidities

Carefully selected low-risk patients may be candidates for oral empiric therapy or outpatient treatment.

ETIOLOGY OF FEVER — The rate of documented infection, when a child presents with fever and therapy-induced neutropenia, ranges between 10 and 40 percent [2,13-15]. No clinical or microbiologic evidence of infection will be established in the remainder. Bacteremia is the most common form of documented infection [2,15]. Other sites of infection include the gastrointestinal tract, with oral or intestinal mucositis or diarrhea caused by organisms such as Clostridium difficile and Salmonella sp.; upper and lower respiratory tract; urinary tract; and skin and soft tissues [1,13].

Rates of bacteremia vary greatly (range approximately 20 to 50 percent) depending upon the institution and underlying malignancy [14-17].

Both gram-positive and gram-negative organisms are isolated frequently from the blood in febrile neutropenic children [2,15,18]. The frequency of pathogenic organisms varies from institution to institution. In general, there is a global shift toward a dominance of gram-positive organisms due to the ubiquitous use of prophylactic antimicrobials and indwelling venous catheters. The most common gram-positive pathogens are coagulase-negative staphylococci, viridans streptococci, and Staphylococcus aureus (including methicillin-resistant S. aureus) [2,15]. Aerobic gram-negative bacilli account for approximately one-third to one-half of bacteremic episodes, with Escherichia coli, Klebsiella sp., Pseudomonas sp., Acinetobacter sp., and Enterobacter sp. among the more common isolates [2,13-15,18].

Fungi, typically Candida sp., are more likely to be recovered after prolonged courses of broad-spectrum antibiotics but occasionally may be the primary pathogen [2]. Other potential fungal organisms include Aspergillus sp., Phycomycetes, and Cryptococcus sp. [19,20]. Fusarium sp. also have been increasingly recognized in these hosts [21]. The increasing use of antifungal prophylaxis is likely to shift the distribution of fungal isolates away from Candida sp. and toward mold infections [22]. This is particularly true in bone marrow/stem cell transplant recipients.

The most significant viral etiologies are herpes simplex and varicella-zoster virus [15,23,24]. Respiratory viruses are also frequently detected in nasopharyngeal aspirates [15,23,25].

EVALUATION — Infection is a major cause of morbidity and mortality in cancer patients. Serious infection may occur in the absence of fever and/or neutropenia and must be considered in the pediatric cancer patient who is febrile and neutropenic; febrile but not neutropenic; or neutropenic and afebrile with signs of infection or clinical deterioration.

Prompt initiation of empiric therapy can be life-saving, so rapid (but thorough) evaluation is critical.

History — Important aspects of the history in a child with fever and neutropenia include [6]:

- New site-specific symptoms
- Antimicrobial prophylaxis
- Infection exposures
- History of documented infections or colonization
- Concomitant noninfectious cause of fever (eg, receipt of blood products)
- Underlying comorbid conditions (eg, diabetes, recent surgery)
- Presence of intravascular catheters or other devices
- Previous chemotherapy, agents used, and the stage of therapy (to anticipate the length of the neutropenic episode)

Physical examination — A careful physical examination should be performed with particular attention paid to those sites most commonly infected, including [6]:

- Skin, especially folds, areas surrounding nail beds, central venous line exit sites and subcutaneous tunnel, if present, and sites of bone marrow aspiration and lumbar puncture
- Sinuses
- Oropharynx, with attention to the gingiva
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Laboratory tests and imaging — The laboratory evaluation for the child with fever and neutropenia should include [6]:

- Complete blood count with differential and platelet count

- Electrolytes, creatinine, and blood urea nitrogen
- Liver transaminases and total bilirubin
- Blood cultures
- Cultures and/or imaging of other sites of suspected infection as clinically indicated (described below)

Blood cultures should be obtained without delay. Blood cultures should be taken from each lumen of the central line when such access is available. Opinions vary as to whether blood should be cultured from peripheral sites, as well [26-28]. The rationale for culturing blood from both peripheral and central sites is to differentiate a catheter-related infection from a bacteremia from another source. A catheter-related bloodstream infection can be diagnosed if the colony count of microbes in blood obtained via the catheter hub is at least threefold greater than that obtained from the peripheral blood or if the culture obtained via the catheter hub becomes positive at least two hours before the peripheral blood when using a continuous read system. However, treatment recommendations for central catheter-related infections and for bacteremias from other sources are similar, and many institutions do not recommend the routine culturing of blood from peripheral sites in addition to central sites even though peripheral cultures are necessary to confirm a diagnosis of catheter-related bloodstream infection. Routine peripheral cultures are not obtained at Texas Children's Hospital, but they are obtained on occasion, to guide decisions about whether to retain or remove a catheter.

Obtaining more than one blood culture is helpful in the interpretation of blood culture results. If coagulase-negative staphylococci are isolated from two or more blood cultures, true bacteremia is more likely than contamination of the specimen, which may be reflected by a single positive blood culture. When obtaining blood from a central venous catheter, the importance of sampling all lumens is supported by studies in which 32 to 43 percent of positive cultures from double lumen catheters were positive from only one of multiple lumens [26,29]. In addition, comparison of microbe colony count or differential time to positivity can be used to diagnose a catheter-related blood stream infection in many cases [30].

If the child remains febrile after initiation of empiric antibiotic therapy, daily blood cultures should be obtained for the next two days, after which blood cultures should be repeated when there is a change in clinical status [6]. Blood cultures also should be repeated if fever recurs following initial defervescence in response to empiric antibiotic therapy.

In addition to the blood, it may be useful to culture urine in febrile, neutropenic girls. In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of those occurred in girls [1]. Additional studies should be obtained only as clinically indicated. Examples include:

- Chest radiographs in children with respiratory signs and symptoms [31,32]. A chest radiogram that is negative for infiltrates should be interpreted with caution because infiltrates might appear with a delay or only when neutrophil counts are recovering.
- Abdominal imaging (radiographs or computed tomography) and/or ultrasonography in children with abdominal signs and symptoms, particularly abdominal pain
- Lumbar puncture for altered mental status or meningeal signs; platelet transfusion may be necessary before lumbar puncture in patients with thrombocytopenia
- Clostridium difficile toxin assay should be performed in patients with diarrhea. Although usually of limited value, stool culture, stool for viral particles, ova, parasites, and viral cultures should be considered if the clinical presentation is suggestive of infection.
- Culture and Gram stain of drainage from any site with drainage

OVERVIEW OF TREATMENT — The cornerstone of therapy for the febrile, neutropenic patient is prompt initiation of empiric broad-spectrum antibiotics. General guidelines have been published for the use of empiric antibiotics during episodes of fever and neutropenia, including those published by the Infectious Diseases Society of America (IDSA), most recently updated in 2010 [6].

Empiric antimicrobial therapy — The 2010 IDSA guidelines for antimicrobial agents in neutropenic patients with cancer provide suggestions for initial empiric antibiotic selection (algorithm 1) [6]. However, they are only meant to be guidelines, and treatment must be individualized for each patient (eg, those at risk for infections with resistant organisms).

The 2010 guidelines emphasize that, when choosing empiric therapy, each practitioner should consider [6]:

- Whether the child is at high or low risk of infection (see 'Risk category' above)
- The types of bacterial isolates found in the institution
- Antibiotic susceptibility patterns
- Drug allergies of the patient, if any
- Presence of organ dysfunction, particularly renal and hepatic
- The particular chemotherapeutic regimen and when it was administered: for example, an association exists between viridans streptococcal infection and high-dose cytarabine therapy [33,34]
- Whether the patient was receiving prophylactic antimicrobials
- Previous colonization with resistant bacteria (eg, methicillin-resistant S. aureus; vancomycin-resistant enterococcus; extended-spectrum beta-lactamase producing organism, including Klebsiella pneumoniae carbapenemase)

Bacterial infections in neutropenic cancer patients may be caused by either gram-positive or gram-negative organisms, and thus, empiric antibiotic therapy must be effective against a broad spectrum of potential pathogens. (See 'Etiology of fever' above.) For patients in whom a site of infection is defined, therapy can be adjusted from broad-spectrum to the most appropriate treatment for the particular infection once the patient has become afebrile [6].

Initial therapy

Suggested regimens — Initial therapy with a broad-spectrum antipseudomonal beta-lactam (eg, cefepime or ceftazidime), a carbapenem (eg, meropenem or imipenem-cilastin), or piperacillin-tazobactam is recommended for uncomplicated episodes of fever in neutropenic patients [6]. Randomized controlled trials and a systematic review have demonstrated that empiric monotherapy with these agents is as efficacious as combination therapy but with fewer adverse events [35-38].

Recommended agents include:

- Cefepime — 50 mg/kg intravenously (IV) every 8 hours up to a maximum of 2 g per dose; OR
- Ceftazidime — 50 mg/kg IV every 8 hours up to a maximum of 2 g per dose; adjust dose for renal dysfunction; OR
- Meropenem — For children ≥3 months of age: 20 mg/kg IV every 8 hours up to a maximum of 1 g per dose for non-central nervous system infections and 40 mg/kg IV every 8 hours up to a maximum of 2 g/dose for central nervous system infections; adjust dose for renal dysfunction; OR
- Imipenem-cilastatin — 25 mg/kg IV every 6 hours up to a maximum of 1 g per dose for infants older than one month of age and children; adjust dose for renal dysfunction, OR
- Piperacillin/tazobactam — For infants <9 months: 80 mg/kg of piperacillin component IV every 8 hours; for infants and children ≥9 months and ≤40 kg: 100 mg/kg of piperacillin component IV every 8 hours; for children >40 kg: 3 g of piperacillin component IV every 6 hours or 4 g of piperacillin component IV every 6 to 8 hours; the maximum daily dose of the piperacillin component is 16 g/day; adjust dose for renal dysfunction

If a carbapenem is to be used, meropenem is preferred because of the risk of seizures with imipenem-cilastin.

Additional antimicrobials may be added to the initial regimen based on the clinical presentation, suspected antimicrobial resistance, or for management of complications. As an example, if abdominal symptoms are present, particularly abdominal pain or blood per rectum, metronidazole should be added if the initial combination does not adequately cover anaerobic organisms [5,6]. Likewise, if infection with methicillin-resistant S. aureus is suspected, the addition of vancomycin may be beneficial.

Vancomycin — Vancomycin is not routinely recommended in the initial empiric regimen for patients with fever and neutropenia [6]. It should be reserved for children with clear indications for gram-positive coverage.

Although up to two-thirds of bacterial isolates from blood in febrile neutropenic cancer patients are gram-positive cocci, frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-

generation cephalosporins, the morbidity and mortality have not differed in patients treated with or without vancomycin in the initial antibiotic regimen [39-41]. Infections with alpha-hemolytic streptococci may be an exception to this observation [42].

The use of vancomycin as part of empiric therapy of febrile neutropenia is discouraged to decrease colonization or infection with vancomycin-resistant enterococci (VRE). Many institutions have implemented guidelines for the use of vancomycin recommended by the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) [43]. These restrictions include using vancomycin in febrile neutropenic patients only when there is a strong suspicion of infection with a gram-positive organism.

The 2010 guidelines from the IDSA recommend that vancomycin be reserved for the following clinical scenarios [6]:

- Hypotension or other signs of cardiopulmonary deterioration
- Radiographically documented pneumonia
- Clinically suspected central venous line site infection (eg, chills or rigors with infusion through the catheter and cellulitis around the catheter entry or exit site)
- Skin or soft tissue infection at any site
- Known colonization with methicillin-resistant S. aureus (MRSA), penicillin- and cephalosporin-resistant Streptococcus pneumoniae
- When a blood culture has been reported to be growing gram-positive bacteria and identification and susceptibility testing are pending

Additional indications for vancomycin may include:

- Substantial mucositis
- Prophylaxis with quinolones during afebrile neutropenia
- Previous history of infection with penicillin-resistant streptococci
- Recent intensive chemotherapy associated with a high risk for infection with such organisms (eg, alpha-hemolytic streptococcal infection following high-dose cytarabine) [15]

If vancomycin is added to the empiric regimen for one of the above indications and susceptible bacteria are not recovered from the patient within two to three days, vancomycin should be discontinued [6].

Initial oral therapy for low-risk patients — Although it has not been studied in children, the combination of ciprofloxacin and amoxicillin-clavulanate is an option for combination therapy for low-risk patients who are candidates for oral empiric therapy [6,44,45]

Modifications of initial therapy — After initiation of the initial antimicrobial regimen, patients should be monitored closely. Modification of the regimen may be warranted based upon a variety of clinical scenarios, including (algorithm 2) [6]:

- Change in clinical status or vital signs
- Isolation of a blood-borne organism
- Documented clinical or microbiologic infection
- Development of signs or symptoms of a localized infection
- Persistent fever for more than four days (algorithm 3)
- Recurrent fever after initial defervescence

Antifungal therapy — Fungi are not often isolated as the initial cause of fever and neutropenia but are often in the differential diagnosis of persistent or recurrent fever. Clinically occult fungal infection must be considered in children with persistent fever (ie, ≥4 days) and neutropenia despite empiric antibacterial therapy [46]. A variety of fungi can cause infection in cancer patients, and early diagnosis can be difficult.

The 2010 IDSA guidelines indicate that the addition of empiric antifungal therapy may be warranted for high-risk patients who have persistent fever after four to seven days of broad-spectrum antibiotics and no identified source of fever [6]. Routine use of empiric antifungal therapy is not recommended for low-risk patients. Before

initiating antifungal therapy, suggested evaluations of the patient may include computed tomography (CT) of the chest and sinuses, serial fungal serology (eg, beta-D-glucan, galactomannan), and biopsy of any suspicious lesions [6].

Antifungal therapy is supported by a randomized, placebo-controlled trial in which empiric intravenous administration of amphotericin B early in the course of febrile neutropenia was effective in the control of clinically occult fungal invasion and in the prevention of fungal superinfections [8].

Despite the potential benefits of empiric amphotericin B therapy, its use is limited by substantial toxicity, particularly nephrotoxicity. Potentially less toxic alternatives include lipid formulations of amphotericin B (liposomal amphotericin or amphotericin B colloidal dispersion), echinocandins (eg, caspofungin), and triazole derivatives (eg, voriconazole). The IDSA guidelines indicate that there is insufficient information to suggest a preferred first-line antifungal agent [6]. Amphotericin B (lipid formulations) often are used in children. In children receiving antifungal prophylaxis with an amphotericin B formulation, an antifungal from a different class should be used as empiric therapy.

Pooled analysis of four randomized trials [47-50] found lipid formulations of amphotericin B to have similar rates of breakthrough fungal infections, but less nephrotoxicity and infusion-related toxicity (liposomal formulations) than conventional amphotericin B [51].

Caspofungin is approved by the US Food and Drug Administration for the treatment of fever and neutropenia in children ≥3 months. However, data regarding its safety and efficacy in children with fever and neutropenia are limited. A multicenter randomized trial comparing caspofungin with liposomal amphotericin B in 82 children with persistent fever and neutropenia found that the two agents had similar response rates and adverse effects, including infusion-related toxicity and nephrotoxicity [52]. However, the trial was not powered to detect statistically significant differences. Further study is indicated.

Voriconazole is another antifungal agent that has been insufficiently studied in children with fever and neutropenia. A systematic review of two trials comparing voriconazole with amphotericin B found liposomal amphotericin B to be more effective than voriconazole [53].

Duration of therapy — The duration of empiric antibiotic therapy depends upon the clinical circumstances of the individual patient. The traditional endpoint has been resolution of neutropenia (ie, ANC >500 cells/microL) [6,54]. However, investigators have studied risk factors for the development of serious infection in an effort to reduce the length of time of hospitalization (if any) and the length of therapy in children and adolescents with low risk for significant complications [13,15,55-57].

Patients with prolonged neutropenia (ie, more than seven days) generally are considered at relatively high risk for both bacterial and fungal infections. However, retrospective review of 33 children with prolonged neutropenia from one institution demonstrated that such patients can be discharged safely before resolution of the neutropenia if they appeared well, were afebrile for at least 24 hours, had sterile blood cultures, had any local infection under control, and showed evidence of bone marrow recovery [16,56]. Bone marrow recovery was defined as any sustained increase in platelet count and ANC or absolute phagocyte count (APC = ANC + absolute monocyte count). These investigators also showed that patients with either transient or prolonged neutropenia could be discharged safely from the hospital with antibiotics discontinued when they met the above criteria [56,57]. Similar criteria are used to guide decisions on the appropriate duration of therapy at other institutions [10].

Data from a small retrospective study suggest that patients who are afebrile for at least 24 hours, are in good clinical condition, have been treated with intravenous antibiotics for a minimum of 72 hours, and have no identified infectious source can be discharged from the hospital without antibiotics before evidence of marrow recovery [58].

Colony stimulating factors

Prophylactic use — Most children treated for cancer in the United States are treated on research protocols, and many of the intensive chemotherapy regimens incorporate the use of granulocyte-colony stimulating factor (G-CSF) immediately after courses of chemotherapy. Potential benefits of prophylactic G-CSF or granulocyte-

monocyte colony stimulating factor (GM-CSF) include a reduction in the duration of neutropenia and, in theory, the risk of infection. (See "Prophylaxis of infection during chemotherapy-induced neutropenia", section on 'Colony stimulating factors (myeloid growth factors)'.)

Although most pediatric studies have demonstrated that prophylactic use of G-CSF reduces the duration of neutropenia, conclusions about its impact on rates of febrile neutropenia, days of fever, days of intravenous antibiotic use, rates of documented infection, and lengths of hospital stay have conflicted [59-63]. The conflicting results may reflect differences in the myelosuppressive intensity of the various chemotherapy regimens, one of many variables among the different studies. In a meta-analysis of 16 randomized, controlled trials of the prophylactic use of CSFs in children, CSFs were associated with a 20 percent reduction in febrile neutropenia and an approximately two-day decrease in hospitalization duration, but no difference in parenteral IV antibiotic therapy or infection-related mortality rate [64].

The 2010 IDSA guidelines for neutropenic patients indicate that prophylactic use of CSFs may be warranted for patients in whom the anticipated risk of fever and neutropenia is ≥20 percent [6].

Interventional use — Significant benefits from initiating CSFs in the midst of febrile neutropenia have not been firmly established. In a randomized study of 186 episodes of febrile neutropenia in pediatric cancer patients, a small but statistically significant reduction in the length of hospital stay (five versus seven days) and days of intravenous antibiotic use (five versus six days) was observed with administration of G-CSF compared with placebo [65]. In another randomized trial in 66 patients with chemotherapy-induced febrile neutropenia (59 with acute lymphoblastic leukemia), those treated with G-CSF had shorter median time to resolution of neutropenia (4 versus 13 days), but no significant differences in duration of fever or antibiotic treatment, addition of antifungal therapy, or incidence of shock [66]. Comparable, modest results were obtained in a study evaluating the effect of the addition of GM-CSF during episodes of fever and neutropenia [67].

Whether high-risk patients (see 'High-risk' above) and/or those with predicted prolonged courses of neutropenia (ie, more than 7 days) might benefit from the use of G-CSF remains unanswered. Nonetheless, interventional G-CSF may be warranted for children with complicated episodes of fever and neutropenia [68-70].

Outpatient management — Outpatient management of fever and neutropenia with intravenous or oral antibiotics may be an option for carefully selected low-risk patients if daily follow-up is ensured [6]. Several studies using strict eligibility criteria suggest that outpatient treatment may be safe and appropriate for children at low risk of serious infection [71-74].

In a retrospective study, hypotension, requirement for fluid resuscitation, and a diagnosis of leukemia or lymphoma correlated with an increased probability of bacteremia and persistent fever and ANC <100 cells/microL after 48 hours of empiric therapy were associated with a high risk of complications [13]. Based upon these observations, the investigators suggested that children who initially present without signs of sepsis and who are afebrile and have an ANC >100 cells/microL after 48 hours of empiric therapy could be considered for early hospital discharge, with continuation of outpatient antibiotics [13].

Another retrospective review of 33 children with prolonged neutropenia demonstrated that such patients can be discharged safely before resolution of the neutropenia if they appeared well, were afebrile for at least 24 hours, had sterile blood cultures, had any local infection under control, and showed evidence of bone marrow recovery [56]. Bone marrow recovery was defined as any sustained increase in platelet count and ANC or absolute phagocyte count (APC = ANC + absolute monocyte count).

SUMMARY AND RECOMMENDATIONS

- Infection is a major cause of morbidity and mortality in cancer patients. Fever may be the first manifestation of a life-threatening infection, particularly during periods of neutropenia. (See 'Introduction' above.)
- Neutropenia, for the purpose of management of the febrile pediatric cancer patient, is defined as an absolute neutrophil count (ANC) of <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL during the next 48 hours. In neutropenic patients, fever is defined as a single oral temperature ≥38.3ºC (101ºF), a temperature ≥38ºC (100.4ºF) for longer than one hour, or two elevations >38ºC (100.4ºF) during a 12-hour period. (See 'Definitions' above.)

- Patients with fever and neutropenia can be categorized as high- or low-risk for severe infection based upon presenting signs and symptoms, ANC, underlying cancer, type of therapy, and medical comorbidities. High-risk is defined by profound neutropenia (ANC ≤100 cells/microL) anticipated to last >7 days; hepatic or renal insufficiency; or comorbid medical problems. Low-risk is defined by neutropenia expected to resolve within 7 days; stable and adequate hepatic and renal function; and no active comorbidities. (See 'Risk category' above.)
- Between 10 and 40 percent of children with fever and chemotherapy-induced neutropenia have a documented infection. Bloodstream infections are the most common and may be caused by gram-positive organisms, gram-negative organisms, or fungi. (See 'Etiology of fever' above.)
- Infection is a major cause of morbidity and mortality in cancer patients. Serious infection may occur in the absence of fever and/or neutropenia and must be considered in the pediatric cancer patient who is febrile and neutropenic; febrile but not neutropenic; or neutropenic and afebrile with signs of infection or clinical deterioration. Prompt initiation of empiric therapy can be life-saving, so rapid (but thorough) evaluation is critical (See 'Evaluation' above.)
- Important aspects of the history include new site-specific symptoms, antimicrobial prophylaxis, infection exposures, recent infections or colonizations, underlying comorbid conditions, and noninfectious causes of fever (eg, receipt of blood products). (See 'History' above.)
- Areas of particular interest on the physical examination include the skin (especially skin folds, nail beds, central line sites, and sites of recent procedures such as bone marrow aspiration or lumbar puncture); sinuses; oropharynx, including the gums; lungs; abdomen; and perineum. Mild erythema or tenderness may be important clues to infection. The physical examination must be repeated at least daily after initiation of empiric antimicrobial therapy. (See 'Physical examination' above.)
- The laboratory/imaging evaluation of the child with fever and neutropenia should include (at minimum) (see 'Laboratory tests and imaging' above):

- Complete blood count with differential and platelet count
- Electrolytes, creatinine, and blood urea nitrogen
- Liver transaminases and total bilirubin
- Blood cultures
- Cultures and/or imaging of other sites of suspected infection as clinically indicated

- The 2010 Infectious Disease Society of North America guidelines for antimicrobial agents in neutropenic patients with cancer provides suggestions for initial empiric antibiotic selection (algorithm 1), modification of the empiric regimen during days two to four of therapy (algorithm 2), and management of high-risk patients with fever for more than four days (algorithm 3). (See 'Overview of treatment' above.)
- Monotherapy with a broad-spectrum antipseudomonal beta-lactam (eg, cefepime, ceftazidime), a carbapenem (eg, imipenem-cilastin or meropenem), or piperacillin-tazobactam is recommended for uncomplicated episodes of fever in neutropenic patients. Vancomycin should be reserved for children with clear indications for gram-positive coverage. (See 'Empiric antimicrobial therapy' above.)
- Empiric antifungal therapy may be warranted for high-risk patients who have persistent fever after four to seven days of broad-spectrum antibiotics and no identified source of fever. (See 'Antifungal therapy' above.)
- The duration of empiric antibiotic therapy depends upon the clinical circumstances of the individual patient. Resolution of neutropenia is the traditional endpoint. Outpatient management of fever and neutropenia with intravenous or oral antibiotics may be an option for carefully selected low-risk patients if daily follow-up is ensured. (See 'Duration of therapy' above and 'Outpatient management' above.)

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Management of fever in children with non-chemotherapy-induced neutropenia

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INTRODUCTION — Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder. The management of children with fever and chronic neutropenic disorders is reviewed here. The definitions of neutropenia, conditions that cause neutropenia, the risk of infection in children with neutropenia, and fever in children with chemotherapy-induced neutropenia are discussed separately. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia".)

GUIDELINES FOR TREATMENT OF FEVER AND NEUTROPENIA — Guidelines for the management of fever and neutropenia in the cancer patient have been derived from controlled clinical trials [1]. Similar validated therapeutic approaches to fever in the patient with other forms of neutropenia have not been developed because of the rarity of the primary neutropenic disorders. Thus, management of the high-risk patient with chronic neutropenia generally is extrapolated from the care of the patient with chemotherapy-induced neutropenia. However, depending on the cause and severity of neutropenia (table 1), the febrile patient with neutropenia not caused by chemotherapy may not have the same risk for viral, fungal, and parasitic infections as the patient receiving long-term or intensive chemotherapy.

Initiation of empiric broad-spectrum antibiotic therapy for fever and neutropenia is required in any ill-appearing patient and for patients with underlying severe aplastic anemia or congenital neutropenia. Patients with chronic neutropenia or cyclic neutropenia who have experienced a life-threatening infection or have recurrent infections should be similarly treated.

DEFINITIONS OF FEVER — Fever in neutropenic patients generally is defined as a single oral temperature >38.3ºC (101ºF) [2]. A temperature ≥38ºC (100.4ºF) for longer than 1 hour or two elevations >38ºC during a 12-hour period are definitions of fever that also are used [1,3].

Fever often is the sole sign of occult infection in the neutropenic host. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

MEASUREMENT OF TEMPERATURE — Measuring the temperature orally is preferable, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Because of associated risks of mucosal trauma and bacteremia, measurement of rectal temperature should be avoided in neutropenic patients.

INITIAL EVALUATION — Children with neutropenia should be evaluated promptly upon developing fever because they are at substantial risk to develop a life-threatening infection. The evaluation ideally should occur at a hospital with subspecialty services or at a facility that can arrange for transport to such a facility.

Physical examination — A careful physical examination should be performed, with particular attention paid to those sites most commonly infected, including:

- Skin, especially folds, areas surrounding nail beds, and central venous line sites and subcutaneous tunnel, if present
- Sinuses; sinus tenderness should be evaluated

- Oropharynx, with particular attention to the gum line and buccal mucosa
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Cultures — Blood cultures should be obtained without delay. Blood cultures should be taken from the central line when such access is available. Opinions vary as to whether blood should also be cultured from peripheral sites in these patients [4-6]. The rationale for culturing both peripheral and central sites is to differentiate a catheter-related infection from bacteremia from another source. However, peripheral cultures may be positive in patients with significant central catheter-related infections [7]. In addition, treatment recommendations for central catheter-related infections and for bacteremia from other sources are the same in cancer patients [1,7]. Thus, we do not recommend the routine culturing of blood from peripheral sites in addition to central sites, unless contrary institutional practice guidelines are in place.

Obtaining more than one blood culture is helpful in the interpretation of blood culture results. As an example, true bacteremia is more likely when coagulase-negative staphylococci are isolated from two or more blood cultures than from a single culture, which may be reflective of a contaminated specimen. In addition, the practice of sampling all lumens of a multiple-lumen central venous catheter is supported by two studies in which 32 to 43 percent of positive cultures from multiple-lumen catheters were positive from only one lumen [4,8].

The only other site that may be useful to culture routinely is urine in febrile neutropenic girls. In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of these occurred in girls [9].

Additional studies — Additional studies should be obtained as clinically indicated. Examples include:

- Chest radiographs in children with respiratory signs and symptoms [10]. A chest radiogram that is negative for infiltrates should be interpreted with caution since infiltrates may not appear until neutrophil counts are recovering.
- Abdominal radiographs and/or ultrasound in children with abdominal signs and symptoms, particularly abdominal pain [11]
- Lumbar puncture for altered mental status or meningeal signs
- Stool culture, Clostridium difficile toxin, ova, parasites, and viral cultures in patients with diarrhea
- Culture and Gram stain of drainage from any site with drainage

EMPIRIC ANTIBIOTICS — The cornerstone of treatment for the febrile, neutropenic patient at high risk for infection is prompt initiation of empiric broad-spectrum antibiotic therapy. Specific sites of infection, if present, will guide the choice of antibiotics. When choosing empiric therapy, the practitioner should consider:

- The types of bacterial isolates found in the institution
- Antibiotic susceptibility patterns
- The patient's drug allergies (if any)
- Presence of organ dysfunction, particularly renal and hepatic
- History and cause of previous life-threatening infections
- Whether the patient was receiving prophylactic antimicrobials
- Previous colonization with resistant bacteria (eg, methicillin-resistant S. aureus; vancomycin-resistant enterococcus; extended-spectrum beta-lactamase producing organism, including Klebsiella pneumoniae carbapenemase)

Suggested regimens — Care for the high-risk hematology patient is extrapolated from the care of the cancer patient with chemotherapy-induced neutropenia. Both groups of patients are at risk for infections caused by gram-positive and gram-negative organisms, and thus, empiric antibiotic therapy should be effective against a broad spectrum of potential pathogens. Although gram-positive organisms represent the majority of isolates in

febrile neutropenia patients, empiric antibiotic therapy should ensure adequate (and preferably synergistic) gram-negative coverage because of the potential for a life-threatening infection with gram-negative organisms.

Many studies have demonstrated that monotherapy with a broad-spectrum antipseudomonal agent (such as ceftazidime) or a carbapenem (such as imipenem-cilastin) is as efficacious as combination therapy for the empiric treatment of most febrile neutropenic patients [12-14]. Monotherapy is considered standard therapy for uncomplicated episodes of fever [1,15].

Acceptable monotherapy regimens include:

- Cefepime — 50 mg/kg (to a maximum of 2 g per dose) intravenously (IV) every 8 hours (see "Cefepime: Pediatric drug information"); OR
- Ceftazidime — 50 mg/kg (to a maximum of 2 g per dose) IV every 8 hours; the dose must be adjusted for renal dysfunction (see "Ceftazidime: Pediatric drug information"); OR
- Meropenem — For children ≥3 months of age with non-central nervous system infection: 20 mg/kg IV (to a maximum of 1 g per dose every 8 hours; for children ≥3 months of age with central nervous system infection: 40 mg/kg IV (to a maximum of 2 g per dose) every 8 hours; the dose must be adjusted for renal dysfunction (see "Meropenem: Pediatric drug information"); OR
- Imipenem-cilastatin — For infants older than one month of age and children: 25 mg/kg IV (to a maximum of 1 g per dose) every 6 hours; the dose must be adjusted for renal dysfunction (see "Imipenem and cilastatin: Pediatric drug information"), OR
- Piperacillin-tazobactam — For infants <9 months: 80 mg/kg of piperacillin component IV every 8 hours; for infants and children ≥9 months and ≤40 kg: 100 mg/kg of piperacillin component IV every 8 hours; for children >40 kg: 3 g of piperacillin component IV every 6 hours or 4 g of piperacillin component IV every 6 to 8 hours; the maximum daily dose of the piperacillin component is 16 g/day; the dose should be adjusted for renal dysfunction (see "Piperacillin and tazobactam sodium: Pediatric drug information").

If a carbapenem (meropenem or imipenem-cilastin) is to be used, meropenem is preferred because of the risk of seizures with imipenem-cilastin.

The alternative to monotherapy is combination therapy with an aminoglycoside (eg, gentamicin) plus an antipseudomonal agent (eg, ticarcillin-clavulanate), cefepime, ceftazidime, or a carbapenem [1]. Combination therapy has potential advantages for the patient at high risk for bacterial infection. These include synergistic effects against some gram-negative and gram-positive organisms and possible reduction in the emergence of resistant organisms during treatment. The major disadvantage of combination therapy is the toxicity, particularly nephrotoxicity, of aminoglycosides.

A sample combination therapy regimen is gentamicin plus ticarcillin-clavulanate as follows:

- Gentamicin — For patients <50 kg: 2.5 mg/kg per dose IV every 8 hours; for patients ≥50 kg: 1.5 to 2.0 mg/kg IV (to a maximum of 120 mg per dose) IV every 8 hours; the dose and dosing interval should be adjusted according to serum concentrations for renal dysfunction. (See "Gentamicin: Pediatric drug information".)
- Ticarcillin-clavulanate — 75 mg/kg per dose (to a maximum of 3.1 g per dose) administered IV every 6 hours; the dose should be adjusted for renal dysfunction. (See "Ticarcillin and clavulanate potassium: Pediatric drug information".)

If abdominal symptoms are present, particularly abdominal pain or blood per rectum, metronidazole should be added to broaden coverage for anaerobes [16].

In selective cases, empiric antibiotic therapy could be transferred to an ambulatory setting after an initial period of 48 hours, when blood culture negativity is insured. Outpatient therapy could have substantial financial implications, in addition to its impact on ancillary resources [17].

Modifications — Regardless of the initial empiric choice, modification of the regimen must be considered in the following circumstances:

- Change in clinical status or vital signs
- Persistent fever for >48 hours
- Isolation of an organism from the blood or other infection site
- Development of signs or symptoms of a localized infection
- Recurrent fever after initial defervescence

For those patients in whom a site of infection has been defined and who are afebrile, therapy can be adjusted to the most appropriate treatment for the particular infection [1].

Vancomycin — Vancomycin is a logical drug to include in a broad-spectrum regimen to improve coverage of gram-positive organisms, but the necessity of doing so has not been proven. One-half or more of bacterial isolates in febrile neutropenic cancer patients are gram-positive cocci, and frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-generation cephalosporins. However, antibiotic regimens without vancomycin have not been associated with increased risk of morbidity or mortality [18-20]. This observation probably also holds true for the febrile neutropenic hematology patient. A history of, or increased risk for, infections with alpha-hemolytic streptococci may be an exception [20].

The administration of vancomycin increases the possibility of colonization or infection with vancomycin-resistant enterococci (VRE). Efforts to decrease the emergence of VRE and the possible spread of vancomycin resistance to other gram-positive organisms, such as Staphylococcus aureus, strongly discourage the empiric use of vancomycin in patients with fever and neutropenia.

The Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) has recommended guidelines for the use of vancomycin that have been implemented by many institutions [21]. These guidelines include using vancomycin in febrile neutropenic patients only when there is a strong suspicion of infection with a gram-positive organism.

Indications — Extrapolating from the 2010 guidelines of the Infectious Diseases Society of America (IDSA) for febrile neutropenia in cancer patients, vancomycin is recommended for febrile neutropenia in hematology patients for the following clinical scenarios [1]:

- Clinically suspected central venous line site infection (eg, chills or rigors with infusion through the catheter and cellulitis around the catheter entry or exit site)
- Known colonization with methicillin-resistant S. aureus (MRSA), or penicillin- and cephalosporin-resistant Streptococcus pneumoniae (see "Treatment of invasive methicillin-resistant Staphylococcus aureus infection in children")
- When a blood culture is reported to be growing gram-positive bacteria, and identification and sensitivity testing are pending
- Hypotension or other signs of cardiopulmonary deterioration
- Radiographically documented pneumonia
- Skin or soft tissue infection at any site

Additional indications for vancomycin may include:

- Prior use of quinolone prophylaxis during afebrile neutropenia
- Previous history of infection with penicillin-resistant streptococci

Consideration should be given to the inclusion of vancomycin in the initial empiric antibiotic regimen in institutions with a high rate of bacteremia caused by penicillin-resistant alpha-hemolytic streptococci [20].

The full text of the IDSA guideline is available separately and can be accessed through the Infectious Diseases Society of America's Web site [22].

Substantial efforts have been focused on modifying the dose schedule of aminoglycosides to achieve a better toxicity profile, such as using single daily dosing or their elimination altogether from empiric (and potentially prolonged) antibiotic regimens [17,23,24]. Although such efforts are promising, larger studies are warranted prior to changing the currently available guidelines.

Antifungal therapy — Patients with persistent fever and neutropenia despite empiric antibacterial therapy could have a clinically occult fungal infection. This is a particularly important consideration for patients with severe aplastic anemia, for whom invasive fungal infections are a major cause of death [25].

Amphotericin B is active against a broad spectrum of fungi, including Aspergillus and Candida sps. It should be administered to patients who have remained febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics [3].

A sample amphotericin B dosing schedule is:

- 0.5 mg/kg per dose administered IV once daily for empiric therapy; 1.0 to 1.5 mg/kg per dose administered IV once daily for documented fungal infections.

Despite the potential benefits of empiric amphotericin B therapy, the substantial toxicity, particularly nephrotoxicity, which may accompany its administration, limits its use in many patients. Less toxic alternatives, including lipid formulations of amphotericin B and voriconazole, are being studied in cancer patients, with promising results. These studies and their results are discussed separately. (See "Fever in children with chemotherapy-induced neutropenia", section on 'Antifungal therapy'.)

Whether similar results would be observed in a population of exclusively neutropenic hematology patients is unclear, particularly among patients with severe aplastic anemia, in whom Aspergillus sp. are frequent pathogens as compared with cancer patients in whom Candida sp. predominate. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia".)

In a multicenter randomized trial, the tolerability, efficacy, and safety of caspofungin were comparable to those of liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia [26].

Fluconazole is not active against Aspergillus species. It is therefore a poor choice for empiric antifungal therapy for the patient with neutropenia and prolonged fever.

Duration of therapy — Unlike patients with cytotoxic therapy-induced neutropenia, the duration of neutropenia in the patient with aplastic anemia and other forms of stable chronic neutropenia is indeterminate, complicating the decision about the duration of empiric therapy when no source of infection is identified. Results of a sentinel study of infection in patients with aplastic anemia suggest that empiric antibiotic therapy should continue for 10 to 14 days, followed by careful observation [27].

GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) — The benefits of initiating granulocyte-colony stimulating factor (G-CSF, filgrastim, lenograstim) in neutropenic hematology patients with established fever remain anecdotal. However, there are data on the use of G-CSF to increase neutrophil counts and reduce episodes of fever and infection in patients with various types of chronic neutropenia, as illustrated below:

- A randomized trial in patients with idiopathic chronic neutropenia, cyclic neutropenia, and congenital neutropenia demonstrated that G-CSF increased neutrophil counts and reduced episodes of fever, infection, and hospitalization [28]. Virtually all of the patients with idiopathic chronic neutropenia and cyclic neutropenia responded, whereas only 83 percent of those with congenital neutropenia did. In addition, higher doses of G-CSF were required to achieve a response in patients with congenital neutropenia than in those with idiopathic chronic neutropenia or cyclic neutropenia (up to 15 mcg/kg per day versus 1 to 5 mcg/kg per day).
- A report on 853 patients from the Severe Chronic Neutropenia International Registry included 429 children with idiopathic, cyclic, and congenital neutropenia, almost all of whom were treated with G-CSF [29]. Ninety-two percent of all treated patients (including adults) responded to G-CSF at doses <30 mcg/kg per day with an increase in mean neutrophils to >1500/microL.

The use of G-CSF in the treatment of each of these disorders is discussed in detail separately. (See "Immune neutropenia", section on 'Chronic idiopathic neutropenia' and "Cyclic neutropenia", section on 'Treatment' and "Congenital neutropenia", section on 'Severe congenital neutropenia'.)

For those children not routinely receiving G-CSF, interventional G-CSF may be appropriate for complicated febrile episodes requiring hospitalization. Such children should be treated in specialized centers by clinicians with expertise in the use of G-CSF. (See "Introduction to recombinant hematopoietic growth factors" and "Recombinant hematopoietic growth factors in inherited bone marrow failure syndromes".)

SUMMARY AND RECOMMENDATIONS

- Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder (table 1). (See 'Introduction' above.)
- The approach to fever in the child with non-chemotherapy-induced neutropenia typically parallels that for the child with chemotherapy-induced neutropenia. (See "Fever in children with chemotherapy-induced neutropenia".)
- Fever in the neutropenic patient may be defined as a single oral temperature >38.3ºC (101ºF), a temperature ≥38ºC (100.4ºF) for longer than one hour, or two elevations >38ºC during a 12-hour period. (See 'Definitions of fever' above.)
- Measuring the temperature orally is preferable; an axillary temperature is an acceptable alternative and is considered to be equivalent to an oral temperature without conversion. However, more conservative guidelines suggest that adding 0.5 degrees to the axillary temperature reading may be warranted. Measurement of rectal temperatures should be avoided in neutropenic patients. (See 'Measurement of temperature' above.)
- The initial evaluation must be conducted promptly because of the substantial risk of a life-threatening infection. Serial examination of the most common sites of infection is essential. (See 'Physical examination' above.)
- Blood cultures should be obtained without delay. Cultures should be obtained from the central line if one is present. We suggest obtaining cultures from all lumens if the central line has multiple lumens. We suggest not obtaining peripheral blood cultures in addition to central line cultures in patients with central lines. (See 'Cultures' above.)
- We suggest that urine culture be obtained in febrile girls with neutropenia. Additional studies should be obtained as clinically indicated. (See 'Cultures' above and 'Additional studies' above.)
- We recommend prompt initiation of empiric broad-spectrum antibiotic therapy that ensures both gram-negative and gram-positive coverage (Grade 1A). The choice of antibiotic is guided by the site of infection if a specific infection is present. (See 'Suggested regimens' above.)

- We suggest monotherapy with cefepime, ceftazidime, meropenem, or piperacillin-tazobactam for uncomplicated episodes of fever (Grade 2B).
- We suggest combination therapy with an aminoglycoside and an antipseudomonal agent for the patient at high risk for bacterial infection (table 1) (Grade 2B).
- We suggest the addition of metronidazole for the patient with abdominal symptoms (Grade 2C).

- The use of vancomycin should be reserved for febrile neutropenic patients with certain well-defined clinical scenarios. (See 'Vancomycin' above.)
- The initial empiric regimen should be modified if there is a change in clinical status or vital signs, fever persists for >72 hours, an organism is isolated from the blood, or the patient develops signs or symptoms of a localized infection. In addition, for those patients in whom a site of infection has been defined and in whom fever has resolved, therapy can be adjusted to the most appropriate treatment for the particular infection. (See 'Modifications' above.)
- We suggest that antifungal therapy be administered to patients who remain febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics (Grade 2C). (See 'Antifungal therapy' above.)
- Empiric antibiotic therapy is usually continued for 10 to 14 days, followed by careful observation. (See 'Duration of therapy' above.)

Management of fever in children with non-chemotherapy-induced neutropenia

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INTRODUCTION — Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder. The management of children with fever and chronic neutropenic disorders is reviewed here. The definitions of neutropenia, conditions that cause neutropenia, the risk of infection in children with neutropenia, and fever in children with chemotherapy-induced neutropenia are discussed separately. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia".)

GUIDELINES FOR TREATMENT OF FEVER AND NEUTROPENIA — Guidelines for the management of fever and neutropenia in the cancer patient have been derived from controlled clinical trials [1]. Similar validated therapeutic approaches to fever in the patient with other forms of neutropenia have not been developed because of the rarity of the primary neutropenic disorders. Thus, management of the high-risk patient with chronic neutropenia generally is extrapolated from the care of the patient with chemotherapy-induced neutropenia. However, depending on the cause and severity of neutropenia (table 1), the febrile patient with neutropenia not caused by chemotherapy may not have the same risk for viral, fungal, and parasitic infections as the patient receiving long-term or intensive chemotherapy.

Initiation of empiric broad-spectrum antibiotic therapy for fever and neutropenia is required in any ill-appearing patient and for patients with underlying severe aplastic anemia or congenital neutropenia. Patients with chronic neutropenia or cyclic neutropenia who have experienced a life-threatening infection or have recurrent infections should be similarly treated.

DEFINITIONS OF FEVER — Fever in neutropenic patients generally is defined as a single oral temperature >38.3ºC (101ºF) [2]. A temperature ≥38ºC (100.4ºF) for longer than 1 hour or two elevations >38ºC during a 12-hour period are definitions of fever that also are used [1,3].

Fever often is the sole sign of occult infection in the neutropenic host. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

MEASUREMENT OF TEMPERATURE — Measuring the temperature orally is preferable, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Because of associated risks of mucosal trauma and bacteremia, measurement of rectal temperature should be avoided in neutropenic patients.

INITIAL EVALUATION — Children with neutropenia should be evaluated promptly upon developing fever because they are at substantial risk to develop a life-threatening infection. The evaluation ideally should occur at a hospital with subspecialty services or at a facility that can arrange for transport to such a facility.

Physical examination — A careful physical examination should be performed, with particular attention paid to those sites most commonly infected, including:

- Skin, especially folds, areas surrounding nail beds, and central venous line sites and subcutaneous tunnel, if present
- Sinuses; sinus tenderness should be evaluated

- Oropharynx, with particular attention to the gum line and buccal mucosa
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Cultures — Blood cultures should be obtained without delay. Blood cultures should be taken from the central line when such access is available. Opinions vary as to whether blood should also be cultured from peripheral sites in these patients [4-6]. The rationale for culturing both peripheral and central sites is to differentiate a catheter-related infection from bacteremia from another source. However, peripheral cultures may be positive in patients with significant central catheter-related infections [7]. In addition, treatment recommendations for central catheter-related infections and for bacteremia from other sources are the same in cancer patients [1,7]. Thus, we do not recommend the routine culturing of blood from peripheral sites in addition to central sites, unless contrary institutional practice guidelines are in place.

Obtaining more than one blood culture is helpful in the interpretation of blood culture results. As an example, true bacteremia is more likely when coagulase-negative staphylococci are isolated from two or more blood cultures than from a single culture, which may be reflective of a contaminated specimen. In addition, the practice of sampling all lumens of a multiple-lumen central venous catheter is supported by two studies in which 32 to 43 percent of positive cultures from multiple-lumen catheters were positive from only one lumen [4,8].

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EMPIRIC ANTIBIOTICS — The cornerstone of treatment for the febrile, neutropenic patient at high risk for infection is prompt initiation of empiric broad-spectrum antibiotic therapy. Specific sites of infection, if present, will guide the choice of antibiotics. When choosing empiric therapy, the practitioner should consider:

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- Antibiotic susceptibility patterns
- The patient's drug allergies (if any)
- Presence of organ dysfunction, particularly renal and hepatic
- History and cause of previous life-threatening infections
- Whether the patient was receiving prophylactic antimicrobials
- Previous colonization with resistant bacteria (eg, methicillin-resistant S. aureus; vancomycin-resistant enterococcus; extended-spectrum beta-lactamase producing organism, including Klebsiella pneumoniae carbapenemase)

Suggested regimens — Care for the high-risk hematology patient is extrapolated from the care of the cancer patient with chemotherapy-induced neutropenia. Both groups of patients are at risk for infections caused by gram-positive and gram-negative organisms, and thus, empiric antibiotic therapy should be effective against a broad spectrum of potential pathogens. Although gram-positive organisms represent the majority of isolates in

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The administration of vancomycin increases the possibility of colonization or infection with vancomycin-resistant enterococci (VRE). Efforts to decrease the emergence of VRE and the possible spread of vancomycin resistance to other gram-positive organisms, such as Staphylococcus aureus, strongly discourage the empiric use of vancomycin in patients with fever and neutropenia.

The Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) has recommended guidelines for the use of vancomycin that have been implemented by many institutions [21]. These guidelines include using vancomycin in febrile neutropenic patients only when there is a strong suspicion of infection with a gram-positive organism.

Indications — Extrapolating from the 2010 guidelines of the Infectious Diseases Society of America (IDSA) for febrile neutropenia in cancer patients, vancomycin is recommended for febrile neutropenia in hematology patients for the following clinical scenarios [1]:

- Clinically suspected central venous line site infection (eg, chills or rigors with infusion through the catheter and cellulitis around the catheter entry or exit site)
- Known colonization with methicillin-resistant S. aureus (MRSA), or penicillin- and cephalosporin-resistant Streptococcus pneumoniae (see "Treatment of invasive methicillin-resistant Staphylococcus aureus infection in children")
- When a blood culture is reported to be growing gram-positive bacteria, and identification and sensitivity testing are pending
- Hypotension or other signs of cardiopulmonary deterioration
- Radiographically documented pneumonia
- Skin or soft tissue infection at any site

Additional indications for vancomycin may include:

- Prior use of quinolone prophylaxis during afebrile neutropenia
- Previous history of infection with penicillin-resistant streptococci

Consideration should be given to the inclusion of vancomycin in the initial empiric antibiotic regimen in institutions with a high rate of bacteremia caused by penicillin-resistant alpha-hemolytic streptococci [20].

The full text of the IDSA guideline is available separately and can be accessed through the Infectious Diseases Society of America's Web site [22].

Substantial efforts have been focused on modifying the dose schedule of aminoglycosides to achieve a better toxicity profile, such as using single daily dosing or their elimination altogether from empiric (and potentially prolonged) antibiotic regimens [17,23,24]. Although such efforts are promising, larger studies are warranted prior to changing the currently available guidelines.

Antifungal therapy — Patients with persistent fever and neutropenia despite empiric antibacterial therapy could have a clinically occult fungal infection. This is a particularly important consideration for patients with severe aplastic anemia, for whom invasive fungal infections are a major cause of death [25].

Amphotericin B is active against a broad spectrum of fungi, including Aspergillus and Candida sps. It should be administered to patients who have remained febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics [3].

A sample amphotericin B dosing schedule is:

- 0.5 mg/kg per dose administered IV once daily for empiric therapy; 1.0 to 1.5 mg/kg per dose administered IV once daily for documented fungal infections.

Despite the potential benefits of empiric amphotericin B therapy, the substantial toxicity, particularly nephrotoxicity, which may accompany its administration, limits its use in many patients. Less toxic alternatives, including lipid formulations of amphotericin B and voriconazole, are being studied in cancer patients, with promising results. These studies and their results are discussed separately. (See "Fever in children with chemotherapy-induced neutropenia", section on 'Antifungal therapy'.)

Whether similar results would be observed in a population of exclusively neutropenic hematology patients is unclear, particularly among patients with severe aplastic anemia, in whom Aspergillus sp. are frequent pathogens as compared with cancer patients in whom Candida sp. predominate. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia".)

In a multicenter randomized trial, the tolerability, efficacy, and safety of caspofungin were comparable to those of liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia [26].

Fluconazole is not active against Aspergillus species. It is therefore a poor choice for empiric antifungal therapy for the patient with neutropenia and prolonged fever.

Duration of therapy — Unlike patients with cytotoxic therapy-induced neutropenia, the duration of neutropenia in the patient with aplastic anemia and other forms of stable chronic neutropenia is indeterminate, complicating the decision about the duration of empiric therapy when no source of infection is identified. Results of a sentinel study of infection in patients with aplastic anemia suggest that empiric antibiotic therapy should continue for 10 to 14 days, followed by careful observation [27].

GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) — The benefits of initiating granulocyte-colony stimulating factor (G-CSF, filgrastim, lenograstim) in neutropenic hematology patients with established fever remain anecdotal. However, there are data on the use of G-CSF to increase neutrophil counts and reduce episodes of fever and infection in patients with various types of chronic neutropenia, as illustrated below:

- A randomized trial in patients with idiopathic chronic neutropenia, cyclic neutropenia, and congenital neutropenia demonstrated that G-CSF increased neutrophil counts and reduced episodes of fever, infection, and hospitalization [28]. Virtually all of the patients with idiopathic chronic neutropenia and cyclic neutropenia responded, whereas only 83 percent of those with congenital neutropenia did. In addition, higher doses of G-CSF were required to achieve a response in patients with congenital neutropenia than in those with idiopathic chronic neutropenia or cyclic neutropenia (up to 15 mcg/kg per day versus 1 to 5 mcg/kg per day).
- A report on 853 patients from the Severe Chronic Neutropenia International Registry included 429 children with idiopathic, cyclic, and congenital neutropenia, almost all of whom were treated with G-CSF [29]. Ninety-two percent of all treated patients (including adults) responded to G-CSF at doses <30 mcg/kg per day with an increase in mean neutrophils to >1500/microL.

The use of G-CSF in the treatment of each of these disorders is discussed in detail separately. (See "Immune neutropenia", section on 'Chronic idiopathic neutropenia' and "Cyclic neutropenia", section on 'Treatment' and "Congenital neutropenia", section on 'Severe congenital neutropenia'.)

For those children not routinely receiving G-CSF, interventional G-CSF may be appropriate for complicated febrile episodes requiring hospitalization. Such children should be treated in specialized centers by clinicians with expertise in the use of G-CSF. (See "Introduction to recombinant hematopoietic growth factors" and "Recombinant hematopoietic growth factors in inherited bone marrow failure syndromes".)

SUMMARY AND RECOMMENDATIONS

- Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder (table 1). (See 'Introduction' above.)
- The approach to fever in the child with non-chemotherapy-induced neutropenia typically parallels that for the child with chemotherapy-induced neutropenia. (See "Fever in children with chemotherapy-induced neutropenia".)
- Fever in the neutropenic patient may be defined as a single oral temperature >38.3ºC (101ºF), a temperature ≥38ºC (100.4ºF) for longer than one hour, or two elevations >38ºC during a 12-hour period. (See 'Definitions of fever' above.)
- Measuring the temperature orally is preferable; an axillary temperature is an acceptable alternative and is considered to be equivalent to an oral temperature without conversion. However, more conservative guidelines suggest that adding 0.5 degrees to the axillary temperature reading may be warranted. Measurement of rectal temperatures should be avoided in neutropenic patients. (See 'Measurement of temperature' above.)
- The initial evaluation must be conducted promptly because of the substantial risk of a life-threatening infection. Serial examination of the most common sites of infection is essential. (See 'Physical examination' above.)
- Blood cultures should be obtained without delay. Cultures should be obtained from the central line if one is present. We suggest obtaining cultures from all lumens if the central line has multiple lumens. We suggest not obtaining peripheral blood cultures in addition to central line cultures in patients with central lines. (See 'Cultures' above.)
- We suggest that urine culture be obtained in febrile girls with neutropenia. Additional studies should be obtained as clinically indicated. (See 'Cultures' above and 'Additional studies' above.)
- We recommend prompt initiation of empiric broad-spectrum antibiotic therapy that ensures both gram-negative and gram-positive coverage (Grade 1A). The choice of antibiotic is guided by the site of infection if a specific infection is present. (See 'Suggested regimens' above.)

- We suggest monotherapy with cefepime, ceftazidime, meropenem, or piperacillin-tazobactam for uncomplicated episodes of fever (Grade 2B).
- We suggest combination therapy with an aminoglycoside and an antipseudomonal agent for the patient at high risk for bacterial infection (table 1) (Grade 2B).
- We suggest the addition of metronidazole for the patient with abdominal symptoms (Grade 2C).

- The use of vancomycin should be reserved for febrile neutropenic patients with certain well-defined clinical scenarios. (See 'Vancomycin' above.)
- The initial empiric regimen should be modified if there is a change in clinical status or vital signs, fever persists for >72 hours, an organism is isolated from the blood, or the patient develops signs or symptoms of a localized infection. In addition, for those patients in whom a site of infection has been defined and in whom fever has resolved, therapy can be adjusted to the most appropriate treatment for the particular infection. (See 'Modifications' above.)
- We suggest that antifungal therapy be administered to patients who remain febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics (Grade 2C). (See 'Antifungal therapy' above.)
- Empiric antibiotic therapy is usually continued for 10 to 14 days, followed by careful observation. (See 'Duration of therapy' above.)

Management of fever in children with non-chemotherapy-induced neutropenia

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INTRODUCTION — Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder. The management of children with fever and chronic neutropenic disorders is reviewed here. The definitions of neutropenia, conditions that cause neutropenia, the risk of infection in children with neutropenia, and fever in children with chemotherapy-induced neutropenia are discussed separately. (See "Risk of infection in children with fever and non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia".)

GUIDELINES FOR TREATMENT OF FEVER AND NEUTROPENIA — Guidelines for the management of fever and neutropenia in the cancer patient have been derived from controlled clinical trials [1]. Similar validated therapeutic approaches to fever in the patient with other forms of neutropenia have not been developed because of the rarity of the primary neutropenic disorders. Thus, management of the high-risk patient with chronic neutropenia generally is extrapolated from the care of the patient with chemotherapy-induced neutropenia. However, depending on the cause and severity of neutropenia (table 1), the febrile patient with neutropenia not caused by chemotherapy may not have the same risk for viral, fungal, and parasitic infections as the patient receiving long-term or intensive chemotherapy.

Initiation of empiric broad-spectrum antibiotic therapy for fever and neutropenia is required in any ill-appearing patient and for patients with underlying severe aplastic anemia or congenital neutropenia. Patients with chronic neutropenia or cyclic neutropenia who have experienced a life-threatening infection or have recurrent infections should be similarly treated.

DEFINITIONS OF FEVER — Fever in neutropenic patients generally is defined as a single oral temperature >38.3ºC (101ºF) [2]. A temperature ≥38ºC (100.4ºF) for longer than 1 hour or two elevations >38ºC during a 12-hour period are definitions of fever that also are used [1,3].

Fever often is the sole sign of occult infection in the neutropenic host. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

MEASUREMENT OF TEMPERATURE — Measuring the temperature orally is preferable, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Because of associated risks of mucosal trauma and bacteremia, measurement of rectal temperature should be avoided in neutropenic patients.

INITIAL EVALUATION — Children with neutropenia should be evaluated promptly upon developing fever because they are at substantial risk to develop a life-threatening infection. The evaluation ideally should occur at a hospital with subspecialty services or at a facility that can arrange for transport to such a facility.

Physical examination — A careful physical examination should be performed, with particular attention paid to those sites most commonly infected, including:

- Skin, especially folds, areas surrounding nail beds, and central venous line sites and subcutaneous tunnel, if present
- Sinuses; sinus tenderness should be evaluated

- Oropharynx, with particular attention to the gum line and buccal mucosa
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Cultures — Blood cultures should be obtained without delay. Blood cultures should be taken from the central line when such access is available. Opinions vary as to whether blood should also be cultured from peripheral sites in these patients [4-6]. The rationale for culturing both peripheral and central sites is to differentiate a catheter-related infection from bacteremia from another source. However, peripheral cultures may be positive in patients with significant central catheter-related infections [7]. In addition, treatment recommendations for central catheter-related infections and for bacteremia from other sources are the same in cancer patients [1,7]. Thus, we do not recommend the routine culturing of blood from peripheral sites in addition to central sites, unless contrary institutional practice guidelines are in place.

Obtaining more than one blood culture is helpful in the interpretation of blood culture results. As an example, true bacteremia is more likely when coagulase-negative staphylococci are isolated from two or more blood cultures than from a single culture, which may be reflective of a contaminated specimen. In addition, the practice of sampling all lumens of a multiple-lumen central venous catheter is supported by two studies in which 32 to 43 percent of positive cultures from multiple-lumen catheters were positive from only one lumen [4,8].

The only other site that may be useful to culture routinely is urine in febrile neutropenic girls. In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of these occurred in girls [9].

Additional studies — Additional studies should be obtained as clinically indicated. Examples include:

- Chest radiographs in children with respiratory signs and symptoms [10]. A chest radiogram that is negative for infiltrates should be interpreted with caution since infiltrates may not appear until neutrophil counts are recovering.
- Abdominal radiographs and/or ultrasound in children with abdominal signs and symptoms, particularly abdominal pain [11]
- Lumbar puncture for altered mental status or meningeal signs
- Stool culture, Clostridium difficile toxin, ova, parasites, and viral cultures in patients with diarrhea
- Culture and Gram stain of drainage from any site with drainage

EMPIRIC ANTIBIOTICS — The cornerstone of treatment for the febrile, neutropenic patient at high risk for infection is prompt initiation of empiric broad-spectrum antibiotic therapy. Specific sites of infection, if present, will guide the choice of antibiotics. When choosing empiric therapy, the practitioner should consider:

- The types of bacterial isolates found in the institution
- Antibiotic susceptibility patterns
- The patient's drug allergies (if any)
- Presence of organ dysfunction, particularly renal and hepatic
- History and cause of previous life-threatening infections
- Whether the patient was receiving prophylactic antimicrobials
- Previous colonization with resistant bacteria (eg, methicillin-resistant S. aureus; vancomycin-resistant enterococcus; extended-spectrum beta-lactamase producing organism, including Klebsiella pneumoniae carbapenemase)

Suggested regimens — Care for the high-risk hematology patient is extrapolated from the care of the cancer patient with chemotherapy-induced neutropenia. Both groups of patients are at risk for infections caused by gram-positive and gram-negative organisms, and thus, empiric antibiotic therapy should be effective against a broad spectrum of potential pathogens. Although gram-positive organisms represent the majority of isolates in

febrile neutropenia patients, empiric antibiotic therapy should ensure adequate (and preferably synergistic) gram-negative coverage because of the potential for a life-threatening infection with gram-negative organisms.

Many studies have demonstrated that monotherapy with a broad-spectrum antipseudomonal agent (such as ceftazidime) or a carbapenem (such as imipenem-cilastin) is as efficacious as combination therapy for the empiric treatment of most febrile neutropenic patients [12-14]. Monotherapy is considered standard therapy for uncomplicated episodes of fever [1,15].

Acceptable monotherapy regimens include:

- Cefepime — 50 mg/kg (to a maximum of 2 g per dose) intravenously (IV) every 8 hours (see "Cefepime: Pediatric drug information"); OR
- Ceftazidime — 50 mg/kg (to a maximum of 2 g per dose) IV every 8 hours; the dose must be adjusted for renal dysfunction (see "Ceftazidime: Pediatric drug information"); OR
- Meropenem — For children ≥3 months of age with non-central nervous system infection: 20 mg/kg IV (to a maximum of 1 g per dose every 8 hours; for children ≥3 months of age with central nervous system infection: 40 mg/kg IV (to a maximum of 2 g per dose) every 8 hours; the dose must be adjusted for renal dysfunction (see "Meropenem: Pediatric drug information"); OR
- Imipenem-cilastatin — For infants older than one month of age and children: 25 mg/kg IV (to a maximum of 1 g per dose) every 6 hours; the dose must be adjusted for renal dysfunction (see "Imipenem and cilastatin: Pediatric drug information"), OR
- Piperacillin-tazobactam — For infants <9 months: 80 mg/kg of piperacillin component IV every 8 hours; for infants and children ≥9 months and ≤40 kg: 100 mg/kg of piperacillin component IV every 8 hours; for children >40 kg: 3 g of piperacillin component IV every 6 hours or 4 g of piperacillin component IV every 6 to 8 hours; the maximum daily dose of the piperacillin component is 16 g/day; the dose should be adjusted for renal dysfunction (see "Piperacillin and tazobactam sodium: Pediatric drug information").

If a carbapenem (meropenem or imipenem-cilastin) is to be used, meropenem is preferred because of the risk of seizures with imipenem-cilastin.

The alternative to monotherapy is combination therapy with an aminoglycoside (eg, gentamicin) plus an antipseudomonal agent (eg, ticarcillin-clavulanate), cefepime, ceftazidime, or a carbapenem [1]. Combination therapy has potential advantages for the patient at high risk for bacterial infection. These include synergistic effects against some gram-negative and gram-positive organisms and possible reduction in the emergence of resistant organisms during treatment. The major disadvantage of combination therapy is the toxicity, particularly nephrotoxicity, of aminoglycosides.

A sample combination therapy regimen is gentamicin plus ticarcillin-clavulanate as follows:

- Gentamicin — For patients <50 kg: 2.5 mg/kg per dose IV every 8 hours; for patients ≥50 kg: 1.5 to 2.0 mg/kg IV (to a maximum of 120 mg per dose) IV every 8 hours; the dose and dosing interval should be adjusted according to serum concentrations for renal dysfunction. (See "Gentamicin: Pediatric drug information".)
- Ticarcillin-clavulanate — 75 mg/kg per dose (to a maximum of 3.1 g per dose) administered IV every 6 hours; the dose should be adjusted for renal dysfunction. (See "Ticarcillin and clavulanate potassium: Pediatric drug information".)

If abdominal symptoms are present, particularly abdominal pain or blood per rectum, metronidazole should be added to broaden coverage for anaerobes [16].

In selective cases, empiric antibiotic therapy could be transferred to an ambulatory setting after an initial period of 48 hours, when blood culture negativity is insured. Outpatient therapy could have substantial financial implications, in addition to its impact on ancillary resources [17].

Modifications — Regardless of the initial empiric choice, modification of the regimen must be considered in the following circumstances:

- Change in clinical status or vital signs
- Persistent fever for >48 hours
- Isolation of an organism from the blood or other infection site
- Development of signs or symptoms of a localized infection
- Recurrent fever after initial defervescence

For those patients in whom a site of infection has been defined and who are afebrile, therapy can be adjusted to the most appropriate treatment for the particular infection [1].

Vancomycin — Vancomycin is a logical drug to include in a broad-spectrum regimen to improve coverage of gram-positive organisms, but the necessity of doing so has not been proven. One-half or more of bacterial isolates in febrile neutropenic cancer patients are gram-positive cocci, and frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-generation cephalosporins. However, antibiotic regimens without vancomycin have not been associated with increased risk of morbidity or mortality [18-20]. This observation probably also holds true for the febrile neutropenic hematology patient. A history of, or increased risk for, infections with alpha-hemolytic streptococci may be an exception [20].

The administration of vancomycin increases the possibility of colonization or infection with vancomycin-resistant enterococci (VRE). Efforts to decrease the emergence of VRE and the possible spread of vancomycin resistance to other gram-positive organisms, such as Staphylococcus aureus, strongly discourage the empiric use of vancomycin in patients with fever and neutropenia.

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The use of G-CSF in the treatment of each of these disorders is discussed in detail separately. (See "Immune neutropenia", section on 'Chronic idiopathic neutropenia' and "Cyclic neutropenia", section on 'Treatment' and "Congenital neutropenia", section on 'Severe congenital neutropenia'.)

For those children not routinely receiving G-CSF, interventional G-CSF may be appropriate for complicated febrile episodes requiring hospitalization. Such children should be treated in specialized centers by clinicians with expertise in the use of G-CSF. (See "Introduction to recombinant hematopoietic growth factors" and "Recombinant hematopoietic growth factors in inherited bone marrow failure syndromes".)

SUMMARY AND RECOMMENDATIONS

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- The initial evaluation must be conducted promptly because of the substantial risk of a life-threatening infection. Serial examination of the most common sites of infection is essential. (See 'Physical examination' above.)
- Blood cultures should be obtained without delay. Cultures should be obtained from the central line if one is present. We suggest obtaining cultures from all lumens if the central line has multiple lumens. We suggest not obtaining peripheral blood cultures in addition to central line cultures in patients with central lines. (See 'Cultures' above.)
- We suggest that urine culture be obtained in febrile girls with neutropenia. Additional studies should be obtained as clinically indicated. (See 'Cultures' above and 'Additional studies' above.)
- We recommend prompt initiation of empiric broad-spectrum antibiotic therapy that ensures both gram-negative and gram-positive coverage (Grade 1A). The choice of antibiotic is guided by the site of infection if a specific infection is present. (See 'Suggested regimens' above.)

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- We suggest combination therapy with an aminoglycoside and an antipseudomonal agent for the patient at high risk for bacterial infection (table 1) (Grade 2B).
- We suggest the addition of metronidazole for the patient with abdominal symptoms (Grade 2C).

- The use of vancomycin should be reserved for febrile neutropenic patients with certain well-defined clinical scenarios. (See 'Vancomycin' above.)
- The initial empiric regimen should be modified if there is a change in clinical status or vital signs, fever persists for >72 hours, an organism is isolated from the blood, or the patient develops signs or symptoms of a localized infection. In addition, for those patients in whom a site of infection has been defined and in whom fever has resolved, therapy can be adjusted to the most appropriate treatment for the particular infection. (See 'Modifications' above.)
- We suggest that antifungal therapy be administered to patients who remain febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics (Grade 2C). (See 'Antifungal therapy' above.)
- Empiric antibiotic therapy is usually continued for 10 to 14 days, followed by careful observation. (See 'Duration of therapy' above.)

Risk of infection in children with fever and non-chemotherapy-induced neutropenia

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INTRODUCTION — Fever may be the first manifestation of a life-threatening infection in the neutropenic child, particularly one with a primary hematologic disease such as severe aplastic anemia or congenital neutropenia. Because of important differences between hematology and oncology patients with neutropenia, the risk of infection in hematology patients with different types of non-chemotherapy-induced neutropenia and fever are reviewed here. The management of fever and neutropenia in these patients and in children with chemotherapy-induced neutropenia are discussed separately. (See "Management of fever in children with non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia", section on 'Definitions'.)

DEFINITIONS — Generally, neutropenia is defined as an absolute neutrophil count (ANC) <1500 cells/microL. The ANC is calculated using the following formula:

ANC = total white blood cell count (cells/microL) x (percent neutrophils + percent bands) ÷ 100

Recognizing that normal ANC levels vary with age and race is important. The lower limit of normal for the ANC in infants between two weeks and six months of age is lower than that for the older child (1000/microL versus 1500/microL) [1]. Also, normal neutrophil values for people of African descent are lower than those of Caucasians [2].

The degree of neutropenia is classified as follows:

- Mild — ANC 1000 to 1500/microL
- Moderate — ANC 500 to 1000/microL
- Severe —ANC <500/microL.

Most studies evaluating the significance of the degree of neutropenia on the risk of infection have been in cancer patients, in whom an increased risk of infection becomes apparent at an ANC <1000/microL, is greater at <500/microL, and greatest at <100/microL [3].

In addition to the ANC, factors that influence a patient's susceptibility to infection include:

- Duration of neutropenia
- Function of the neutrophils
- Ability of the bone marrow to respond to an infectious insult
- Function of other components of the immune system

These factors contribute to the differences in infectious complications that are observed between hematology patients with neutropenia and cancer patients with therapy-induced neutropenia. For example, neutropenia in the oncology patient is related to cytotoxic therapy and generally is self-limited, whereas in the patient with severe aplastic anemia, neutropenia may be prolonged for months to years. However, the neutropenic oncology patient often has defects in several arms of the immune system because of the underlying disease and/or chemotherapeutic agents used, which may not exist in the hematology patient.

FEVER AND NEUTROPENIA IN THE OTHERWISE HEALTHY CHILD — The afebrile child with the finding of isolated neutropenia may be followed with serial blood counts and examinations since, in most cases, the neutropenia arises in association with a viral infection and is transient, resolving in one to two weeks [4]. Drugs, such as antibiotics and anticonvulsants, also can cause neutropenia that most often resolves after

cessation of the drug. However, if such a child develops fever, or if a previously healthy child is found to have isolated neutropenia during a febrile illness, appropriate management requires consideration of the risk of serious bacterial infection. Such scenarios are not uncommon. In contrast to the wealth of studies on oncology patients with fever and neutropenia, only a few have been conducted on patients with non-chemotherapy-induced neutropenia.

One retrospective study to establish the risk of infection was performed in 119 well-appearing children without underlying co-morbid illnesses who were found to be neutropenic, nine severely so, during minor acute illnesses, routine preoperative screening, or treatment for common childhood conditions [5]. No patients with neutropenia lasting for less than 30 days developed infectious complications. Of the 36 patients found to be neutropenic for more than 30 days, only four (11 percent) developed infectious complications. The four infections were stomatitis (2), cellulitis (1), and pneumonia (1).

Another retrospective study examined the outcomes of patients presumed to be immunocompetent who presented to a pediatric primary care clinic or pediatric emergency department with fever and newly identified moderate to severe neutropenia, leukopenia, or both [6]. This study found that leukopenia and neutropenia did not necessarily occur together. The prevalence of bacteremia was 5.5 percent, and while neither the degree of neutropenia nor leukopenia predicted bacteremia, nearly all bacteremic children were toxic-appearing at presentation. The prevalence of other infections was 14 percent, and the most common of these was pneumonia.

These, albeit limited, observations suggest that the otherwise well-appearing child with isolated neutropenia and fever can be managed safely with age-appropriate treatment of any minor acute illness and frequent follow-up. However, any ill-appearing child with fever and neutropenia must be considered at risk for a serious bacterial infection and should receive empiric intravenous antibiotic therapy. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

INFECTION IN PATIENTS WITH SEVERE CHRONIC NEUTROPENIA — The patient with severe chronic neutropenia presents a different problem from that of the well-appearing patient with transient neutropenia. Severe chronic neutropenia has multiple causes. Among the primary hematologic diagnoses are:

- Chronic benign neutropenia (see "Immune neutropenia")
- Cyclic neutropenia (see "Cyclic neutropenia")
- Severe congenital neutropenia (infantile agranulocytosis or Kostmann syndrome) (see "Congenital neutropenia").
- Aplastic anemia (see "Inherited aplastic anemia in children" and "Acquired aplastic anemia in children and young adults")

The types and risk of infection vary among the conditions, as does the management in response to fever (table 1).

Chronic autoimmune and idiopathic neutropenia — Chronic neutropenia is defined as neutropenia lasting longer than eight weeks. The most common cause of chronic neutropenia in children is chronic benign neutropenia, which can be autoimmune or idiopathic. Autoimmune neutropenia typically occurs in infants 5 to 15 months of age; antineutrophil antibodies are characteristic, and spontaneous recovery occurs [7]. By contrast, chronic idiopathic neutropenia is seen more often in older children or adolescents and is less frequently associated with recovery [8]. (See "Immune neutropenia", section on 'Autoimmune neutropenia' and "Immune neutropenia", section on 'Chronic idiopathic neutropenia'.)

Despite these differences, most patients with autoimmune or chronic idiopathic neutropenia have a benign course, as illustrated by the following data.

- In one natural history study conducted over a 13-year period, only 2 of 45 patients with chronic neutropenia of both idiopathic and autoimmune types had severe and recurrent infections [4]. Upper respiratory tract infections, otitis media, and skin infections were relatively frequent in all of the patients. Among the 43 patients without severe courses, 11 nevertheless had significant infections, including six girls with cellulitis or abscess of the labia (three of these infections were caused by Pseudomonas aeruginosa), three with recurrent gingivitis or mouth ulcers, and one each with periorbital cellulitis and pneumonia.

- Similar rates of infection were observed in a separate study of 240 infants with autoimmune chronic neutropenia [7]. Minor infections developed in 80 percent of the patients, whereas severe infections such as pneumonia, meningitis and sepsis developed in 12 percent. Most patients were followed for up to six years.

In the natural history study, 76 percent of the patients experienced ANCs <200/microL, with occasional fluctuations into the normal range. All patients were treated with antibiotics during febrile episodes, usually by mouth. Hospitalizations other than for the initial evaluation were infrequent. Bone marrow was evaluated in 28 patients and demonstrated either normal or decreased numbers of neutrophils. Only three patients had maturation arrest at an early stage in myeloid maturation, and two of these were among the patients who suffered severe infectious complications.

These data suggest that the majority of patients with either idiopathic or autoimmune chronic neutropenia generally have a benign course and do not require hospitalization and parenteral antibiotics for uncomplicated febrile illnesses. Patients with adequate marrow reserves most often can be treated appropriately with oral antibiotics and close outpatient management. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

Cyclic neutropenia — Patients with cyclic neutropenia experience bouts of severe neutropenia at approximately 21-day intervals, which last for three to six days. During these periods they often have fevers, oral ulcers, gingivitis, periodontitis, pharyngitis, adenopathy, and malaise. Significant infections such as bacteremia, cellulitis, acute otitis media, sinusitis, pneumonia, or appendicitis occur less frequently [9]. Life-threatening illnesses, particularly necrotizing enterocolitis caused by Clostridium species [10,11], may occur, although they are uncommon. (See "Cyclic neutropenia".)

To minimize oral complications, meticulous mouth care is important. Patients generally do not require antibiotics for the fevers or mucocutaneous inflammatory lesions that are typical during their neutrophil nadirs [9]. However, antibiotics should be administered if patients develop:

- Uncharacteristic fever patterns
- Atypical oral lesions
- Significant infections such as acute otitis media, sinusitis, or lower respiratory tract infection.

Complaints of abdominal pain should raise the possibility of Clostridium necrotizing enterocolitis. If this entity is suspected, the patient should be hospitalized and receive broad-spectrum antibiotics that include anaerobic coverage [12].

The prophylactic use of granulocyte colony-stimulating factor (G-CSF) can reduce the risk and severity of infection in patients with cyclic neutropenia. The use of G-CSF and the management of fever in these patients is discussed separately. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

Severe congenital neutropenia — Unlike chronic benign neutropenia or cyclic neutropenia, severe congenital neutropenia (infantile agranulocytosis or Kostmann syndrome) manifests itself shortly after birth with frequent and severe infections. Omphalitis, cellulitis, and perirectal abscesses are common during the first few months of life [13]. Disseminated infections, which may be life-threatening, are frequently caused by Staphylococcus aureus, Escherichia coli, and Pseudomonas sp. (See "Congenital neutropenia", section on 'Infantile agranulocytosis'.)

Because of the risk of serious infection, these patients should be treated aggressively when febrile. Similar to its benefits in patients with cyclic neutropenia, the prophylactic use of G-CSF can reduce the risk and severity of infection in patients with severe congenital neutropenia. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

Aplastic anemia — With the availability of platelet transfusions, infection has replaced bleeding as the major cause of death in patients with severe aplastic anemia. (See "Inherited aplastic anemia in children" and "Acquired aplastic anemia in children and young adults".)

A sentinel retrospective study reviewed the types of infections in 150 patients, including children, with aplastic anemia treated at the Clinical Hematology Branch of the National Heart, Lung and Blood Institute (NHLBI) between 1978 and 1990 [14]. By the end of the study period, 24 percent of patients died of infectious complications.

Infection was documented microbiologically in 47 percent of febrile episodes in this study and clinically in another 22 percent [14]. The infected sites included respiratory tract (32 percent), soft tissues (24 percent), blood (22 percent), gastrointestinal tract (17 percent), and urinary tract (6 percent).

Among the pathogens identified, the vast majority were bacterial (67 percent), with fungal, viral, and parasitic accounting for 23, 7, and 3 percent, respectively. Gram-positive and gram-negative bacteria accounted for equal numbers of bacteremic episodes, with Staphylococcus epidermidis, Klebsiella pneumoniae, P. aeruginosa, S. aureus, and E. coli isolated most frequently. The majority of invasive fungal disease was caused by Aspergillus sp., followed by Candida sp. Ten of 11 Aspergillus infections were pulmonary. Although fungal organisms caused only 5 percent of primary infections, these pathogens accounted for 30 percent of secondary infections that arose during antibiotic therapy.

The spectrum of pathogens isolated from these patients with aplastic anemia was similar to that observed in cancer patients with therapy-induced neutropenia. The major exception was the finding that Aspergillus sp. were the dominant fungi; Candida sp. are most common in cancer patients. These data indicate that patients with severe aplastic anemia and fever are at very high risk of serious infectious complications and must receive urgent evaluation and empiric antimicrobial therapy. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

Similar findings were reported in a retrospective analysis of the types of infections and outcomes in patients with aplastic anemia treated in a five-year interval between 1994 and 2000 [15]. One hundred four infectious events were documented in 42 patients (81 percent of the sample that ranged in age from 3 to 82 years). The number of severe infectious episodes was significantly higher in patients who were neutropenic. Fungal infections occurred only in neutropenic patients. Five patients in the study population died of infection. All of these patients had prolonged pancytopenia and invasive fungal infections, most of which were caused by molds. Four of the five patients who died also had bacterial coinfections.

Other bone marrow failure syndromes — Many syndromes, including Shwachman-Diamond syndrome, Fanconi anemia, dyskeratosis congenita, cartilage-hair hypoplasia and reticular dysgenesis, are associated with isolated neutropenia or bone marrow failure. The risk of infection caused by chronic profound neutropenia appears to be similar to that of patients with non-constitutional causes of severe aplastic anemia. (See appropriate topic reviews).

SUMMARY AND RECOMMENDATIONS

- Neutropenia is defined as an absolute neutrophil count (ANC) <1500 cells/microL, with mild, moderate, and severe neutropenia defined by ANC of 1000 to 1500/microL, 500 to 1000/microL, and <500/microL, respectively. (See 'Definitions' above.)
- The risk of serious infection in otherwise healthy children with isolated transient neutropenia (eg, in the setting of a viral illness or in association with drugs such as antibiotics or anticonvulsants) is reflected in the general appearance of the child. Ill-appearing children are at greater risk for serious infection. (See 'Fever and neutropenia in the otherwise healthy child' above.)

- The well-appearing child can be managed safely with age-appropriate treatment of any minor acute illness and frequent follow-up.
- The ill-appearing child should receive empiric intravenous antibiotic therapy.

(See "Management of fever in children with non-chemotherapy-induced neutropenia".)

- The risk and types of infection in children with fever and severe chronic neutropenia vary according to the underlying hematologic disorder (table 1). The appropriate evaluation and specific management of these patients is discussed separately. (See "Management of fever in children with non-chemotherapy-induced neutropenia".)

- Children with idiopathic or autoimmune chronic neutropenia have a low to moderate risk of infection. They often can be managed with appropriate oral antibiotic therapy and close outpatient follow-up.

(See "Immune neutropenia".)

- Children with cyclic neutropenia generally have a low to moderate risk of infection, but should receive antibiotics if they develop uncharacteristic fever patterns, atypical oral lesions, or recurrent or significant infections (eg, acute otitis media, sinusitis, or lower respiratory tract infection). Complaints of abdominal pain in addition to fever should prompt consideration of Clostridium necrotizing enterocolitis and may warrant hospitalization and broad-spectrum antibiotics, including coverage for anaerobic organisms.

(See "Cyclic neutropenia".)

- Children with severe congenital neutropenia and aplastic anemia are at high risk for infection. They should undergo aggressive evaluation, hospitalization, and initiation of broad-spectrum antibiotics.

(See "Congenital neutropenia", section on 'Severe congenital neutropenia' and "Acquired aplastic anemia in children and young adults" and "Inherited aplastic anemia in children" and "Management of fever in children with non-chemotherapy-induced neutropenia".)

Roseola infantum (exanthem subitum)

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INTRODUCTION — Roseola infantum (also known as exanthem subitum, sixth disease, pseudorubella, exanthem criticum, and three-day fever) is a clinical syndrome characterized by three to five days of high fever (may exceed 40ºC [104ºF]) that resolves abruptly and is followed by development of a rash (picture 1) [1,2]. Roseola usually is caused by human herpesvirus 6 [3].

The clinical manifestations, diagnosis, and treatment of roseola infantum will be reviewed here. The virology, pathogenesis, epidemiology, and other clinical manifestations of human herpesvirus 6 in children are discussed separately. (See "Virology; pathogenesis; and epidemiology of human herpesvirus 6 infection" and "Human herpesvirus 6 infection in children: Clinical manifestations; diagnosis; and treatment".)

MICROBIOLOGY — Human herpesvirus 6 (HHV-6) is the most frequent cause of roseola [1]. Other causes include human herpesvirus 7 (HHV-7), enteroviruses (coxsackieviruses A and B, echoviruses), adenoviruses, and parainfluenza virus type 1 [1,4,5].

PATHOGENESIS — The pathogenesis of roseola is not known [1]. In a prospective study of 38 children with roseola, HHV-6 viremia was detected in all of the children during the first two days of illness (before the onset of the rash) [3]. By days five to seven, only 7 percent of children were viremic. HHV-6 antibody was first detected on day three of illness, and present in all patients by day eight of illness. This pattern of viremia preceding rash, and rash coincident with development of antibody, suggests that the rash may result from antigen-antibody complexes [2].

EPIDEMIOLOGY — Roseola is an illness of young children, with a peak prevalence between 7 and 13 months [6]. Ninety percent of cases occur in children younger than two years. Roseola occurs equally in boys and girls [1,7]. It occurs throughout the year, although cases may occur in groups according to season [1,6].

Transmission — Most cases of roseola occur sporadically, without known exposure [1,6,8]. However, secondary cases and horizontal transmission have been reported [1,9,10].

The modes of transmission, duration of shedding, and incubation periods vary depending upon the etiologic agent [4]. HHV-6 most likely is transmitted by asymptomatic shedding of virus in secretions of close contacts [6,11]. The duration of shedding for HHV-6 is not known but is thought to be lifelong [12]. The mean incubation period for HHV-6 is 9 to 10 days [11]. (See "Virology; pathogenesis; and epidemiology of human herpesvirus 6 infection", section on 'Incubation period and transmission'.)

The modes of transmission, duration of shedding, and incubation periods of less common causes of roseola are discussed separately. (See "Human herpesvirus 7 infection" and "Epidemiology; pathogenesis; treatment; and prevention of enterovirus infections", section on 'Transmission' and "Epidemiology and clinical manifestations of adenovirus infection" and "Parainfluenza viruses in children".)

CLINICAL FEATURES

Clinical course — The clinical course of roseola is characteristic: three to five days of fever that resolves abruptly and is followed by development of a rash.

Fever — Classical roseola begins with a fever that may exceed 40ºC (104ºF) and lasts for three to five days (mean 3.8 days) [6-8,13,14]. The fever often is accompanied by irritability, although most children with roseola are otherwise well-appearing, active, and alert [1,6,8].

Other clinical manifestations may include malaise, palpebral conjunctivitis, edematous eyelids, inflammation of the tympanic membranes, uvulopalatoglossal junctional macules or ulcers (sometimes called Nagayama spots), upper and lower respiratory symptoms, vomiting, diarrhea, and a bulging fontanelle [1,14,15]. Cervical, postauricular, and/or occipital lymphadenopathy are common, but later, findings [8,14,16].

In one series of 80 children with roseola, associated findings included [14]:

- Lymphadenopathy — 98 percent
- Erythematous tympanic membranes — 93 percent
- Irritability — 92 percent
- Nagayama spots — 87 percent
- Anorexia — 80 percent
- Upper respiratory tract symptoms — 25 percent
- Diarrhea — 15 percent
- Cough — 11 percent
- Convulsions — 4 percent

During the febrile phase, a diagnosis of acute otitis media is common [17]. The combination of high fever and bulging fontanelle, which occurs in as many as 26 percent of infants [7], frequently results in an evaluation for possible meningitis.

Rash — As the child's fever abates, a blanching macular or maculopapular rash develops, starting on the neck and trunk and spreading to the face and extremities (picture 1). Occasionally the rash is vesicular. It is generally nonpruritic [14]. The rash typically persists for one to two days, but occasionally may come and go within two to four hours [1,6,18]. In children receiving antibiotics, the later onset of the rash frequently is misinterpreted as a drug allergy. (See 'Differential diagnosis' below.)

Laboratory features — Laboratory investigation is seldom necessary for patients with classic roseola. However, it may be undertaken in children with atypical features (eg, simultaneous fever and rash) or as part of the evaluation of fever. (See "Fever without a source in children 3 to 36 months of age".)

Laboratory features of roseola include relative neutropenia and mild atypical lymphocytosis [1,6,19-21]. Early in the febrile period, the white blood cell (WBC) count may be elevated, but reaches its nadir (frequently in the range of 3000 cells/microL) by day three to six of illness, then gradually returns to normal over the following 7

to 10 days. Children with roseola also may have thrombocytopenia, which is thought to be caused by bone marrow suppression rather than immune-mediated peripheral consumption [21].

Complications — Roseola is usually a benign, self-limited illness. Complications may include seizures, aseptic meningitis, encephalitis, and thrombocytopenic purpura. Seizures generally are related to fever. The frequency of seizures in case series ranges from 0 to 6 percent [6,9,22]. (See "Human herpesvirus 6 infection in children: Clinical manifestations; diagnosis; and treatment", section on 'Clinical manifestations'.)

DIAGNOSIS — Roseola is diagnosed clinically based on the characteristic features: fever for three to five days followed by abrupt defervescence and development of a rash [1,4].

Laboratory evaluation is seldom necessary. In most patients with roseola caused by HHV-6, by the time the rash appears, viremia has resolved [2,3]. (See 'Pathogenesis' above.)

Virologic studies may be warranted in immunocompromised patients and those with an atypical presentation or complications. The diagnostic approach for potential pathogens is discussed separately:

- HHV-6 (see "Human herpesvirus 6 infection in children: Clinical manifestations; diagnosis; and treatment").
- HHV-7 (see "Human herpesvirus 7 infection", section on 'Diagnosis').
- Enterovirus (see "Clinical manifestations and diagnosis of enterovirus infections", section on 'Laboratory diagnosis').
- Adenovirus (see "Diagnosis and treatment of adenovirus infection").
- Parainfluenza virus type 1 (see "Parainfluenza viruses in children", section on 'Diagnosis').

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of roseola includes several other infectious exanthems and drug allergy [6]. Roseola generally can be distinguished from these conditions by epidemiologic or clinical features (eg, age group, temporal relation between fever and rash).

The infectious exanthems include [4]:

- Rubella, in which the rash (picture 2) and fever occur simultaneously. The rash classically begins on the face and spreads down the body. (See "Rubella".)
- Rubeola (measles) (picture 3), which is distinguished by a prodrome of coryza, cough, and Koplik spots (picture 4). The rash classically begins on the face and spreads down the body. (See "Clinical presentation and diagnosis of measles".)
- Enteroviral infections, which usually occur in epidemics in the summer and fall and occur in children of all ages, not just young children. (See "Clinical manifestations and diagnosis of enterovirus infections", section on 'Laboratory diagnosis'.)
- Erythema infectiosum, in which the rash is prominent on the cheeks (picture 5), and which usually affects school-age children. (See "Clinical manifestations and pathogenesis of human parvovirus B19 infection".)
- Scarlet fever, in which the rash may be confluent (picture 6), and which may be preceded by pharyngitis. (See "Complications of streptococcal tonsillopharyngitis", section on 'Scarlet fever'.)

Drug allergy is another consideration in children with fever who are treated with antibiotics and then develop a rash (picture 7). Clinical features that help to distinguish drug allergy from roseola include the duration of rash (longer in drug allergy than in roseola), and pruritus (present in drug allergy, not in roseola) [1,14]. (See "Allergy to penicillins".)

TREATMENT — In most cases, roseola is a benign and self-limited disease. Treatment is supportive [4]. Fever can be controlled with antipyretics (eg, acetaminophen). The rash resolves without treatment.

PROGNOSIS — Most children with roseola recover spontaneously without sequelae.

PREVENTION

Hygiene — Roseola may be caused by several viruses. Transmission of HHV-6, the most common cause, probably results from asymptomatic shedding of virus in secretions of close contacts, which is difficult to prevent [11]. The other viruses that cause roseola typically are spread through respiratory secretions or the fecal-oral route. Simple hygienic measures, such as handwashing, may help to prevent spread. (See "Epidemiology; pathogenesis; treatment; and prevention of enterovirus infections" and "Diagnosis and treatment of adenovirus infection", section on 'Prevention'.)

Child care — There is no recommended period of exclusion from out-of-home child care for children with roseola [23]. Children with sporadic cases of roseola are not considered to be contagious [1,6].

SUMMARY AND RECOMMENDATIONS

- Human herpesvirus 6 (HHV-6) is the most frequent cause of roseola. Other causes include HHV-7, enteroviruses, adenovirus, and parainfluenza virus type 1. (See 'Microbiology' above.)
- Roseola is an illness of young children, with a peak prevalence between 7 and 13 months. It occurs throughout the year. Most cases occur sporadically, without known exposure. (See 'Epidemiology' above.)
- Roseola classically begins with three to five days of fever that may exceed 40ºC (104ºF); as the fever abates, a blanching macular or maculopapular rash develops, starting on the neck and trunk and spreading to the face and extremities (picture 1). (See 'Clinical course' above.)
- Laboratory investigation is seldom necessary for patients with classic roseola. However, it may be undertaken in children with atypical features or as part of the evaluation of fever. Laboratory features of roseola include relative neutropenia and mild atypical lymphocytosis. (See 'Laboratory features' above.)
- Roseola is diagnosed clinically. (See 'Diagnosis' above.)
- The differential diagnosis of roseola includes several other infectious exanthems and drug allergy. (See 'Differential diagnosis' above.)
- Roseola is usually a benign self-limited disease. Treatment is supportive. (See 'Treatment' above.)
- Standard hygienic measures, such as handwashing, may help to prevent spread of the viral pathogens that cause roseola. There is no recommended period of exclusion from out-of-home child care for children with roseola. (See 'Prevention' above.)

Clinical assessment of the child with suspected cancer

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INTRODUCTION — Childhood cancer often is difficult to detect in its early stages because the associated signs and symptoms are nonspecific, insidious in onset, and mimic more common disorders [1]. The time from onset of symptoms to diagnosis of pediatric cancer is variable and ranges from a median time of 21 days for neuroblastoma to 72 days for Ewing Sarcoma [2].

Primary practitioners have little experience in diagnosing childhood malignancies and may be reluctant to consider the diagnosis because of the ominous implications. Nonetheless, whether or not they express their concern, patients and parents often are worried about childhood cancer, and the possibility of cancer should be discussed when the initial signs and symptoms are suspicious [3].

Optimal treatment of childhood cancer requires a high level of suspicion by the primary care practitioner and early referral to the pediatric oncologist. Early detection and treatment may reduce disease-related morbidity and complications.

The topic will provide an overview of childhood cancer and reviews the evaluation of children and adolescents who present with common signs and symptoms that are suspicious for cancer. The evaluation and treatment of specific malignancies are discussed separately. (See appropriate topic reviews).

OVERVIEW — The following facts about childhood cancer set the stage for a discussion of issues surrounding clinical assessment of the child with suspected cancer:

- Although childhood cancers are rare events, they are the fourth leading cause of death in individuals between 1 and 19 years of age in the United States after unintentional injury, homicide, and suicide. Boys have significantly higher death rates than girls and adolescents have significantly higher death rates than children.
- Common sites include blood and bone marrow, brain, bone, lymph nodes, nervous system, kidneys, and soft tissues (table 1).
- Five-year survival rates vary by site, but are approximately 70 to 80 percent when all sites of cancer are considered [4,5]. Survival has increased over the past 15 years with a decrease in mortality rate per one million population at or below 19 years of age of 34.2 to 27.3 between 1990 and 2004 [6].
- At least 85 percent of pediatric cancers are associated with the presenting signs and symptoms discussed in this topic review; the remaining 10 to 15 percent of tumors are associated with unusual signs and symptoms and are more difficult to diagnose in the early stages [3].

  Delays in diagnosis have been shown to be related to the child's age (older children are at a higher risk for delay), type of cancer, presentation of symptoms, tumor site, cancer stage, and first medical specialty consulted [7].
- Although any type of cancer can develop in children of all ages, the frequency of particular histologic types of cancer varies depending upon the age of the child (table 1). Neuroblastoma and Wilms' tumor, for example, occur most commonly in children between birth and four years of age, whereas leukemia occurs most often in one- to four-year-old children, and Ewing sarcoma, Hodgkin lymphoma, and thyroid cancer are more common in children older than 10 years of age [1]. (See appropriate topic reviews).

GENERAL PRINCIPLES OF EVALUATION — Obtaining a detailed history is the first step in evaluating the child with suspected cancer. Emphasis should be placed on the chief complaint. Many of the symptoms that the general public associates with cancer are those that occur with adult-onset malignancies (eg, a change in bowel or bladder habits, a sore that does not heal, unusual bleeding or discharge, thickening or lump in the breast or elsewhere, indigestion or difficulty swallowing, an obvious change in a wart or mole, and a nagging cough or hoarseness). These complaints are unusual in children.

The following mnemonic was developed by the American Cancer Society to help clinicians remember the early warning signs of childhood cancer [2]:

- Continued, unexplained weight loss
- Headaches with vomiting in the morning
- Increased swelling or persistent pain in bones or joints, sometimes accompanied by limping
- Lump or mass in abdomen, neck, or elsewhere
- Development of a whitish appearance in the pupil of the eye or sudden changes in vision
- Recurrent fevers not caused by infections
- Excessive bruising or bleeding (often sudden)
- Noticeable paleness or prolonged tiredness

In addition to these warning signs, early detection of childhood cancer requires knowledge of the child's past medical and family history. Certain genetic conditions and immune deficiency syndromes are associated with an increased risk of developing cancer (table 2 and table 3) [8-10]; survivors of certain types of childhood cancer (eg, retinoblastoma) are at risk for developing secondary malignancies [11-13]. The family history should include information about parents, siblings, and first cousins; age, serious illnesses, congenital anomalies, and cause of death for deceased family members should also be elicited [3]. (See "Overview of retinoblastoma".)

As a general rule, the diagnostic work-up for and initial management of childhood cancer should be completed under the direction of a pediatric oncologist and preferably in a pediatric oncology center where the necessary

subspecialists and tests required for diagnosis and/or treatment protocols are available [3,14]. In some cases, administration of emergent therapy is necessary at the time of presentation and may necessitate providing immediate therapy to stabilize the child's condition. In these cases, telephone consultation with a pediatric oncologist is critically important.

The importance of establishing the correct diagnosis and accurately determining the extent of disease before therapy begins must be emphasized to the parents and the child (if of appropriate age) at the initial evaluation. Such care helps to ensure appropriate therapy and prevents the need for performing repeat examinations and biopsies after the initiation of treatment [3].

COMMON SIGNS AND SYMPTOMS — Childhood cancer may present with signs and symptoms that are shared by other childhood illnesses (table 4) . Although assessment for these findings does not always require an evaluation for cancer, certain associated features (eg, headaches associated with vomiting in the morning) are worrisome and warrant immediate evaluation for malignancy (table 5). In addition, certain findings (eg, abdominal or mediastinal mass) are independently worrisome and also require immediate evaluation and consultation.

Fever — Fever is a common complaint in children. Fever and infection may initially appear to be routine; suspicion for noninfectious causes should be raised when the illness fails to respond to seemingly appropriate therapy. Even when fever is prolonged, infection is the most common cause [15-17]. In one retrospective series of children with prolonged fever, 2 to 9 percent of cases were attributed to a malignancy [15-17]. (See "Etiologies of fever of unknown origin in children".)

In the absence of infection, unresolving or recurring fever may reflect an occult neoplasm, such as lymphoma; rarely, it may be secondary to tumor-related necrosis, such as with neuroblastoma or Wilms' tumor [18]. Cyclic fever, in which periods of fever lasting from 3 to 10 days are separated by an afebrile period of approximately the same length (Pel-Ebstein fever), can occur in children, but is uncommon. Persistent fever also may be the only complaint in children with Langerhans cell histiocytosis, leukemia, and Ewing sarcoma [3,10]. Approximately two-thirds of children with leukemia have fever at the time of presentation [19]. (See "Overview of the presentation and classification of acute lymphoblastic leukemia in children" and "Langerhans cell histiocytosis" and "Clinical presentation, staging, and prognostic factors of the Ewing sarcoma family of tumors".)

Evaluation — A thorough physical examination may reveal additional worrisome findings such as lymphadenopathy or hepatosplenomegaly. The initial diagnostic evaluation for the child with a fever that does not respond to seemingly appropriate therapy should include (but is not limited to) a complete blood count with differential, examination of the peripheral blood smear, blood culture, and chest radiography. Additional studies may be indicated for fever of unknown origin. (See "Approach to the child with fever of unknown origin".)

The white blood cell (WBC) differential and examination of the peripheral blood smear may help distinguish the underlying cause of fever. As an example, the presence of circulating blasts or profound neutropenia or thrombocytopenia can suggest the diagnosis of leukemia. A bone marrow aspirate and biopsy usually can confirm or exclude malignant diseases involving the bone marrow. Chest radiography may reveal an intrathoracic mass. On the other hand, the presence of atypical lymphocytes, as seen in mononucleosis and other viral illnesses, can help to establish that the illness is not cancer. (See 'Mediastinal masses' below and "Clinical manifestations and evaluation of thrombocytopenia in children" and "Approach to the patient with lymphocytosis".)

Headache — Headache is another common symptom in general pediatric practice. Intracranial tumors are a rare cause of headache in children, but they must be considered when headaches are persistent or worsening in intensity, particularly if they are associated with vomiting or coordination difficulties [20,21]. (See "Clinical presentation and diagnosis of brain tumors" and "Approach to the child with headache", section on 'Worrisome findings'.)

Evaluation — The history of headache for a child, particularly a child who is younger than 10 years of age, is best obtained with input from the parents. The following information should be obtained:

- What is the location of the headache? Headaches caused by intracranial tumors often are described as generalized or occipital [22].
- How long do the headaches last?
- When in the course of the day do the headaches occur?
- How severe are the headaches? (This measure can be approximated by asking how many days of school or activities the child has missed because of headache.)
- Are there any precipitating events?
- What is the mode of onset of the headache?
- Are there any associated findings (visual symptoms, educational or behavioral problems) [21]?

Careful neurologic examination is the best method to screen for a brain tumor in the child with headache. In one retrospective study of 72 children who had headaches caused by brain tumor, 94 percent had abnormal neurologic findings (eg, ataxia, head tilt) at initial presentation [22]. Independent predictors for the presence of a space-occupying lesion were identified in another retrospective analysis of 315 children with headache and no known neurologic disorders who underwent magnetic resonance imaging (MRI) at a pediatric tertiary care center [23]. Thirteen children (4 percent) had space-occupying lesions. In multivariate analysis, seven independent predictors were identified (the odds ratios are presented below); at least three of these predictors were present in all children who required surgical intervention:

- Sleep-related headache — odds ratio (OR) = 26
- Absence of family history of migraine — OR = 20
- Vomiting — OR = 20
- Absence of visual symptoms — OR =16
- Headache of less than six months' duration — OR =15
- Confusion — OR =12
- Abnormal neurologic examination — OR = 8

Neuroimaging — Neuroradiologic imaging is the major diagnostic modality in the evaluation for a possible brain tumor. These studies often provide information as to the exact etiology of the mass lesion, and if a malignant tumor is present, they are critical for preoperative planning. (See "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Headache'.)

Children who have headaches and any of the following features should undergo immediate neuroimaging to rule out brain tumor:

- Recurrent morning headaches
- Headaches that awaken the child from sleep
- Intense and incapacitating headaches
- Recent changes in the quality, severity, frequency, and pattern of headaches
- Presence or new onset of neurologic abnormality
- Ocular findings such as papilledema, diplopia, cranial nerve palsy, decreased visual acuity, or visual loss [20]
- Vomiting that is persistent, increasing in frequency, or preceded by recurrent headaches
- Increasing head circumference (see "Etiology and evaluation of macrocephaly in infants and children", section on 'Mass lesions').
- Short stature or deceleration of linear growth (see "Causes of short stature")
- Rapid growth or precocious puberty (see "The child with tall stature or abnormally rapid growth" and "Definition, etiology, and evaluation of precocious puberty")
- Diabetes insipidus (see "Clinical manifestations and causes of central diabetes insipidus")
- Age of three years or younger
- Neurofibromatosis (see "Neurofibromatosis type 1 (von Recklinghausen's disease)")
- History of acute lymphoblastic leukemia treated with irradiation of the central nervous system (CNS) (see "Overview of the treatment of acute lymphoblastic leukemia in children")

Gadolinium-enhanced MRI is the preferred neuroimaging modality for a suspected brain tumor [24]. In addition to permitting visualization of the tumor and its relationship to the surrounding normal parenchyma, MRI is superior to computed tomography (CT) for evaluation of the meninges, the subarachnoid space, the posterior

fossa, and the vascular distribution of the abnormality. (See "Clinical presentation and diagnosis of brain tumors", section on 'Diagnostic neuroimaging'.)

Cranial CT remains useful if a question of bone or vascular involvement exists. CT also is the neuroimaging modality of choice for detecting metastasis to the skull base. In some situations, although MRI is the preferred imaging technique, it may not be readily available or feasible (eg, in an unstable patient with evidence of increased intracranial pressure); CT with and without contrast may be used in such cases even though it is less desirable. Because CT can be performed quickly and safely, imaging should never be delayed for a child with a suspected space-occupying intracranial lesion in order to obtain an MRI [23,25]. CT scan will detect almost all lesions. However, MRI may be required for better definition of the tumor or when CT is inconclusive or fails to detect an intracranial mass in a patient who has symptoms that are suggestive of one. (See "Approach to neuroimaging in children".)

Lymphadenopathy — Lymphadenopathy is another common complaint and physical finding in children. The size of normal lymph nodes in children varies widely as children are exposed to new viruses and bacteria. Most children have palpable, small cervical, axillary, and inguinal lymph nodes at some time during childhood. As a general rule, regardless of cause, a lymph node is considered enlarged if it is >10 mm in its greatest diameter. Epitrochlear nodes, which are considered enlarged if they are >5 mm, and inguinal nodes, which are considered enlarged if they are >15 mm, are the exceptions to this general rule.

The causes of and diagnostic approach to lymphadenopathy in children are discussed separately. (See "Causes of peripheral lymphadenopathy in children", section on 'Overview' and "Approach to the child with peripheral lymphadenopathy", section on 'Evaluation'.)

Most enlarged nodes are related to benign causes such as infection [26,27]. However, lymphadenopathy may be the presenting sign of leukemia, lymphoma, histiocytosis, neuroblastoma, and germ cell tumors; in contrast, lymphadenopathy is uncommon with soft tissue and bone tumors [1,26]. The site of the adenopathy and the child's age may help narrow the range of possible diagnoses. The most common cancers associated with lymphadenopathy of the head and neck are neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, and leukemia in children younger than six years, whereas lymphomas (both Hodgkin's and non-Hodgkin's) predominate in children between 7 and 13 years of age; Hodgkin lymphoma is the most common histology in children older than 13 years.

The prevalence of malignancy in lymph node biopsies performed in pediatric referral centers ranges from 11 to 29 percent [26-28]. In a typical primary care practice, however, the incidence is much lower [29,30]. The incidence of cancer in children who have lymphadenopathy is higher if certain clinical characteristics are present:

- Constitutional symptoms (ie, fever, night sweats, or weight loss), although these can occur in both malignancy and infection.
- In contrast to reactive lymph nodes, which are associated more often with tenderness, erythema, warmth, or fluctuance, cancerous nodes typically are firm, rubbery, matted, and nontender. They usually increase in size over the course of several examinations.
- Adenopathy in the posterior auricular, epitrochlear, or supraclavicular area is more concerning for malignancy than is adenopathy in other areas [3,27]. In particular, supraclavicular (or lower cervical) lymphadenopathy is associated with a high risk of malignancy (as much as 75 to 100 percent) in children [26,28]. Right supraclavicular adenopathy can occur in conjunction with cancers involving the mediastinal lymph nodes. In contrast, left supraclavicular adenopathy ("the Virchow's node") suggests intraabdominal malignancy, most often lymphoma. The differential diagnosis of epitrochlear lymphadenopathy includes infections of the forearm or hand, leukemia, lymphoma, and atypical mycobacterial infections.
- Any asymptomatic node that is larger than 2.5 cm warrants further investigation and early consideration for excisional biopsy.
- The consistency of the lymph nodes is of limited help. Rock-hard nodes can be found in cancers that induce fibrotic (scirrhous) changes and when previous inflammation has resulted in fibrosis. Firm, rubbery nodes typically are found in lymphomas and chronic leukemia, whereas nodes in acute leukemia tend to be softer.
- Abnormal lymph nodes can become fixed to adjacent tissues or to each other ("matted") by invading cancers, and less commonly by inflammation in tissue surrounding the nodes.

Diagnostic tests — When lymphadenopathy is unexplained after the initial evaluation, the subsequent work-up depends upon whether the adenopathy is localized or generalized. Evaluation of localized and generalized adenopathy in children is discussed separately (figure 1). (See "Approach to the child with peripheral lymphadenopathy", section on 'Diagnostic approach'.)

Biopsy indications — Lymph node biopsy is indicated in the following circumstances [3]:

- Suspicious circulating cells on CBC or an abnormal chest radiograph (eg, mediastinal mass or lymphadenopathy)
- Other findings suggestive of malignancy (eg, weight loss, constitutional symptoms, matted lymphadenopathy)
- Increase in node size or failure of the lymph nodes to decrease in size, despite four weeks of appropriate antibiotic therapy
- Any asymptomatic node that is larger than 2.5 cm
- Lymph nodes that are not enlarging but that fail to diminish in size after five to six weeks, or return to normal size by 10 to 12 weeks of observation. Biopsy may be performed sooner if the enlarged nodes are associated with unexplained fever, weight loss, or hepatosplenomegaly. Enlarged lymph nodes in the lower neck or supraclavicular area are exceptions to this guideline and should be biopsied upon presentation in the absence of a history of infection.

Bone and joint pain — Pain is an unusual early presenting symptom of cancer [31], except for tumors that involve the bone or bone marrow (eg, primary or metastatic bone tumors, leukemias). (See "Overview of hip pain in childhood" and "Approach to the child with a limp" and "Evaluation of the child with back pain".)

Ewing sarcoma and osteosarcoma are the two most common malignant bone tumors in children, and bone pain occurs in 80 and 90 percent of cases, respectively. The pain associated with primary bone tumors typically begins as intermittent pain and increases in severity over the course of time, although the pain associated with Ewing sarcoma may disappear spontaneously for weeks or months [32-35].

In one series of 149 patients younger than 30 years of age with osteosarcoma or Ewing sarcoma, pain related to strain was present in 78 percent, pain at night in 20 percent, and a palpable mass in 37 percent [34]. Pathologic fractures occur in approximately 5 to 10 percent of cases of Ewing sarcoma or osteosarcoma [36]. Because fever may be present at diagnosis, particularly in patients with Ewing sarcoma, osteomyelitis must be considered in the differential diagnosis of such cases. (See "Clinical presentation, staging, and prognostic factors of the Ewing sarcoma family of tumors" and "Evaluation and diagnosis of hematogenous osteomyelitis in children", section on 'Differential diagnosis'.)

Bone pain is a presenting symptom in 21 to 33 percent of cases of acute leukemia [37-39], and musculoskeletal symptoms may be present in as many as 62 percent [40]. In one retrospective review, radiographic changes were present at the time of diagnosis in 44 percent of children with musculoskeletal complaints [37].

The musculoskeletal pain associated with acute leukemia, particularly if it occurs in the joints, may be mistaken for rheumatologic pain [3,41-43]. A combination of clinical and laboratory findings may be helpful in distinguishing between the two conditions, as illustrated by the two studies described below.

In a retrospective review, the clinical and laboratory features present at the initial visit to the pediatric rheumatology clinic for unexplained musculoskeletal complaints were compared between 71 children who ultimately were diagnosed with acute lymphoblastic leukemia (ALL) and 206 who ultimately were diagnosed with juvenile rheumatoid arthritis (JRA, now called juvenile idiopathic arthritis, JIA) [3]. The following findings were noted:

- The combination of low white blood cell (WBC) count (<4000/microL), low-normal platelet count (150,000 to 250,000/microL), and a history of nighttime pain was 100 percent sensitive and 85 percent specific for ALL.
- The combination of two abnormal parameters on complete blood count (WBC count <4000/microL; platelet count 150,000 to 250,000/microL; hemoglobin <11 g/dL) was 96 percent sensitive and 88 percent specific for ALL.

- Rash, objective signs of arthritis, and antinuclear antibody positivity occurred with similar frequency in both groups.

In a smaller study, morning stiffness and rash occurred more commonly in patients with JRA, whereas nocturnal pain and nonarticular bony pain were more common manifestations in patients with leukemia [44]. The frequency of lymphadenopathy, hepatomegaly, and splenomegaly were similar in both groups. (See "Overview of the presentation and classification of acute lymphoblastic leukemia in children".)

Evaluation — Radiographs should be obtained in a timely manner for any child who complains of persistent bone or joint pain, especially if the pain is abrupt in onset, nocturnal, or associated with swelling; a palpable mass; or limited range of motion. Laboratory evaluation including a CBC, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), alkaline phosphatase, and lactate dehydrogenase (LDH) also should be obtained.

Radiographic signs characteristic of malignant bone tumors include "onion skinning" and the "sunburst" phenomenon. The appearance of onion skin is caused by repetitive periosteal reactions, each depositing a layer of calcium, as the tumor grows beyond the periostium (picture 1) [45,46]. The onion skin periosteal reaction is most common in Ewing sarcoma, but may occur in other conditions. The sunburst phenomenon occurs when malignant osteoclasts deposit calcium blood vessels that radiate perpendicularly from the tumor [47]. This phenomenon is most commonly seen in osteosarcoma. When present, radiographic features of leukemia may include osteopenia, lytic lesions, metaphyseal bands, periosteal new bone, and sclerotic lesions [37].

Because the presenting features of childhood malignancy and rheumatologic disorders may overlap, any child with suspected arthritis whose diagnosis is not definitive or who has atypical features (table 6), peripheral blood cytopenia, elevated serum lactate dehydrogenase [3,31,43,44,48], or abnormalities on bone scan should undergo a bone marrow examination. This is particularly true if treatment with corticosteroids is considered because corticosteroids can induce a transient tumor response in some children with leukemia or lymphoma, which may seriously interfere with the diagnostic evaluation [49]. Although abnormal findings on either plain radiographs or bone scan can raise suspicion for malignancy, they do not obviate the need for obtaining a tissue biopsy, because no findings are pathognomonic for malignancy.

Magnetic resonance imaging (MRI) is the imaging method of choice for evaluation of bone and soft tissue lesions because it can demonstrate the extent of both medullary and soft tissue involvement, and it is the most sensitive means of detecting skip lesions (ie, medullary disease within the same bone, but not in direct contiguity with the primary lesion) [36]. All children with bone tumors will need whole body technetium bone scanning to screen for additional lesions, and computed tomography (CT) of the chest to complete the staging evaluation [36,50]. (See "Bone sarcomas: Principles of surgical management", section on 'Radiographic imaging'.)

Mediastinal masses — Children with tumors involving the mediastinum may be asymptomatic or have symptoms such as cough, shortness of breath, hoarseness, or wheezing that result from extrinsic compression or involvement of adjacent structures, such as the recurrent laryngeal nerve [18]. These masses commonly are discovered on routine chest radiographs.

The mediastinum is divided into three anatomic compartments (figure 2). The compartment in which the mass is located can provide information about its likely nature [51]:

- Masses commonly found in the anterior mediastinum include lymphomas, thymomas, teratomas, angiomas, lipomas, and thyroid tumors [52].
- Masses commonly found in the middle mediastinum include lymphoma, metastatic cancer, infection-related lymphatic lesions, malignancies that extend directly from the abdomen, pericardial cysts, bronchogenic cysts, esophageal lesions, and hernias.
- Masses commonly found in the posterior mediastinum include neurogenic tumors such as neurofibromas, neuroblastomas, ganglioneuroblastomas, neurilemomas, ganglioneuromas, enterogenous cysts, thoracic meningoceles, and malignancies such as Ewing sarcoma (either osseous or extraosseous), lymphoma, and rhabdomyosarcoma. (See appropriate topic reviews).

Evaluation — Mediastinal masses that are discovered on plain radiography require additional investigation to establish a diagnosis of tumor. CT and MRI are the most useful imaging modalities, but tomography, barium swallow, fluoroscopy, and ultrasonography may occasionally be required. In addition, bone marrow

aspiration and biopsy may be indicated for evaluation of possible tumor or infection. If these tests do not yield a diagnosis, performing more invasive diagnostic procedures may be necessary to provide histologic specimens for definitive diagnosis. (See "Evaluation of mediastinal masses".)

Abdominal masses — A palpable abdominal mass, which often is detected by a family member or primary care provider, is one of the most common presenting signs of malignant solid tumors in children [3,53]. The presenting symptom may be pain, vomiting, constipation, or less commonly, intestinal obstruction. Although some abdominal masses are benign, all require early, thorough workup so that the proper diagnosis can be made and treatment initiated.

Wilms' tumor and neuroblastoma are the most common intra-abdominal tumors; others include leukemia, lymphoma, hepatic tumors, ovarian tumors, and soft tissue sarcomas. The age of the child helps in the differential diagnosis. Wilms' tumor and neuroblastoma occur more commonly in infants, whereas leukemic or lymphomatous involvement of the liver, spleen, or retroperitoneal lymph nodes occurs more commonly in older children [3].

Evaluation — The history should focus on the genitourinary tract, because abdominal masses in infants and young children often have renal origin [3]. When obtaining the history, it is important to determine whether the child has had symptoms related to the mass, and if so, the duration and intensity of the symptoms. These features may help to determine how rapidly the mass is growing, or to distinguish malignancy from another more chronic illness.

Physical examination should characterize the location and extent of the abdominal mass. Palpation is easier if the child is relaxed. The following structures are normally palpable in children and sometimes are mistaken for abdominal masses: the liver edge, spleen, kidneys, aorta, sigmoid colon, and spine. Administration of an enema or bladder catheterization may be necessary before reexamination if the mass is thought to represent stool or a full bladder. These procedures should be undertaken only if the child has a normal absolute neutrophil count (ANC). Rectal, vaginal, and pelvic examinations may be warranted in adolescent females but also should be performed only if the ANC is normal, to avoid predisposing the neutropenic patient to bacteremia and sepsis.

After the history, examination, and routine laboratory studies (including a CBC, serum chemistries, blood urea nitrogen, creatinine, and urinalysis) are obtained, the workup should proceed to abdominal ultrasound and chest radiograph. These studies may suggest the need for further tests, such as abdominal CT, bone marrow examination, or additional laboratory studies.

Bleeding — When bleeding is the initial sign of childhood cancer, it usually is caused by thrombocytopenia, which in turn is most often caused by neoplastic involvement of the bone marrow. Bleeding also can be related to impaired platelet function caused by the administration of ibuprofen or other nonsteroidal antiinflammatory drugs for fever or pain. (See "Approach to the child with a bleeding disorder" and "Clinical manifestations and evaluation of thrombocytopenia in children".)

A bleeding diathesis caused by a coagulopathy commonly accompanies acute promyelocytic leukemia (APL), especially in the presence of leukocytosis [54]. This complication also has been reported for patients with acute lymphoblastic leukemia (ALL, especially T-cell ALL), lymphoma, and neuroblastoma [55]. Other disseminated malignancies may be associated with a coagulopathy, but signs or symptoms are rare findings unless disseminated intravascular coagulation (DIC) supervenes. (See "Clinical manifestations, pathologic features, and diagnosis of acute promyelocytic leukemia in adults" and "Pathogenesis and etiology of disseminated intravascular coagulation" and "Clinical features, diagnosis, and treatment of disseminated intravascular coagulation in adults".)

When a child presents with significant bleeding and thrombocytopenia, the differential diagnosis includes malignancy (particularly acute leukemia), infection, and immune-mediated thrombocytopenia. (See "Clinical manifestations and evaluation of thrombocytopenia in children" and "Overview of the presentation and classification of acute lymphoblastic leukemia in children" and "Clinical manifestations and diagnosis of immune (idiopathic) thrombocytopenic purpura in children".)

Evaluation — The diagnosis usually requires a complete blood count (CBC), reticulocyte count, platelet count, and examination of the peripheral blood smear; examination of the bone marrow may be required to establish a definitive diagnosis.

Blood count abnormalities — Anemia, leukopenia, and thrombocytopenia often occur either as isolated findings or in combination in tumors that involve the bone marrow. Acute leukemias are the most common bone marrow tumors. In one study of 936 children with untreated, newly diagnosed ALL, 51 percent presented with hemoglobin concentration less than 7.5 g/dL, 73 percent with platelet count less than 150,000/microL, and 30 percent with a total peripheral white blood cell (WBC) count of less than 5000/microL [56]. In a similar study of 171 children with acute nonlymphocytic leukemia, 82 percent presented with platelet counts less than 100,000/microL and 39 percent with WBC less than 5000/microL [57].

After leukemia, the childhood malignancies that most often involve the bone marrow are neuroblastoma, lymphoma, Ewing sarcoma and rhabdomyosarcoma. In these tumors, the cytopenias are attributed to infiltration of the bone marrow by tumor [3]. (See "Approach to the child with anemia" and "Overview of neutropenia".)

Childhood leukemia also can present with elevation of the WBC count or leukemoid reaction (the presence of a striking increase in leukocyte concentration [eg, >50,000 cells/microL] or immature cells [≥5 percent] in the peripheral blood). Immature WBCs, normally only present in the bone marrow, may be observed in the peripheral blood in a variety of disorders including infection, sudden erythropoietic stimulation caused by hemolysis or hemorrhage, bone marrow recovery phase after bone marrow depression, and rheumatoid arthritis [58]. Infectious causes of leukemoid reactions include septicemia, particularly that caused by Staphylococcus aureus, Haemophilus influenza type b, Neisseria meningitidis, and Salmonella [58].

Peripheral WBC counts greater than 100,000/microL are almost always indicative of leukemia. In addition, hypereosinophilia, a finding more often present in parasitic infections and hypersensitivity reactions, can be seen in Hodgkin lymphoma, ALL, and rarely, eosinophilic leukemia [3,59].

Evaluation — The evaluation of a patient with abnormal peripheral blood counts must include investigation for an infectious cause. A bone marrow study often is the most appropriate means to rule out malignant causes, particularly if numerous immature cells are found in the peripheral circulation. In addition, bone marrow aspiration and biopsy are required to determine morphology and marrow cellularity. The indications for bone marrow examination include [3]:

- Finding of atypical or blast cells on peripheral blood smears
- Significant depression of more than one peripheral blood cell element without obvious explanation
- Association with unexplained lymphadenopathy or hepatosplenomegaly
- Absence of an infectious cause for the blood abnormality
- Abdominal or mediastinal mass

ESTABLISHING THE DIAGNOSIS — The treatment for malignancy can begin only after the tumor has been accurately diagnosed and the extent of disease defined precisely. Noninvasive imaging techniques such as CT, diagnostic ultrasonography, MRI, positron emission tomographic (PET) scans, and nuclear medicine scans have improved the assessment and staging for cancer. However, histologic confirmation (ie, tissue biopsy) is the only absolute means of definitive diagnosis.

Thus, once malignancy is suspected on the basis of clinical, laboratory, and imaging studies, selecting the most rapid and reliable means to establish the histologic diagnosis is necessary. The primary physician should confer with the pediatric oncologist, surgeon, and pathologist to determine the biopsy site, amount of tissue needed, and specimens to be obtained. Four general principles should be considered in these discussions:

- Enough material must be obtained so that additional biopsies are not necessary
- The obtaining of biopsy material for diagnosis should not compromise future therapy
- Excisional biopsy is preferred when the malignancy involves an organ
- Proper timing and handling of the biopsy material is essential

Incisional or core needle biopsies are the standard techniques for obtaining diagnostic tissue. Incisional biopsies are preferred by most pathologists, because they yield a greater amount of tissue with fewer artifactual

distortions. However, they must be planned and performed carefully, and only after consultation with the surgeon and oncologist. This procedure is particularly important for the patient with a suspected extremity sarcoma, in whom a poorly planned or incorrectly performed biopsy can compromise the ability to perform a limb-sparing procedure. (See "Bone sarcomas: Principles of surgical management", section on 'Tissue biopsy'.)

A total excision may be recommended for suspicious lesions that are smaller than 4 cm and located superficially in the dermis or subcutaneous tissues. Larger masses or tumors in deeper locations require an incisional or core needle biopsy. As a general rule, if the mass appears to be localized to an organ such as the adrenal gland or the kidney, surgical exploration with attempted total resection is the usual approach, often in lieu of a biopsy, provided no evidence of metastatic disease is found.

Proper timing and handling of biopsy material is essential because the information obtained from them can affect treatment decisions and prognosis. Biopsy specimens should be placed in normal (0.9 percent) saline and then transported immediately on ice to the surgical pathology laboratory. Biopsy specimens should not be placed in formalin. Gross examination of the tissue by the pathologist before processing helps to ensure that the specimen is adequate. Intraoperative frozen sections may be necessary to ensure diagnostic material, particularly if an immediate diagnosis will alter a planned operation. Placement of a central venous catheter and/or performance of a bone marrow aspirate/biopsy may be performed at the time of biopsy, if such procedures are indicated by the operative findings. (See "General aspects of cytogenetic analysis in hematologic malignancies" and "Genetic abnormalities in hematologic and lymphoid malignancies".)

SUMMARY — Childhood cancer is potentially fatal, but early diagnosis may improve outcome. The diagnosis of pediatric cancer may be delayed because of failure to recognize the following warning signs, particularly in children who are only moderately ill:

- Continued, unexplained weight loss
- Headaches with vomiting in the morning
- Increased swelling or persistent pain in bones or joints, sometimes accompanied by limping
- Lump or mass in abdomen, neck, or elsewhere
- Development of a whitish appearance in the pupil of the eye or sudden changes in vision
- Recurrent fevers not due to infections
- Excessive bruising or bleeding (often sudden)
- Noticeable paleness or prolonged tiredness

A high level of suspicion by the primary care practitioner and early referral to the pediatric oncologist are necessary for optimal treatment of children with cancer. Referral to tertiary care centers may facilitate rapid and accurate diagnosis, effective treatment, and enrollment in clinical trials.

Rat bite fever

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INTRODUCTION — Rat-bite fever (RBF) (also known as Haverhill fever) is a rarely diagnosed, systemic illness caused by infection with either Streptobacillus moniliformis or Spirillum minus. S. moniliformis causes most cases of the disease in the United States; S. minus causes RBF primarily in Asia, although it probably is present worldwide.

EPIDEMIOLOGY — S. moniliformis is commonly found in the nasal and oropharyngeal flora of rats and probably other rodents. The rate of nasopharyngeal carriage of S. moniliformis by healthy laboratory rats has

been reported to vary between 10 and 100 percent [1]. Human infection can result from a bite or scratch from an infected or colonized rat, handling of an infected rat, or ingestion of food or water contaminated with infected rat feces [2,3].

Contamination of food and water with S. moniliformis has caused several outbreaks of RBF [3,4]. In 1926, 86 persons in Haverhill, Massachusetts, developed a febrile illness (Haverhill fever) following the consumption of contaminated unpasteurized milk [3]. In 1983 an outbreak involving 304 boarding school children occurred in Chelmsford, England caused by water contaminated with rat excretions [4].

Approximately 30 percent of patients with RBF do not report having been bitten or scratched by a rat [5,6]. Risk factors for RBF include handling rats at home and in the workplace (eg, laboratories or pet stores).

RBF is rare in the United States, with only a few cases documented each year. However, because RBF is not a nationally notifiable disease, and it is likely to respond to empiric antibiotic therapy without diagnosis, its actual incidence is not known.

MICROBIOLOGY — S. moniliformis and S. minus are pleomorphic fastidious branching Gram negative bacilli (picture 1). They stain irregularly and can be mistaken for Gram positive pleomorphic rods. The bacteria are aerobic, facultatively anaerobic, and require specific media for isolation (10 to 20 percent serum) and incubation in a 5 to 10 percent CO2 environment.

S. moniliformis grows slowly. As a result, cultures should be held for at least five days to allow identification. On solid agar plates, pinpoint colonies representing cell wall-defective variants (L-forms) may surround larger gray-white colonies [7]. Inoculation into thioglycolate broth enriched with serum produces growth in typical "puff-ball" colonies [6].

S. moniliformis can be identified by a characteristic fatty acid profile on gas chromatography [8]. In contrast, biochemical testing is often difficult and results are inaccurate because of the fastidious nature of the organism.

CLINICAL MANIFESTATIONS — The symptoms of RBF caused by S. moniliformis start abruptly two to ten days following exposure with fever, myalgias, arthralgias, vomiting, and headache. The fever is often irregularly relapsing. The initial symptoms are followed by a maculopapular rash on the extremities [9], followed by polyarthritis in up to 50 percent of patients [10,11].

The rash is typically seen on the extensor surface of the extremities and may involve the palms and soles [12]. Although usually maculopapular, it can be petechial, purpuric, or pustular.

In contrast, RBF caused by S. minus has a longer incubation period (one to three weeks), and the initial wound may reappear at the onset of the systemic illness or persist with edema and ulceration. Arthritis is not a common clinical finding.

The infection can be rapidly fatal both in children and adults [2,13,14]. Two cases of fulminant sepsis and death in previously healthy adults occurred in the United States in 2003, one following a rat bite in a pet store and the other most likely from a sick pet rat [2].

Complications — The complications reported in the Chelmsford and Haverhill outbreaks included:

- Chelmsford — Four patients with moderately severe symptoms had bacteremia [15]. No further complications were noted.
- Haverhill — Eleven of 17 patients tested had positive blood cultures; two patients developed pneumonia [3].

Most of the serious invasive infections have appeared as case reports and include meningitis [14], endocarditis [16,17], including prosthetic valve endocarditis [18], myocarditis, pneumonia [13], focal abscesses [7], bacteremia, septic arthritis [19,20], and multiple organ failure [16].

DIAGNOSIS — Clinicians should consider RBF in the differential diagnosis of an unexplained febrile illness or sepsis in patients reporting rat exposure especially if the fever pattern is relapsing or intermittent, a maculopapular rash is present, and/or the patient has asymmetrical polyarthritis.

Blood or synovial fluid collected in tubes without sodium polyanethol sulfonate, an anticoagulant that can inhibit growth of the organism, should be submitted for culture. The microbiology laboratory should be alerted to the suspicion of RBF so that specific media and culture conditions are used to optimize isolation of the organism. In addition, the laboratory should incubate the blood cultures for 21 days. No serologic test is available.

Molecular techniques, such as polymerase chain reaction (PCR), have been developed to assist in the diagnosis of RBF. While not clinically available to most practitioners, these techniques show considerable promise for a quick, accurate diagnosis [21].

TREATMENT — The case-fatality rate is as high as 25 percent in untreated patients [1,22-25]. Treatment of RBF associated with an animal bite should begin with appropriate management of the bite wound. Such management includes copious irrigation of wounds and determination of the need for tetanus or rabies postexposure prophylaxis.

Rats and other small rodents are almost never infected with rabies, and there has never been a case of transmission to a human from one of these animals. If the animal is not available for testing, postexposure prophylaxis for bites should be considered individually in consultation with the public health authorities. (See "Soft tissue infections due to dog and cat bites", section on 'Wound management' and "Rabies immune globulin and vaccine", section on 'Postexposure prophylaxis'.)

In vitro, S. moniliformis is usually sensitive to penicillin, ampicillin, cefotaxime, azithromycin, and doxycycline; and resistant to polymyxin B, gentamicin, tobramycin, ciprofloxacin, and levofloxacin [6]. Strains appear to be variably sensitive to erythromycin [5], and clinical failures have occurred with erythromycin treatment [2,26].

Intravenous penicillin is the treatment of choice, and prompt therapy can prevent severe complications. Empiric therapy should be immediately begun in patients with a compatible clinical presentation and exposure history, since laboratory confirmation is difficult and may take several days.

Recommendations — We suggest the following treatment regimens:

Adults

- Intravenous penicillin (200,000 units every four hours) for five to seven days, followed if clinically improving by oral penicillin or ampicillin (500 mg four times per day) for seven days.
- In patients with penicillin allergy, alternative treatment with tetracycline (500 mg orally four times a day) or doxycycline (100 mg orally or intravenously twice daily)

Children

- Intravenous penicillin (20,000 to 50,000 units per kg per day divided in six doses) to a maximum of 1.2 million units per day. Children who do not require hospitalization can be treated with penicillin V (25 mg/kg per day orally in three or four divided doses). Duration of treatment is 7 to 10 days.
- In patients with penicillin allergy, in whom RBF is a serious consideration, alternative treatment is with doxycycline. Although tetracycline can cause dental staining when administered to children, the risk of dental staining with doxycycline is minimal if a short course is administered. Children weighing more than 45 kg should receive the adult dose; smaller children should receive 2 to 4 mg/kg in two divided doses.

Streptomycin is an alternative therapy in both adults and children with RBF. However, several limitations make its use impractical for the treatment of RBF, including: drug-related toxicity, the need for parenteral administration, and that many pharmacies do not stock streptomycin, making it difficult to obtain promptly.

PREVENTION — The clinical course of rat-bite fever can be rapid and fatal. As a result, prevention of severe disease depends upon increasing the awareness of appropriate risk-reduction activities and possible symptoms of RBF among persons who have exposure to rats.

A three-day course of oral penicillin (2 g per day in adults; 25,000 to 50,000 units per kg per day in children) is reasonable following a rat bite, although efficacy of antimicrobial prophylaxis is unknown.

Measures to limit the incidence of RBF include eradication of rats in urban areas, avoidance of unpasteurized milk and potentially contaminated water, and the use of gloves by laboratory workers when handling rodents or cleaning rat cages.

SUMMARY AND RECOMMENDATIONS

- Rat-bite fever is a rarely diagnosed, systemic illness caused by infection with either Streptobacillus moniliformis or Spirillum minus. S. moniliformis causes most cases of the disease in the United States; S. minus causes rat bite fever primarily in Asia, although it probably is present worldwide. (See 'Introduction' above.)
- Human infection can result from a bite or scratch from an infected or colonized rat, handling of an infected rat, or ingestion of food or water contaminated with infected rat feces. (See 'Epidemiology' above.)
- The symptoms of rat-bite fever start abruptly with fever, myalgias, arthralgias, vomiting, and headache followed by a maculopapular rash on the extremities. Polyarthritis occurs in approximately half of patients. Complications include meningitis, endocarditis, pneumonia, and multiorgan failure. (See 'Clinical manifestations' above.)
- The diagnosis is established through culturing of blood or synovial fluid specimens; blood cultures should be held for 21 days. No serologic testing is available. (See 'Diagnosis' above.)
- Intravenous penicillin is the treatment of choice. Empiric therapy should be immediately begun in patients with a compatible clinical presentation and exposure history, since laboratory confirmation is difficult and may take several days. (See 'Treatment' above.)
- A three-day course of oral penicillin (2 g per day in adults; 25,000 to 50,000 units per kg per day in children) is reasonable following a rat bite, although efficacy of antimicrobial prophylaxis is unknown. (See 'Prevention' above.)

Epidemiology and pathogenesis of acute rheumatic fever

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INTRODUCTION — Acute rheumatic fever (ARF) is a delayed, nonsuppurative sequela of a pharyngeal infection with the group A streptococcus (GAS). Following the initial pharyngitis, a latent period of two to three weeks occurs before the first signs or symptoms of ARF appear [1]. The disease presents with various manifestations that may include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.

The epidemiology and pathogenesis of ARF will be reviewed here. The clinical manifestations, diagnosis, treatment, and prevention of this disorder are discussed separately. (See "Clinical manifestations and diagnosis of acute rheumatic fever" and "Treatment and prevention of acute rheumatic fever".)

EPIDEMIOLOGY — In developing areas of the world, acute rheumatic fever and rheumatic heart disease are estimated to affect nearly 20 million people and are the leading causes of cardiovascular death during the first 5 decades of life [2]. Worldwide, there are 470,000 new cases of rheumatic fever and 233,000 deaths attributable

to rheumatic fever or rheumatic heart disease each year; most occur in developing countries and among indigenous groups [2,3]. The mean incidence of ARF is 19 per 100,000 [4].

In the United States and other developed countries, the incidence of ARF is much lower at 2 to 14 cases per 100,000; this is probably due to improved hygienic standards and routine use of antibiotics for acute pharyngitis [5,6]. Many cases that do occur are part of localized outbreaks [7-12]. (See "Evaluation of acute pharyngitis in adults" and "Approach to diagnosis of acute infectious pharyngitis in children and adolescents".)

During epidemics in the mid 1900s, as many as 3 percent of untreated acute streptococcal sore throats were followed by rheumatic fever; in endemic infections, the incidence of rheumatic fever is substantially less [13].

Rheumatogenic strains — The observation in some studies that only a few M serotypes (types 3, 5, 6, 14, 18, 19, 24, and 29) were implicated in outbreaks of rheumatic fever in the United States suggested a particular "rheumatogenic" potential of certain strains of GAS [7,14-16].

To address the "rheumatogenic" potential of GAS, a serologic surveillance study compared the M types of GAS recovered from children in Chicago with acute pharyngitis during the time period 1961 to 1968 to the GAS strains recovered from Chicago children and children from across the United States in the time period 2000 to 2004 [15]. Rheumatogenic strains (eg, types 3, 5, 6, 14, 18, 19, and 29) were less prevalent among the latter isolates (10.6 versus 49.7 percent in the earlier time period) [15].

The authors hypothesized that the marked decrease in the incidence of acute rheumatic fever in the United States correlates with the replacement of rheumatogenic types by nonrheumatogenic types. However, an accompanying editorial noted that although the prevalence of rheumatogenic strains decreased two- to fivefold, the reduction in the incidence of ARF over the same period was ≥20-fold [17]. Thus, a shift in the prevalence of rheumatogenic M type GAS strains is not solely responsible for the decrease in ARF.

Our own series, gathered over a 20-year period, has produced different results. We isolated a large number of different M serotypes, including six strains that were nontypable. In addition, several different M types were isolated from the patients seen during a mid-1980s outbreak of ARF in Utah; these strains were both mucoid and non-mucoid in character [18]. In addition, M serotypes different from those in the United States have been associated with ARF in Trinidad and Hawaii [19-21].

Thus, the issue of potential "rheumatogenic" strains remains unresolved. A streptococcal strain capable of causing a well-documented pharyngitis almost always is potentially capable of causing rheumatic fever, although some exceptions have been recorded [22]. The lack of specific rheumatogenic strains also can explain the relatively high risk of recurrent disease with new streptococcal infections, in contrast to poststreptococcal glomerulonephritis, in which only a few "nephritogenic" strains appear to be capable of inducing the disease (eg, type 12 with pharyngitis and type 49 with impetigo), and recurrent disease is uncommon [23,24].

PATHOGENESIS — The pathogenic mechanisms that lead to the development of acute rheumatic fever remain incompletely understood. Clearly streptococcal pharyngeal infection is required, and genetic susceptibility may be present. On the other hand, evidence is sparse that toxins produced by the streptococcus are important.

Within this framework, molecular mimicry is thought to play an important role in the initiation of the tissue injury (see 'Molecular mimicry' below). However, the factors responsible for maintenance of the process remain unclear.

Role of the streptococcus — Despite the lack of evidence for the direct involvement of GAS in the affected tissues of patients with ARF, significant epidemiologic and immunologic evidence indirectly implicates the GAS in the initiation of disease.

- Outbreaks of rheumatic fever closely follow epidemics of streptococcal pharyngitis or scarlet fever with associated pharyngitis [22,25].
- Adequate treatment of a documented streptococcal pharyngitis markedly reduces the incidence of subsequent rheumatic fever [26].
- Appropriate antimicrobial prophylaxis prevents the recurrence of disease in patients who have had ARF [14,27].

- Most patients with ARF have elevated antibody titers to at least one of (if not all) three antistreptococcal antibodies (streptolysin "O", hyaluronidase, and streptokinase), whether or not they recall an antecedent sore throat [28].

In contrast to the high sensitivity of antistreptococcal antibodies for the documentation of streptococcal infection, the rate of isolation of GAS from the oropharynx of patients with ARF is extremely low, even in populations that generally do not have access to microbial antibiotics. The clinical documentation of an antecedent pharyngitis also appears to have an age-related discrepancy. One study, for example, noted that the recollection of pharyngitis approached 70 percent in older children and young adults versus only 20 percent in younger children [8]. Thus, a high index of suspicion of ARF is important, particularly in children or young adults presenting with signs of arthritis and/or carditis, even in the absence of a documented episode of pharyngitis.

In certain areas, it has been suggested that ARF might be due to non-group A streptococcal strains (eg, group C and group G) that inherited certain group A streptococcal antigens or enzymes that are important for initiating ARF [29]. (See "Clinical manifestations and diagnosis of acute rheumatic fever", section on 'Predisposing factors'.)

Importance of pharyngitis — Streptococcal pharyngitis is the only streptococcal infection that has been associated with ARF. As an example, there have been many documented outbreaks of impetigo that can cause glomerulonephritis but almost never ARF [24,30]. In addition, a study of patients in Trinidad, where both impetigo and rheumatic fever can be concomitant infections, found that the strains colonizing the skin were different from those associated with rheumatic fever and that the presence of impetigo did not influence the incidence of ARF [30].

In communities of aboriginal Australians, pharyngeal carriage of GAS is uncommon although rates of ARF are high [29]. Such findings have led to the hypothesis that ARF may arise from GAS pyoderma or from pharyngitis due to non-group A streptococcal strains that inherited certain group A streptococcal antigens or enzymes that are important for initiating ARF [29]. These issues are discussed separately. (See "Clinical manifestations and diagnosis of acute rheumatic fever", section on 'Predisposing factors'.)

Bacterial genetic factors may be an important determinant of the site of GAS infection. Five chromosome patterns of emm genes, which code for M and M-like surface proteins, have been recognized and labeled A-E. Pharyngeal strains typically have patterns A-C, whereas almost all impetigo strains show D and E patterns [31]. (See 'Rheumatogenic strains' above.)

Another factor affecting localization to the pharynx may be CD44, a hyaluronic acid binding protein that appears to act as a pharyngeal receptor for GAS. After intranasal inoculation, GAS colonize the oropharynx in wild-type mice but not transgenic mice that do not express CD44 [32].

A few theories have tried to explain why ARF is only associated with streptococcal pharyngitis, but the exact explanation remains obscure. GAS fall into two main classes based upon differences in the C repeat regions of the M protein [33]. One class is associated with streptococcal pharyngeal infection; the other (with some exceptions) belongs to strains commonly associated with impetigo. Thus, the particular strain of streptococcus may be crucial in initiating the disease process. The pharyngeal site of infection, with its large repository of lymphoid tissue, also may be important in the initiation of the abnormal humoral response by the host to those antigens crossreactive with target organs.

Impetigo strains do colonize the pharynx. However, they do not appear to elicit as strong an immunologic response to the M protein moiety as the pharyngeal strains [34,35]. This observation may prove to be an important factor, especially in light of the known cross-reaction between various streptococcal structures and mammalian proteins.

Molecular mimicry — As a result of molecular mimicry, antibodies directed against GAS antigens crossreact with host antigens [36-40]. In addition to the role of antibody, observations suggest a role for cellular immunity in molecular mimicry in ARF. A study of human heart-intralesional T cell clones found that 63 percent of patients reacted with meromyosin [41]. Furthermore many of these clones cross-reacted with myosin, valve-derived proteins, as well as streptococcal M5 peptides.

Carditis — Streptococcal M protein and N-acetyl-beta-D-glucosamine (NABG, the immunodominant carbohydrate antigen of GAS) share epitopes with myosin [37,38,40]. Rodents immunized with recombinant streptococcal M protein type 6 develop both valvulitis and focal cardiac myositis [42].

The potential clinical significance of these observations was illustrated in a study in which monoclonal antibodies were generated from tonsillar or peripheral blood lymphocytes of patients infected with GAS [39]. Some of these antibodies crossreacted with myosin and certain other proteins. In addition, antimyosin antibodies purified from patients with acute rheumatic fever crossreacted with GAS and M protein. Similar antibodies were present in much lower concentrations in some normal subjects.

In a later report, a monoclonal antibody isolated from a patient with rheumatic carditis was directed against myosin and NABG [40]. The antibody was cytotoxic for human endothelial cell lines and reacted with human valvular endothelium; this reactivity was inhibited by myosin>laminin>NABG. The reactivity with the extracellular matrix protein laminin may explain the reactivity against the valve surface.

Chorea — Molecular mimicry may also be involved in the development of Sydenham chorea. In an animal model, monoclonal antibodies that caused chorea bound to both NABG and mammalian lysoganglioside [43]. Exposure of cultured human neuronal cells to either monoclonal antibodies or serum from patients with chorea led to induction of calcium/calmodulin protein kinase. Exposure to serum from patients following streptococcal infection that was not complicated by chorea did not have this effect on neuronal cells. (See "Sydenham chorea".)

Genetic susceptibility — The concept that rheumatic fever might be the result of a host genetic predisposition has intrigued investigators for more than 100 years [44]. During that time, suggestions have included the theory that the disease is transmitted in an autosomal dominant fashion [45], in an autosomal recessive fashion with limited penetrance [46], or via genes related to determinants of blood group secretor status [47].

Renewed interest in the genetics of rheumatic fever occurred with the recognition that gene products of the human MHC were associated with certain clinical diseases. Several studies have reported genetic associations with ARF; some appear to be MHC-related, others are non-MHC-related.

- Using an alloserum from a multiparous donor, an increased frequency of a B cell alloantigen that was not MHC-related was reported in several genetically distinct and ethnically diverse populations of individuals with ARF [48].
- In another report, monoclonal antibodies were generated by immunizing mice with B cells from patients with rheumatic fever. One of these antibodies, D8/17, was found to identify a marker expressed on increased numbers (>20 percent) of B cells in 100 percent of patients with ARF of diverse ethnic origins [49]. The percentage of D8/17+ B cells ranged from 4 to 6 percent in approximately 90 to 95 percent of nonaffected normal subjects. In contrast, the number of D8/17+ B cells was one standard deviation above normal (10 to 12 percent) in 4 to 7 percent of subjects. Thus, this marker might identify a population of rheumatic fever-susceptible individuals. The antigen defined by this monoclonal antibody showed no association with or linkage to any known MHC allele, nor did it appear to be related to B cell activation antigens.
- An increased frequency of the classic MHC class II alleles, HLA-DR4 and DR2, has been noted in Caucasian and black patients with rheumatic heart disease [50]. Other studies have implicated DR1 and DRW6 as susceptibility factors in South African black patients with rheumatic heart disease [51] and a close association with HLA-DR7 and DW53 has been noted in RF patients in Brazil [52].

These apparently differing results concerning HLA antigens and RF susceptibility have led to speculation that the reported associations might be of genes close to, but not identical to, the RF susceptibility gene. Alternatively, and more likely, susceptibility to ARF is polygenic, and the D8/17 antigen might be associated with only one of the genes conferring susceptibility; whereas another might be the MHC complex encoding for DR antigens. Although the exact explanation remains to be determined, the presence of an increased percentage of D8/17+ B cells appears to identify a population at special risk of contracting ARF.

Treatment and prevention of Q fever

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INTRODUCTION — Q fever is a widespread zoonotic infection caused by the pathogen Coxiella burnetii that has both acute and chronic manifestations [1]. The designation Q fever (from Query) was made in 1935 following an outbreak of febrile illness in an abattoir in Queensland, Australia. The name remains apt, however, since many questions persist about this special organism and interesting infection. The disease is reportable in the United States and its agent, Coxiella burnetii, is a potential agent of bioterrorism [2]. (See "Identifying and managing casualties of biological terrorism".)

The treatment and prevention of Q fever will be reviewed here. The clinical manifestations, diagnosis, microbiology and epidemiology of Q fever, and Q fever endocarditis, are discussed separately. (See "Clinical manifestations and diagnosis of Q fever" and "Microbiology and epidemiology of Q fever" and "Q fever endocarditis".)

TREATMENT — Acute Q fever is usually a mild disease that resolves spontaneously within two weeks. Thus, clinical evaluation of the efficacy of antibiotic therapy is difficult, and comparative studies are scarce. Consideration of therapy is warranted only in patients who are symptomatic. There is no value to treating patients after spontaneous cure of the disease.

Medical therapy — A randomized trial comparing tetracycline with placebo showed a reduction in fever in the tetracycline group [3]. Doxycycline therapy is now recommended instead of tetracycline due to its improved pharmacokinetic properties and less frequent gastric intolerance [3]. In children, doxycycline should be prescribed when the disease is life threatening.

Clinical trials have assessed the utility of antimicrobials such as ofloxacin (200 mg three times a day) and pefloxacin (400 mg twice a day), which have been used successfully. However, fluoroquinolones are contraindicated in children and pregnant women.

Macrolides may represent a potential alternative in these populations. The efficacy of erythromycin is in some dispute and it is now rarely used because there is a small risk of sudden cardiac death due to QT interval prolongation that is higher when other drugs metabolized by CYP3A4 are taken concurrently [4]. (See "Acquired long QT syndrome".) Newer macrolides are more potent in vitro than erythromycin [5] and preliminary clinical studies showed that they may be of clinical use [6].

Anecdotal reports indicate that other antibiotics may be effective in the treatment of Q fever pneumonia, including lincomycin, trimethoprim-sulfamethoxazole, and chloramphenicol. Pneumonia again is usually a self-limited febrile illness; thus it is difficult to ascertain the clinical benefits of such antibiotic regimens. In vitro experiments have shown that cotrimoxazole may represent a potential alternative in patients for whom both tetracyclines and fluoroquinolones are contraindicated, but more clinical data are needed.

The slow regression of symptoms in patients with Q fever hepatitis has led to anecdotal reports of possible benefit from the combination of prednisone and an antibiotic. However, this may favor evolution to chronic disease.

Pregnancy — The treatment of the pregnant woman with Q fever infection is difficult because many of the drugs recommended above are contraindicated during pregnancy (eg, doxycycline, fluoroquinolones). We suggest the use of long-term cotrimoxazole therapy (320 mg trimethoprim and 1600 mg sulfamethoxazole for ≥35 days) due to retrospective data suggesting a benefit of this approach in decreasing the risk of placentitis, obstetrical complications, and maternal chronic Q fever infection. Clinicians need to be aware that cotrimoxazole has only a

bacteriostatic effect and carries a theoretical risk of inducing neonatal hyperbilirubinemia if used prior to delivery.

Q fever endocarditis — Prolonged therapy (minimum of 18 months) with hydroxychloroquine in combination with doxycycline is the preferred treatment regimen for Q fever endocarditis [3]. (See "Q fever endocarditis", section on 'Treatment'.)

Recommendations — Doxycycline (100 mg PO twice a day for 14 days) is the recommended regimen for symptomatic acute Q fever. We suggest adding hydroxychloroquine to doxycycline (minimum duration 18 months) for the treatment of Q fever endocarditis and for 12 months for prophylaxis in patients with underlying valvular disease [3].

Fluoroquinolones are a reliable alternative to doxycycline, particularly in patients with Q fever meningoencephalitis because they penetrate the cerebrospinal fluid. A macrolide or trimethoprim-sulfamethoxazole may be other alternatives. No reliable antibiotic regimen can be recommended for children.

PREVENTION

Vaccination — An effective whole-cell vaccine for Q fever has been developed in Australia and has protected humans in occupational settings. Efficacy of the vaccine was illustrated in a retrospective cohort survey of all employees at abattoirs between 1985 and 1990 [7]. Q fever occurred in 2 of 2555 (0.08 percent) vaccinated employees compared with 55 of 1365 (4 percent) unvaccinated employees. The two cases in vaccinated employees occurred within a few days of vaccination, before immunity had developed, and represented preexisting disease and not vaccine failure. However, this vaccine is not commercially available in the United States.

An acellular vaccine (CMR) is available in the United States for individuals engaged in research with pregnant sheep or live C. burnetii [8]. But, few data from human studies are available on this vaccine [9,10].

Prior to vaccination, persons should have a skin test to determine of history of previous exposure to C. burnetii, as those with previous exposure should not receive the vaccination because of severe local reactions.

Other measures — In addition to vaccination, other measures used to prevent and control Q fever include [11]:

- Educate the public on sources of infection
- Dispose appropriately of placenta, birth products, fetal membranes, and aborted fetuses from facilities housing sheep and goats
- Follow biosafety protocols for bagging, autoclaving, and washing of laboratory clothing
- Consume only pasteurized milk and milk products
- Quarantine imported animals
- Locate holding facilities for sheep away from populated areas. Routinely test animals for C. burnetii antibodies.
- Exclude from high risk situations, unless immune, persons at high risk for developing chronic Q fever (eg, cardiac valvular disease, those with vascular grafts, pregnant women)

SUMMARY AND RECOMMENDATIONS

- Acute Q fever is usually a mild disease that resolves spontaneously within two weeks. If the patient has moderate to severe symptoms, we suggest doxycycline (100 mg twice daily) for faster clinical resolution. (See 'Treatment' above.)
- The treatment of the pregnant woman with Q fever infection is difficult because many of the drugs recommended above are contraindicated during pregnancy (eg, doxycycline, fluoroquinolones). We suggest the use of long-term cotrimoxazole therapy (320 mg trimethoprim and 1600 mg sulfamethoxazole for ≥35 days) to decrease the risk of obstetrical complications. (See 'Pregnancy' above.)
- For patients with Q fever endocarditis, we suggest dual therapy with doxycycline and hydroxychloroquine for a minimum duration of 18 months. (See 'Q fever endocarditis' above.)

- An effective whole-cell vaccine for Q fever has been developed and has been demonstrated to be protective among humans at occupational risk for Q fever. (See 'Prevention' above.)

Approach to the child with a limp

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INTRODUCTION — Limp is defined as an uneven, jerky, or laborious gait, usually caused by pain, weakness, or deformity [1]. It is a common complaint in childhood, accounting for 4 per 1000 visits in one pediatric emergency department [2]. Limp can be caused by both benign and life-threatening conditions (table 1); the management varies from reassurance to major surgery depending upon the cause [2,3].

The cause of limp usually can be determined by obtaining a careful history and physical examination. Radiographic studies often are necessary to confirm clinical suspicions, but diagnostic procedures rarely are required. Although most cases of limp are caused by trauma or benign self-limiting conditions, life- or limb-threatening conditions must be diagnosed promptly (table 2) [4,5].

The evaluation of the limping child is reviewed here. An overview of specific causes of limp in children is presented separately. (See "Overview of the causes of limp in children".)

EPIDEMIOLOGY — In the emergency department or primary care practice, minor trauma predominates as the typical etiology for limp. Observational studies of children without a clear history of trauma who were evaluated in tertiary care centers or orthopedic clinics tend to emphasize serious infectious disease diagnoses such as osteomyelitis or septic arthritis [2,3,6,7]. One prospective study that evaluated 243 children younger than 14 years of age who presented to a pediatric emergency department with limp and no history of trauma had the following findings [4]:

- Boys outnumbered girls by almost two to one.
- Median age was 4 years.
- The limp was painful in 80 percent of patients with localization to the hip in 34 percent and knee in 19 percent.
- Transient synovitis or irritable hip were the most common diagnoses (40 percent of cases).
- Most patients (77 percent) had a benign cause that could be managed without subspecialty follow up or hospital admission.

These data suggest that the majority of limping children who undergo emergency evaluation have a benign cause that is self-limiting. However, a significant portion of children still require additional diagnostic studies and subspecialty care to diagnose and manage serious underlying etiologies.

HISTORY — Several historical features help identify possible causes for limp (table 3) [5,8-10].

Duration — Limps of recent onset are typically due to trauma or acute infection. Chronic limps more often arise from overuse syndromes, apophysitis, Legg-Calve-Perthes disease, slipped capital femoral epiphysis (SCFE), or systemic illness (rheumatic disease, tumor).

Trauma — Soft tissue injury (eg, contusion, sprain, strain) and fractures often have a history of prior trauma. Toddlers fractures are notable because the trivial trauma that can cause this injury may often be unknown or overlooked by the caregiver. The history of fever or recent illness may obscure the diagnosis of a traumatic etiology [11]. Similarly, the history of trauma can be misleading in patients with an infection. As an example, in one retrospective study of 163 infants and children with osteomyelitis of the long bones, a history of preceding

blunt trauma was elicited in one-third of cases [12]. (See "Clinical features of hematogenous osteomyelitis in children".)

Fever — Fever suggests possible osteomyelitis and septic arthritis. Toxic synovitis may also present with an associated viral illness and fever. Rheumatic disease and leukemia are rare causes of fever and limp. (See "Clinical features of hematogenous osteomyelitis in children" and "Bacterial arthritis: Clinical features and diagnosis in infants and children" and "Systemic onset juvenile idiopathic arthritis: Clinical manifestations and diagnosis", section on 'Clinical manifestations' and "Overview of the presentation and classification of acute lymphoblastic leukemia in children".)

Pain characteristics — Children with limp often have difficulty describing and localizing pain [5,11]. However, certain pain features can help narrow the anatomic region and diagnoses of concern [3,8,10,13]:

- Constant severe pain that is localized, and consistently reproducible is seen with fractures, septic arthritis, osteomyelitis, and sickle cell disease [13].
- Intermittent, less severe pain is characteristic of juvenile idiopathic arthritis (JIA), Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, Osgood-Schlatter disease, and transient synovitis.
- Knee pain may signify referred pain from hip pathology (eg, SCFE, Legg-Calvé-Perthes disease) rather than knee joint disease [3].
- Symptoms that occur at night or wake the child are found more commonly in neoplastic conditions (eg, leukemia, osteogenic sarcoma, Ewing sarcoma) and benign tumors (eg, osteoid osteoma) [10]. (See "Clinical assessment of the child with suspected cancer" and "Overview of benign bone tumors in children and adolescents", section on 'Osteoid osteoma'.)
- Bilateral pain may indicate myositis, particularly in the setting of recent viral illness [8].
- The preference to crawl or walk on the knees may indicate foot pain [10].
- Lateral thigh pain may indicate lumbar spine abnormality (eg, discitis, ruptured lumbar disc, vertebral osteomyelitis). (See "Overview of hip pain in childhood" and "Slipped capital femoral epiphysis".)
- Pain that worsens with activity suggests stress fracture, overuse injury, or hypermobility syndrome. Pain that improves with activity is characteristic of rheumatologic conditions and complex regional pain syndrome (reflex sympathetic dystrophy). Complex regional pain syndrome is also suggested by pain that is out of proportion to the history [8].

Other symptoms — Associated symptoms can help suggest specific etiologies:

- Morning stiffness ("gel phenomenon") is often found in patients with JIA.
- Incontinence, sciatica, or leg weakness suggest a spinal cord problem or pelvic mass.
- Back pain may indicate discitis, vertebral osteomyelitis, spondylolisthesis, or herniated disc.
- Recent viral or streptococcal illness or use of antibiotics may indicate post-infectious arthritis, myositis, or immune complex mediated disease (eg, Henoch-Schönlein purpura, serum sickness or serum sickness-like reactions) (see appropriate topic reviews).
- Recent history of antibiotic use may alter the presentation of septic arthritis or osteomyelitis. (See "Overview of the causes of limp in children".)
- Patients with hypothyroidism, panhypopituitarism, and hypogonadism are at increased risk for developing slipped capital femoral epiphysis. (See "Slipped capital femoral epiphysis".)

PHYSICAL EXAMINATION — The examination of the young child with a limp can be performed with the child sitting in the lap of his or her parent after observation of the gait [14] . If the source of the limp cannot be localized clearly by the history and simple observation (which is often the case in the young or nonverbal child), the examiner must proceed systematically through examination of the central nervous system (CNS), spine, peripheral nervous system, abdomen, hips, knees, ankle, and feet [9]. In addition, the back (especially the paravertebral region), abdomen, and external genitalia should be examined to identify unusual causes of limp (eg, discitis, psoas abscess, testicular torsion). Obvious trauma in the absence of a credible history suggests inflicted injury. (See "The pediatric physical examination: Back, extremities, nervous system, skin, and lymph nodes", section on 'Extremities' and "Evaluation of scrotal pain or swelling in children and adolescents" and "Emergent evaluation of the child with acute abdominal pain" and "Physical abuse in children: Epidemiology and clinical manifestations".)

General — Ill appearance or significant pain suggests a more serious cause of limp (table 2). Infectious or inflammatory etiologies are often associated with fever.

Gait evaluation — Evaluation of gait is essential in all children with a limp. Most children are able to walk with assistance by the time they are 12 months of age, to walk independently at 15 months, and to run by 18 months [15,16]. The normal gait is smooth, rhythmic, and seemingly effortless.

Gait physiology — Gait has two phases: stance and swing [4,17]. The stance phase includes the time during which the foot is in contact with the floor (figure 1):

- Heel-strike to foot-flat (contact)
- Foot-flat to heel-off (mid-stance)
- Heel-lift to toe-off (propulsion)

The swing phase consists of the time from toe-off to heel-strike. (See "Evaluation of foot and ankle pain in the young athlete", section on 'Gait cycle'.)

The gait of children younger than 3 to 3.5 years of age is different from that of an adult [4,17]. These differences include:

- Increased flexion of the hips, knees, and ankles, which provides a lower center of gravity and facilitates balance.
- Rotation of the feet externally and more spread in relation to the shoulder width, providing a wider base of support.
- A smaller percentage of the gait cycle is spent in single limb stance.
- A faster cadence but slower velocity because of shorter stride length in younger children.

Gait examination — To examine the child's gait, the child should be asked to walk up and down the corridor several times with the legs exposed, permitting observation of several gait cycles. When the physician suspects pathology in the foot or toes, the feet should be bare, as well, or in socks. The child may need to be distracted to achieve the natural gait (versus trying to walk correctly for the examiner). Having the parents point out their specific concerns may be helpful [4].

Listening to the gait can provide clues to particular gait abnormalities [18,19]. The cadence may be irregular because of an uneven or asymmetric gait. A foot slap may be heard in patients with a foot drop. Scraping may be heard in patients with spasticity.

The particular type of gait abnormality helps to localize the problem, narrow the differential diagnosis, and direct the radiologic and laboratory evaluation (table 4). Asking the child to run may unmask an abnormality that is caused by weakness or otherwise hidden by the child's compensation or self-consciousness. Asking the child to hop on one leg and then the other, and to walk on his or her heels and then toes (if developmentally able) , also may disclose otherwise undetected weakness.

When examining the child's gait, the examiner should pay particular attention to the following features (table 4) [20]:

- With an antalgic gait, the stance phase is shorter on the affected side.
- Circumduction (circular movement of the limb during swing phase) suggests an ankle or foot problem.
- Downward pelvic tilt during the swing phase (Trendelenburg gait) suggests hip pathology (eg. developmental dysplasia of the hip, slipped capital femoral epiphysis).
- Toe-to-heel sequence (toe-walking gait, as opposed to the normal heel-to-toe pattern) may indicate a neurologic problem, cerebral palsy, or idiopathic heel cord tightness.
- Lack of full knee extension in the stance phase implies knee pathology or possible limb length discrepancy.
- Elevation of the arm sometimes accompanies hemiplegia.

Musculoskeletal — Examination of the musculoskeletal system should include evaluation of muscle strength, muscular atrophy, joint tenderness, bony tenderness, bony deformity, joint effusion, range of motion (active and passive), and inflammation of joints, tendons, or muscles.

The examination should proceed from areas of least concern to the site of suspected pathology [21].

- Inspection of the knees may reveal bowing of the tibias (genu varum), which is normal from infancy through age two years, or knock knees (genu valgum), which can be normal until the child is two to four years of age. (See "Approach to the child with knock-knees" and "Approach to the child with bow-legs", section on 'Physiologic varus'.)
- Inspection of the soles of the feet may reveal foreign bodies, plantar warts, or calluses from poorly fitting shoes. Inspection of the shoes can indicate a wear pattern that suggests a particular gait abnormality (eg, toe walking) or a rough surface that is causing pain. Claw toes or a high arch (pes cavus) suggests an underlying neurologic condition, particularly if these findings are unilateral [10].
- Joint swelling may be present in several conditions that cause limp. Swelling and inflammation of a single joint, particularly in a febrile child, is suggestive of septic arthritis. Joint swelling and pain in a child with no history or a history of minor trauma may still be infectious or may indicate hemarthrosis as the initial presentation of a bleeding disorder [8]. Hemarthrosis is very common in children with hemophilia. Bleeding occurs most frequently in the ankle for the small child, but after age 5 hemarthrosis occurs more frequently in the knee and the elbow [22].
- Painful palpation of the appropriate tendon or fascia insertion points, particularly in the absence of fever, trauma, or systemic symptoms, may indicate Osgood-Schlatter disease, Sever disease, Köhler disease, Freiberg disease, Sinding-Larsen-Johannson syndrome or plantar fasciitis. (See "Osgood-Schlatter disease" and "Overview of the causes of limp in children".)
- Limb length discrepancy should be assessed by measuring the length of the leg from the anterior superior iliac spine to the medial malleolus of the ankle. This finding may become apparent in young children with congenital hip dislocation, missed at birth, at the time they begin to walk. Comparison of the thigh and calf circumference between the affected and unaffected limbs may reveal atrophy (more than 1 to 2 cm difference between sides) in patients whose function has been limited for more than one to two months [4].
- Severe soft tissue pain and swelling in the setting of bruise or crush injury may indicate compartment syndrome; the affected muscle feels hard to palpation and pain is increased by passive extension of the affected area [8].

Hip rotation — Evaluation of hip rotation helps to differentiate problems in the hip joint from periarticular hip disease. One method of evaluating hip rotation in children is to roll the thigh of the child while he or she is in the supine position. Rotation produces pain in all traumatic, infectious, or inflammatory conditions of the hip (figure 2) [20].

Evaluation of internal rotation of the hips is performed with the child in the prone position and with the knees flexed; the ankles and feet are then rotated away from the body to compare the amount of internal rotation in the symptomatic versus the asymptomatic hip [10]. The pelvis must be kept flat on the examining table; otherwise, asymmetry of internal rotation may not be appreciated. Decreased or absent hip rotation, a "lag of internal rotation," is particularly useful in raising the suspicion for slipped capital femoral epiphysis and Legg-Calvé-Perthes disease; children with septic arthritis of the hip and even transient synovitis of the hip usually cannot tolerate this maneuver because of pain (figure 3).

Galeazzi test — The Galeazzi test (also known as Allis or Perkins test) is useful in diagnosing developmental hip dysplasia or leg length discrepancy. This test is performed by putting the child in a supine position and then flexing the hips and knees. The feet should be placed side-by-side with the heels touching the buttocks [4]. The test is positive when the knees are of different heights (figure 4). (See "Clinical features and diagnosis of developmental dysplasia of the hip".)

Leg length discrepancy can be caused by abnormal shortening or lengthening of either leg. Abnormal shortening of the leg can be caused by congenital aplasia or hypoplasia, developmental dysplasia of the hip, clubfoot, disuse or paralysis, ischemia, Legg-Calvé-Perthes disease, physeal injury or malunion after trauma, or a tumor that involves the physis. Abnormal lengthening of the leg can be caused by hyperplasia (eg, in hemihypertrophy syndromes), arteriovenous fistula, vascular tumors, and fractures (through distraction or stimulation) [23]. (See "Overview of the causes of limp in children".)

Trendelenburg test — Asking the child to stand on the affected leg (the Trendelenburg test) causes a pelvic tilt (the unaffected hip is lower) in children with slipped capital femoral epiphysis, Legg-Calvé-Perthes disease, or developmental dysplasia of the hip because of gluteal muscle weakness in the affected side (figure 5) [24].

FABERE test — The sacroiliac joint is examined with the "figure of four" maneuver (also referred to as the Patrick or FABERE test). This maneuver consists of Flexion of the hip and knee, with ABduction and External Rotation at the hip, so that the ankle of one leg is on top of the opposite knee (a figure four configuration) (figure 6) [25]. Downward force is applied simultaneously to the bent knee and the opposite hip causing Extension of the sacroiliac joint. Pain with this maneuver in the absence of pain with passive hip joint motion suggests discomfort arising from the sacroiliac joint. However, its sensitivity and specificity are limited [26]. (See "Back pain in children and adolescents: Overview of causes".)

Other findings

- Skin — Examination of the skin may reveal the characteristic rash of serum sickness, Henoch-Schönlein purpura (picture 1), acute rheumatic fever (picture 2A-B), or Lyme disease (picture 3). These disorders are discussed in detail separately. (See "Clinical manifestations and diagnosis of Henoch-Schönlein purpura" and "Diagnosis of Lyme disease" and "Clinical manifestations and diagnosis of acute rheumatic fever".)
- Abdomen and genitalia — Abdominal tenderness, rebound, guarding, or a positive psoas sign suggests appendicitis. Right lower quadrant pain may masquerade as right hip pain, especially in the toddler or preschool child. (See "Acute appendicitis in children: Clinical manifestations and diagnosis".)

Testicular torsion manifests with an exquisitely painful, swollen testicle and loss of the cremasteric reflex. Adolescent boys may not reveal significant testicular pain on history and often walk with a wide-based shuffling gait. (See "Evaluation of scrotal pain or swelling in children and adolescents".)

Penile or vaginal discharge may accompany gonococcal arthritis in the sexually active adolescent. (See "Disseminated gonococcal infection".)

- Neurologic and spine — The spine should be examined for abnormal curvature (kyphosis or scoliosis) or limited range of motion in flexion or extension. Limitations or asymmetry on forward bending may indicate spinal cord tumors or discitis. Midline abnormalities (eg, hair tuft, dimple, vascular or pigmentary lesions) may indicate an underlying spinal dysraphism [8,10]. Abnormalities in deep tendon reflexes may indicate peripheral neuropathy (delayed or absent), or involvement of the central nervous system with spasticity (increased).

Altered mental status, meningismus, and fever require evaluation for possible meningitis. (See "Clinical features and diagnosis of acute bacterial meningitis in children older than one month of age", section on 'Evaluation'.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis can be organized according to the location of abnormal physical findings (table 1), age and duration of symptoms (table 5) or type of gait abnormality (table 4) [4,21,27,28] . Conditions that are life- or limb-threatening must be diagnosed promptly (table 2).

Limp can be caused by abnormalities of the nervous system, back, leg, abdomen, or genitourinary tract (see 'Physical examination' above). The location of pain does not always reflect the location of pathology; problems in the hip can cause pain in the knee or thigh and back problems may refer pain down the back of the leg or to the lateral thigh [3,4].

Bacterial arthritis of the hip — Early diagnosis and treatment of a septic hip is essential to preserving ambulatory function but is often difficult to differentiate from transient (toxic) synovitis, a self-limited reactive swelling of the synovium of the hip associated with a viral illness. Observational studies have found that bacterial arthritis of the hip is associated with the following findings [29-31]:

- Fever ≥38.5º C (101ºF)
- Inability to bear weight
- White blood cell count >12,000/mm3
- Erythrocyte sedimentation rate >40 mm per hour

- C-reactive protein > 2.0 mg/dL (20 mg/L)

In small observational studies, children with four or more of these findings had bacterial arthritis of the hip 59 to 99.6 percent of the time [29-31]. However, in one study where hip aspiration was performed in all patients, septic hip was diagnosed in 4 of 34 children who met one or none of these criteria [31]. Thus, the clinician should not rely solely on these findings to identify which limping child should undergo hip ultrasound and arthrocentesis, but should take into account the entire clinical picture. Physicians with expertise in evaluating joint disease in children should be consulted for patients with equivocal findings. (See "Bacterial arthritis: Clinical features and diagnosis in infants and children".)

LABORATORY EVALUATION — The laboratory evaluation of the child with a limp should be directed by the history and physical examination findings. Laboratory tests usually are not indicated in the afebrile child with normal physical examination, especially if the limp is associated with an isolated injury. The efficacy of routine screening laboratory tests in the limping child has not been evaluated in randomized trials.

Blood studies — Complete blood count (CBC), acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), and blood culture are useful in the evaluation of acutely limping patients in whom infection is a possible cause [10,13,32,33]. Lyme studies are also indicated for patients who live in Lyme endemic areas. These studies should also be considered in the evaluation of the afebrile child with a several day history of limp and no abnormalities on plain radiography [4,10,33]. (See "Diagnosis of Lyme disease", section on 'Indications for serologic testing' and "Evaluation and diagnosis of hematogenous osteomyelitis in children" and "Bacterial arthritis: Clinical features and diagnosis in infants and children", section on 'Blood tests'.)

Although physical or radiologic findings of significant hip effusion (eg, fever, marked pain with movement, effusion by plain radiograph or ultrasound) are the primary indicators for hip joint aspiration, blood studies may also be helpful in deciding whether hip aspiration is indicated. In particular, elevations of ESR or CRP have high sensitivity for joint infection although the specificity varies [32,34,35]:

- A review of 250 children undergoing evaluation for joint complaints found that fever and elevated ESR was 93 percent sensitive for infectious or autoimmune joint disease [32]. Elevated white blood cell count was not a sensitive indicator in these patients.
- An observational study of 94 children with septic arthritis and 38 children with transient synovitis who presented to a pediatric emergency department with hip pain, found that the combination of ESR greater than 20 mm per hour and/or temperature greater than 37.5ºC detected 97 percent of those with septic arthritis, but 50 percent had unnecessary hip aspiration [34]. Elevation of the peripheral WBC count did not help in differentiating these two conditions.
- An observational study of 278 with arthritis showed that an elevated CRP and a temperature above 38.5º C (101º F) had 100 percent sensitivity and 87 percent specificity for septic arthritis [35].

In limping patients with chronic or polyarticular arthritis an antinuclear antibody test may assist in the diagnosis of juvenile idiopathic arthritis or other rheumatic disease. (See "Polyarticular onset juvenile idiopathic arthritis: Clinical manifestations and diagnosis".)

Synovial fluid analysis — Joint aspiration is warranted if septic arthritis is suspected on the basis of a swollen, inflamed joint, the presence of isolated unilateral hip effusion in a febrile child, or painful, limited range of motion at the hip. Synovial fluid analysis should include WBC count, Gram stain, anaerobic and aerobic cultures, and measurement of protein and glucose [4]. Teenagers with synovial fluid suggesting bacterial arthritis should also undergo appropriate testing for genital gonococcal infection (see "Synovial fluid analysis and the diagnosis of septic arthritis" and "Disseminated gonococcal infection", section on 'Laboratory studies').

RADIOLOGIC EVALUATION

Plain radiograph — Most children who limp require radiographic evaluation. Plain radiographs of the areas of concern usually are obtained first because they are readily available and are specific for fractures, destructive lesions, and avascular necrosis [5,27,36,37]. Both anteroposterior and lateral views should be obtained. In situations where hip pathology is suspected, AP and frog leg views of the pelvis are the correct radiographs to

obtain. The clinician should not order an unilateral hip series because a small SCFE could be missed in the absence of direct comparison with the opposite hip.

Radiographs may be helpful in the diagnosis of fracture, osteomyelitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, bone tumors (both benign and malignant), apophysitis (formerly, osteochondroses), and congenital abnormalities. The initial radiographs in children with stress fractures, toddlers fracture, Salter-Harris type I fractures, early osteomyelitis, and septic arthritis are often normal [8]. (See "Evaluation and diagnosis of hematogenous osteomyelitis in children", section on 'Imaging'.)

Comparison views — With the exception of radiographic evaluation of the hip, most experts recommend that radiographs of the normal extremity not be obtained routinely for comparison [8,18,19,38]. In one study, pediatric radiologists requested comparison views in only 8 percent of 300 cases of suspected extremity injury in children and in no case did the comparison view alter the initial diagnosis [38]. In another study, diagnostic accuracy was not improved by obtaining comparison views in children with elbow trauma [19]. The decision to obtain comparison views in children with limp should be individualized depending upon the physician's experience and the diagnosis in question. [15,36].

Children with isolated limp — Unfortunately, many children who present with an isolated limp have no history of trauma and no localized findings on physical examination [4]. The prevalence of occult radiographic findings in children without a history of trauma and a normal physical examination has not been determined in prospective studies, and the prevalence in retrospective studies is inconsistent [27,37].

We suggest plain radiographs in children who demonstrate a limp on physical examination, even when a history of antecedent trauma and or other localizing abnormalities on physical examination are lacking. Up to 20 percent of such children may have an occult fracture, especially toddlers [27]. (See "Overview of the causes of limp in children", section on 'Toddlers fractures'.):

Magnetic resonance imaging (MRI) — MRI is favored over radionuclide scan for diagnosing osteomyelitis, stress fracture (patients with continued limp and pain but normal plain radiographs), and early avascular necrosis, (eg, Legg-Calvé-Perthes disease) because of its superior ability to differentiate among these possible disease states [36]. (See "Evaluation and diagnosis of hematogenous osteomyelitis in children", section on 'Magnetic resonance imaging' and "Stress fractures of the tibia and fibula".)

MRI is also indicated when spine pathology is suggested by physical examination or plain radiographs (eg, discitis, herniated disc, spinal cord anomalies, or spinal tumors). (See "Back pain in children and adolescents: Overview of causes".)

In addition, patients with evidence of bone tumors on plain radiograph should have further delineation of the extent of disease (including the presence of skip lesions) by MRI. (See "Bone tumors: Diagnosis and biopsy techniques".)

Observational studies suggest that contrast MRI may be able to differentiate bacterial arthritis of the hip from transient synovitis in patients with hip effusion by ultrasound [39,40]. However, aspiration of the hip is still recommended for patients with hip effusion and concerning physical findings consistent with a septic hip.

Radionuclide scan — Bone scintigraphy is a sensitive means of detecting alterations in the metabolic rate of bone and thus a sensitive means of localizing pathology. However, bone scintigraphy lacks specificity because such alterations in bone metabolism can occur in Legg-Calvé-Perthes disease, osteomyelitis, discitis, avascular necrosis, osteoid osteoma, stress fractures, and malignant bone tumors or metastases [5,17,36,41]. Magnetic resonance imaging has greater ability to distinguish among these etiologies. (See 'Magnetic resonance imaging (MRI)' above.)

Bone scintigraphy is an alternative means of evaluation if MRI is unavailable, especially in children with prolonged limp and localized bone or back pain, fever, leukocytosis with polymorphonuclear predominance, and/or elevated acute phase reactants (eg, erythrocyte sedimentation rate, C-reactive protein) [41]. Bone scan is also an alternative to repeated plain radiographs over time in toddlers with suspected occult fractures, especially those with persistent limp [17,42,43].

Ultrasonography — Ultrasonography is an excellent technique for identifying joint effusions of the hip and should be used when plain radiographs are normal but the suspicion of septic hip remains high. Ultrasonography also may be used to guide aspiration of the hip when that procedure is deemed appropriate (eg, isolated unilateral hip effusion in a febrile child). Hip effusions are seen in children with transient synovitis AND bacterial arthritis of the hip. Thus, it cannot distinguish between these disease entities. (See 'Bacterial arthritis of the hip' above and "Bacterial arthritis: Clinical features and diagnosis in infants and children".)

Bilateral effusions suggest a systemic arthritic disorder or transient synovitis because as many as one-quarter of patients with symptomatically unilateral transient synovitis have bilateral effusions. (See "Overview of hip pain in childhood", section on 'Ultrasonography'.)

Computed tomography (CT) — CT is rarely needed in the evaluation of a limping child. Among the possible causes of limp, CT is useful in the diagnosis of appendicitis, deep soft tissue infections of the paraspinal and retroperitoneal regions, and tarsal coalition. (See "Acute appendicitis in children: Clinical manifestations and diagnosis", section on 'Imaging'.)

DISPOSITION — The disposition of the child with a limp depends upon the results of the initial evaluation. Specialty consultation and/or hospital admission should occur for children whose findings indicate life- or limb-threatening conditions (table 2) [13]. Management is dictated by the specific diagnosis:

- Patients with bone or joint infection require orthopedic consultation, emergent bone or joint aspiration followed by rapid initiation of antibiotic therapy. Surgical drainage of a septic hip should occur as soon as possible once the diagnosis is made (see "Treatment of hematogenous osteomyelitis in children" and "Bacterial arthritis: Treatment and outcome in infants and children", section on 'Overview of treatment').
- Children with a slipped capital femoral epiphysis require emergent operative reduction and pinning. (See "Slipped capital femoral epiphysis".)
- A child with a likely oncologic process (eg, leukemia or bone tumor) needs admission for staging workup and initiation of treatment. (See "Bone tumors: Diagnosis and biopsy techniques" and "Overview of the presentation and classification of acute lymphoblastic leukemia in children".)

Most children have a benign or nonemergent cause for their limp and can be managed as outpatients with appropriate medical follow up:

- Afebrile children with normal radiographs and pain managed by a nonsteroidal antiinflammatory medication (eg, ibuprofen) may be discharged to home with followup by the primary care provider to ensure that symptoms resolve.
- Patients in whom a toddlers fracture is suspected but not apparent on plain radiograph should undergo splinting of the affected leg and outpatient follow up with an orthopedic surgeon. (See "Splinting of musculoskeletal injuries".)
- Febrile children without joint effusion and with normal radiographic and blood studies may also be followed as an outpatient if clinical findings are most suggestive of myositis or transient synovitis [13].
- Children in whom a non-emergent provisional diagnosis is apparent or being considered (eg, JIA, Legg-Calvé-Perthes disease) should have follow-up arranged with an appropriate specialist.

SUMMARY — The diagnostic approach to the child with a limp and hip pain is summarized in the algorithm (algorithm 1). A history of trauma and the presence of fever are two key decision points in the evaluation of these children. The tables summarize the causes of limp, highlighting the common presentations based on location of physical findings, the patient's age and duration of symptoms, or type of gait (table 1 and table 5 and table 4).

Management of fever in sickle cell disease

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INTRODUCTION — Fever is a common presenting symptom in many manifestations of sickle cell disease (SCD). In particular, fever is frequently the first indication of serious and life-threatening bacterial infections. It is also present in other serious SCD-associated conditions, such as acute chest syndrome or vasoocclusive crisis. As a result, patients with SCD and fever should be evaluated and treated promptly to avoid significant morbidity and mortality.

Although patients with sickle cell anemia (Hb SS) and the closely related sickle cell-beta (0) thalassemia are at highest risk of bacteremia because of their predictable early loss of splenic function, many centers evaluate patients with the variant hemoglobinopathies sickle hemoglobin C disease (Hb SC) and sickle cell-beta (+) thalassemia in a similar fashion when a predetermined level of fever develops.

The management of the patient with SCD and fever will be reviewed here. Overviews of the other clinical manifestations and their management of SCD are presented separately. (See "Overview of the clinical manifestations of sickle cell disease".)

RATIONALE FOR MANAGEMENT APPROACH — In children with SCD, the major cause of death historically has been infection [1,2]. In the United States, prior to the availability of Haemophilus influenzae type b (H. influenzae) and pneumococcal vaccines, young children (below five years of age) with SCD had a 13 percent risk of developing bacterial sepsis or meningitis with mortality rates of 30 and 10 percent in patients with sepsis and meningitis, respectively [2]. Although mortality has significantly decreased since the introduction of vaccines, particularly since licensure of the conjugate pneumococcal vaccine (Prevnar) in 2000, about one-quarter of deaths between 1999 and 2002 in children with SCD in the first nine years of life continue to be due to infectious causes [3]. (See "Overview of the management of sickle cell disease", section on 'Causes of death'.)

Patients with SCD disease are more susceptible to infections because of functional asplenia. Autoinfarction caused by sickling of red blood cells results in a nonfunctioning spleen, which is unable to filter bacteria from the blood stream. Functional asplenia increases the risk of invasive infection by encapsulated organism, such as Streptococcus pneumoniae (S. pneumoniae) and H. influenzae. Prior to universal vaccination for S. pneumoniae and H. influenzae, young children with HbSS had a 400-fold increased risk of pneumococcal sepsis and a two- to four-fold increased risk of H. influenzae sepsis compared to age-matched children without SCD [4]. (See "Clinical features and management of sepsis in the asplenic patient", section on 'Role of the spleen in host defense'.)

The Cooperative Study of Sickle Cell Disease (CSSCD) described 20 of 64 infants with Hb SS between 8 and 13 months of age with functional asplenia, detected by the inability of their spleens to normally take up radiolabeled technetium sulfur-colloid [5]. An increased number of pocked or pitted red blood cells, a laboratory indicator of functional asplenia, was present in 94 percent of patients by 60 months of age [5]. More recently, baseline data from the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) showed using both of these techniques that only 12 percent of 193 infants with a mean age of 12.2 months had normal spleen function [6].

With the recognition of the increased risk of bacterial infection with SCD, preventive measures (eg, immunizations) and the use of daily prophylactic and empiric antibiotic therapy for fever have reduced the mortality rate in patients with SCD. This was best illustrated in the Dallas Newborn Cohort, a prospective study of 711 children identified by newborn screening, born in Texas on or after November 1, 1983 and treated at a single center up to 18 years of age [7]. The overall mortality rate was 0.59 per 100 patient years compared to rates of 3 per 100 patient years for children less than five years of age reported before the implementation of prophylactic penicillin and routine pneumococcal vaccination [7,8]. This improved survival in childhood has continued, only to be balanced by increased rate of death in young adulthood [9].

Although the universal use of pneumococcal conjugate vaccine in the United States has led to a decrease in the incidence of invasive pneumococcal disease [10-12] and death from an infectious cause [3], young children with SCD remain at a high risk for invasive pneumococcal infection defined as an incidence of ≥150 cases per 100,000 people per year [10]. In Tennessee, the rate of invasive pneumococcal disease in children under two years of age with SCD decreased from 3650 to 335 cases per 100,000 person years between the prevaccine to postvaccine periods of 1995-1999 and 2000-2004 [11]. Similar reductions from 2044 to 134 cases per 100,000 person years were seen in children under five years of age. Thus, patients with SCD remain at risk for bacteremia from S pneumoniae as well as organisms that are not prevented by immunization, such as Salmonella, Escherichia coli (E. coli), and Staphylococcus aureus (S. aureus) [13,14]. More recently, an increase in invasive Streptococcus pneumonia infections with non-vaccine strains has been reported [15].

In conclusion, despite the universal availability of pneumococcal and H. influenzae vaccines and the general use of penicillin prophylaxis in the United States, children with SCD and fever remain at risk for invasive infections from pneumococcus and other organisms.

ACUTE MANAGEMENT — Because fever may be the first indication of a serious bacterial infection in a patient with SCD, patients and/or parents should be counseled to seek prompt medical attention for a predetermined elevated temperature. This should occur even if the fever rapidly goes away with or without antipyretics.

Although not rigorously studied, most centers suggest medical evaluation when the patient's temperature exceeds 38.5ºC (101.5ºF) [16]. Patients should be evaluated within four hours of the onset of the fever and, if possible, the assessment should be performed by medical personnel who are knowledgeable about SCD and the particular patient's baseline hematologic values and status.

The immediate evaluation and management of patients with either a history or measurement of an elevated temperature consists of the following [16-18]:

- A brief history for symptoms suggesting systemic or localized infection.
- An abbreviated physical examination focused upon the following:

- Vital signs, cardiopulmonary status to look for signs of hemodynamic instability or intrapulmonary pathology such as acute chest syndrome.
- Degree of pallor to detect signs of accelerated anemia, which can be associated with aplastic crisis or splenic sequestration crisis.
- Signs of localized infection.
- Spleen size to detect splenic enlargement and any change from baseline, which may be associated with splenic sequestration crisis.
- Neurologic examination looking for evidence of acute stroke. While not associated with fever, acute stroke is a common enough complication of SCD that it must be considered whenever a patient with SCD presents for medical evaluation.

- Blood culture, complete blood count including white blood cell count and differential, and reticulocyte count.
- Parenteral antibiotics that are active against common bacterial pathogens. (See 'Empiric antibiotic therapy' below.)

Once antibiotics have been administered, then consider:

- Chest radiograph only if signs of symptoms of pulmonary consolidation (ie, chest pain, tachypnea, hypoxia, decreased breath sounds) are present. (See 'Further evaluation' below.)
- Lumbar puncture and cerebral spinal fluid culture only if meningeal signs are present.
- Urinalysis and urine culture only if signs or symptoms of urinary tract infection are present.
- If there is evidence of extreme pallor, severe pulmonary or neurologic symptoms, or significant acute increase in spleen size, a type and crossmatch for packed red blood cells for simple or exchange transfusion should be obtained.

Empiric antibiotic therapy — Empiric parenteral antibiotics are promptly administered after the initial laboratory studies are obtained. Antibiotic therapy is initiated before imaging evaluations are performed or test results are available.

In an observational study of children with Hb SS, the rapid administration of empiric antibiotic therapy appeared to reduce rates of meningitis and deaths due to pneumococcal infection [19]. One study of nonimmunized children who did not receive prophylactic penicillin reported that 8 of the 23 children with pneumococcal septicemia died and 15 developed meningitis prior to the initiation of a clinical program empiric antibiotic therapy of rapid administration of empiric antibiotic therapy. In contrast, after establishment of this clinical program, there were no deaths and only two cases of meningitis in the 11 children with pneumococcal septicemia. (See "Clinical features and management of sepsis in the asplenic patient", section on 'Empiric antibiotics'.)

Antibiotic recommendations are based upon the epidemiology and antimicrobial sensitivity patterns of the pathogens most likely to cause infection. In the United States, the most common bacteria include S. pneumoniae, Salmonella, E. coli, and S. aureus.

Several observational studies from equatorial Africa reported infection with S. aureus [20-23], Klebsiella [20,22,23], and Salmonella [20,24] were more common than S. pneumoniae. However, a subsequent large case-control study of hospitalized rural Kenyan children under 14 years of age found S. pneumoniae (41 percent) to be the most common isolate in children with SCD and bacteremia, followed by non typhi Salmonella species (18 percent), and Haemophilus influenzae type b (12 percent) [25]. Admitted children with SCD had a 26-fold increased risk of being bacteremic than those patients admitted without SCD. The results of the last study suggest that the organisms that cause bacteremia in children with SCD in Africa are the same as found in developed countries.

In the United States, the following antibiotic therapeutic approach is most commonly used in patients with SCD and fever [16,17]:

- Ceftriaxone is administered parenterally at a dose of 50 to 75 mg/kg (maximum single dose 2 g). In regions with a high prevalence of antibiotic resistant S. pneumoniae, higher does of 75 to 100 mg/kg (maximum dose 2 g) may be given. Although there have been rare reports of intravascular hemolysis with this agent, it is still the antibiotic of choice in this setting [26].
- Vancomycin is generally reserved for patients with suspected meningitis or who are too hemodynamically unstable for a lumbar puncture. Vancomycin is administered at a dose of 15 mg/kg IV (maximum dose 1 g). (See "Treatment and prognosis of acute bacterial meningitis in children older than one month of age", section on 'Empiric regimen' and "Septic shock: Initial evaluation and management in children", section on 'Initial antimicrobial therapy'.)
- For patients who are allergic to cephalosporin, clindamycin is given at a dose of 10 to 15 mg/kg (maximum dose 1.6 g). Note that the crossreactivity between penicillin and cephalosporins is small and many penicillin-allergic patients tolerate cephalosporins without problem. Drug allergies should be carefully documented in patients with SCD, and if possible, an individualized plan for management of febrile illness should be developed.
- The identification of a localized infection (such as acute otitis media) does not alter the need for empiric parenteral antibiotics because bacteremia with the potential to progress to septicemia may also be present.
- Blood culture and empiric parenteral antibiotics are recommended in persons with SCD even in the presence of a documented viral infection (influenzae or respiratory syncytial virus) because of the risk of secondary bacterial infection.

Further evaluation — After the initial laboratory testing and administration of empiric parenteral antibiotics, further evaluation and management are dependent upon the clinical status of the patient.

Fever is a presenting finding in other manifestations of SCD including:

- Acute chest syndrome (ACS) — Chest radiography and evaluation of oxygen saturation by pulse oximetry should be considered if the patient exhibits any signs suggestive of acute chest syndrome such as: (See "The acute chest syndrome in children and adolescents with sickle cell disease".)

- Respiratory signs or symptoms including cough, rales, rhonchi, wheezes, retractions, or tachypnea
- Chest wall pain that is not typical for the patient (eg, not due to either asthma or painful crisis)
- Unexplained upper abdominal pain (not due to a painful crisis)

- Aplastic crisis due to parvovirus B19 infection — Common manifestations of aplastic crisis include fever, extreme pallor due to exaggerated anemia, and tachycardia [27,28]. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Aplastic crisis'.)
- Vasoocclusive crisis — The acute onset of pain involving the chest or chest wall is a common finding in a vasoocclusive (painful) crisis. This may be accompanied by fever that is usually less than 100.5ºF. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Acute painful episodes'.)

A review of the patient's last comprehensive evaluation and comparison of steady state baseline hematologic parameters to current values may be helpful in determining the cause of fever. A fall in hemoglobin of two or more grams below baseline may suggest acute chest syndrome, splenic sequestration, or an aplastic crisis. An elevated white blood cell count may be normal in a patient with SCD or suggest an invasive infection. Past history of SCD complications should also be reviewed, as a previous history of pneumococcal bacteremia increases the risk of recurrence and must be considered when deciding on the need for hospitalization [29-31]. (See 'Decision about admission' below.)

Inpatient versus outpatient management

Decision about admission — The universal recommendation to admit all patients with SCD and fever may lead to the predictable but undesirable outcome of parents choosing to seek medical attention only if the child is very ill or has a persistent fever. However, no set of criteria has been firmly established that accurately predicts which patient with SCD and fever will have invasive bacterial infection requiring hospital admission. Reports of risk factors for invasive bacterial infection were primarily published prior to the use of pneumococcal conjugate vaccine, but still may serve to guide clinical decision making [13,18,29-36].

A regional network of pediatric hematologists with expertise in the care of children with SCD established guidelines for the comprehensive care of these patients including indications for admission [16]. Our institution was one of the participating institutions and our criteria for admission are in accordance with these guidelines.

We admit patients with SCD and fever for inpatient management when several of the following conditions are present:

- Children younger than two years of age with Hb SS or sickle beta (0) thalassemia – The risk of bacteremia is increased in young children who have these genotypes [11,13,18]. In patients with Hb SC disease who are less likely to have invasive bacterial infections, age alone is not an indication for admission. (See 'Management in variant sickle cell syndromes' below.)
- Temperature greater than 40ºC (104ºF) [18,32-36].
- White cell count (WBC) greater than 30,000/microL or less than 5,000/microL [18,32-36]. Both are associated with an increased risk of bacteremia in febrile patients with SCD.
- Hemoglobin that is two gm/dL or more below baseline in patient with Hb SS or sickle beta (0) thalassemia.
- History of previous episode of bacteremia — Patients with SCD who had a previous invasive infection are at an increased risk for subsequent infection, particularly with Streptococcus pneumoniae [29-31].
- Patients who have indwelling central venous lines [36].
- Signs of systemic toxicity, hemodynamic instability, and/or meningitis.
- Children treated with either clindamycin or vancomycin instead of ceftriaxone because of the shorter half-life of these antibiotics.
- The presence of other manifestations of SCD that require in-patient management, such as acute chest syndrome, painful crisis, aplastic crisis, or splenic sequestration. (See "Overview of the management of sickle cell disease".)
- Concerns about the ability of the family to recognize changes in the patient's condition, be contacted should a culture become positive, and/or return for follow-up as directed.

Inpatient management — Inpatient management of patients with SCD and fever includes the following [16]:

- Hemodynamic monitoring (ie, blood pressure and heart rate) and, as needed, supportive care. (See "Septic shock: Initial evaluation and management in children".)
- Monitoring of oxygen saturation (transcutaneous oxygen saturation). Provide supplemental oxygen to maintain the oxygen saturation at patient's baseline value, generally above 90 percent. Aggressively wean oxygen as soon as possible to avoid prolonged oxygen saturation above 94 percent, as this may suppress red cell production.
- Continuation of antibiotic coverage (ceftriaxone, clindamycin, or vancomycin as discussed above) and readjustment of antibiotics when culture results are available.

- If culture results are negative, antibiotics should be discontinued when the patient has been afebrile for 24 to 48 hours even if a need for continued hospitalization remains.
- If culture results are positive, the treatment for bacteremia is based upon antibiotic sensitivity and local standards. In our practice, once the blood culture becomes sterile after initiation of treatment and there is no other focus of infection, oral antibiotics are started when the patient has been afebrile for 24 to 48 hours. A 7 to 10 day total course of antibiotics is used to complete the treatment.

- Treatment for acute chest, which is indistinguishable from pneumonia in patients with SCD, should include a macrolide antibiotic (eg, azithromycin or erythromycin) in addition to the above antibiotic regimen. Treatment of meningitis, urinary tract infection, and osteomyelitis is not different than treatment in normal hosts. Treatment for each of these infections is discussed separately. (See "The acute chest syndrome in children and adolescents with sickle cell disease" and "Treatment and prognosis of acute bacterial meningitis in children older than one month of age" and "Acute management, imaging, and prognosis of urinary tract infections in children", section on 'Antibiotic therapy' and "Treatment of hematogenous osteomyelitis in children".)
- Maintenance of adequate hydration with fluids, generally administer at a maintenance rate. Increased fluids may be required if the patient is hypovolemic or if insensible losses are increased (such as with persistent fever). Overhydration should be avoided, especially in patients with respiratory symptoms because excessive fluids may precipitate or exacerbate acute chest syndrome. (See "The acute chest syndrome in children and adolescents with sickle cell disease".)
- Further evaluation, if necessary, is based upon the patient's clinical condition. As an example, in a patient with persistent fever and epigastric or severe abdominal pain, abdominal ultrasound, liver function tests, or serum amylase and lipase may be performed to assess if the symptoms are related to an underlying abdominal process such as cholelithiasis, cholecystitis, hepatitis, or pancreatitis.
- Patients can be discharged if there is no growth in their blood cultures for greater than 24 hours. In patients with SCD, the time to detect bacteria in positive blood cultures is generally less than 24 hours [37]. At discharge, patients may receive a dose of ceftriaxone for an additional 24 hours of coverage. In addition to negative culture results, criteria for discharge include ALL of the following conditions [16]:

- The patient is afebrile
- There is no evidence of any other active complication of SCD
- The patient is clinically stable, without any evidence of hemodynamic compromise
- The patient is taking adequate fluids by mouth, and is able to take oral medications, especially prophylactic penicillin in patients less than five years of age. (See 'Prevention of infection' below.)
- Providers have established a clear method for immediate recall and readmission, if the culture should become positive after discharge

Outpatient management — In patients who do not meet the above criteria for admission, outpatient management can be considered. Patients are treated with an initial dose of parenteral ceftriaxone, which provides antibiotic coverage for 24 hours. They should be observed for two hours after drug administration while the blood count results are obtained.

At the end of the observation period, patients are discharged to home if they meet ALL of the following criteria:

- The patient is clinically stable.
- There is a specific plan for follow-up the next day. Depending upon the clinical setting, this may be a telephone assessment for continued fever and general clinical status, or a mandated repeat clinical visit with a second dose of ceftriaxone.

- The patient/family must have a working telephone number recorded in the medical record at which they can be reached to return should a positive culture be reported.
- The patient/family must be able to recognize worsening of the patient's condition and have a reliable means of transportation to return should that occur or if recalled for a positive culture.
- There are no other health problems that require inpatient management.

The safety of this therapeutic approach was illustrated in a randomized controlled trial of 86 children with SCD and fever [32]. After evaluation in the emergency department and a single dose of intravenous ceftriaxone, patients (age range 6 months to 12 years) were randomly assigned to inpatient or outpatient treatment. Children who were treated as outpatients returned 24 hours later for a second dose of ceftriaxone. Children who were considered to be at high risk for sepsis (defined by temperatures greater than 40ºC (104ºF), white cell count (WBC) greater than 30,000/microL or less than 5000/microL, and the presence of pulmonary infiltrates on chest radiography) were excluded from the study and were all treated as inpatients. No patient in either study group developed sepsis, compared to 7 of 86 episodes in high-risk patients who were excluded from randomization. Outpatient therapy saved a mean of $1195 per febrile episode in 1993 dollars [32].

PREVENTION OF INFECTION — Preventive measures that reduce the risk of infection are primarily focused on young children with SCD. These measures can only be effective with early identification of infants with SCD. In the United States, infants with SCD are identified through universal newborn screening for all hemoglobinopathies. (See "Newborn screening".)

Newborn screening is coupled to follow-up that includes early initiation of penicillin prophylaxis (if indicated by genotype), referral to a pediatric hematologist, genetic counseling, and a program of parental education about the common complications of sickle cell disease. This education includes a plan for seeking medical attention for a predetermined elevated temperature, and institution of the following preventive measures to reduce infection [16,38]:

- Immunization
- Prophylactic penicillin

Immunization — Children with SCD should receive all routinely recommended childhood vaccines. Care must be taken that pneumococcal and H. influenzae vaccines are given at the earliest possible age. At every medical contact, a review of the patient's immunization should be performed to ensure that their immunizations are up to date. (See "Standard immunizations for children and adolescents".)

Pneumococcal vaccination — The universal use of pneumococcal conjugate vaccine in the United States has led to a decrease in the incidence of invasive pneumococcal disease in children with SCD [11,12,17].

In the United States, both a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent pneumococcal polysaccharide vaccine (PPSV23) are now available. As of early 2010, PCV13 has replaced the 7-valent conjugate vaccine (PCV7). Current recommendations are that all children with SCD who are less than six years of age receive at least one dose of PCV13 at least eight weeks after their last dose of any pneumococcal vaccine. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Vaccine schedule' and "Pneumococcal (Streptococcus pneumoniae) polysaccharide vaccines in children", section on 'Indications'.)

Administration of both the conjugate and polysaccharide vaccine provides protection at the earliest possible age and subsequently broadens protection against most of the invasive pneumococcal serotypes [39]. The pneumococcal conjugate vaccine (PCV7 or PCV13) can be administered as early as six weeks of age and elicits an effective immunologic response during the first two years of life. The pneumococcal polysaccharide vaccine (PPSV23) includes a greater number of serotypes but is not immunogenic in children younger than two years of age.

In the United States, we recommend administering both vaccines using the American Academy of Pediatrics (AAP) guideline as follows [40,41]:

- The pneumococcal conjugate vaccine (PCV13) is administered as four doses before 23 months of age on the same schedule as is routinely given to all children. The first three doses are administered at two,

four, and six months of age. The first dose can be given as early as six weeks of age. A minimum of four weeks between the three doses is acceptable. The fourth dose should be given at 12 to 15 months of age but at least two months after the third dose.

- The pneumococcal polysaccharide vaccine (PPSV23) is given as two doses: the first dose at 24 months (at least 8 weeks after the last dose of PCV13). A second dose three to five years after the first dose of the pneumococcal polysaccharide vaccine was used in clinical trials, and probably provides additional protection [42].

In patients below five years of age who did not receive the full complement of pneumococcal immunization based upon the above schedule, catch-up doses of vaccines should be given. The timing and number of doses depend upon the number of total doses of the conjugate and/or polysaccharide vaccines that have been given by five years of age [40]. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Vaccine schedule'.)

In a small French study of 49 of 51 infants with SCD, administration of an earlier version of the pneumococcal conjugate vaccine (PCV7) at two, three, and four months of age, followed by booster vaccination with the polysaccharide vaccine at 15 to 18 months of age, was shown to be well-tolerated and highly immunogenic [43]. After the polysaccharide vaccine booster, geometric mean antibody concentrations were high for all 23 serotypes, ranging from 6.32 to 29.49 µg/mL. However, no change has been made in the recommended United States immunization schedule.

Other vaccinations — In addition to other routine immunizations given to all children, the AAP recommends that children with SCD should also receive the following vaccinations [17,26,44]:

- Meningococcal vaccine — The AAP recommends that a single dose of tetravalent meningococcal polysaccharide vaccine (MPS4) be given to children with SCD between two and ten years of age [44]. Patients with SCD should receive one dose of the relatively new tetravalent meningococcal conjugate vaccine (MCV4) starting at age 11. The MCV4 is not licensed or recommended below age 11 [26]. However, the efficacy of meningococcal vaccines in asplenic children has not been established, thus many clinicians do not provide the MPS4 vaccine to children with SCD.
- Influenza vaccine — Influenza vaccines should be administered annually during flu season beginning at six months of age. Influenza vaccination may potentially decrease the number of febrile illnesses, thereby reducing the number of febrile episodes that require evaluation and treatment.

Analysis of Healthcare Cost and Utilization Project (HCUP) 2003 to 2005 state inpatient data indicated that although children with SCD were hospitalized for influenza 56 times more often than those without SCD, neither the length or cost of hospitalization differed [45]. Thus there was no difference in the severity of hospitalized cases of influenza between the two groups. As a result, effective influenza vaccination may decrease the hospitalization rate by decreasing the number of febrile illnesses.

Prophylactic penicillin — Randomized trials have demonstrated that prophylactic penicillin decreased the incidence of invasive pneumococcal infection [46,47]. Prophylactic penicillin is recommended for young children who remain at high risk for pneumococcal infection despite the widespread use of the PCV13 [11,44]. In our practice, children with Hb SS and sickle beta (0) thalassemia are all prescribed twice daily oral penicillin prophylaxis. The risk of functional asplenia is much lower in children with Hb SC and sickle beta (+) thalassemia, so penicillin prophylaxis may be omitted in patients with these variant hemoglobinopathies. (See 'Management in variant sickle cell syndromes' below.)

Beyond five years of age, a randomized controlled study demonstrated no statistically significant increase in episodes of bacteremia or death in patients who stopped taking penicillin at age five [42]. Thus penicillin can be safely discontinued at age five following a second dose of pneumococcal polysaccharide vaccine (PPSV23) if the child has not had a prior severe pneumococcal infection or surgical splenectomy.

In our practice, we use the AAP recommendations for prophylactic penicillin in children with SCD as follows [44]:

- Birth to three years of age — Penicillin is administered twice a day at a dose of 125 mg.
- Over three years to five years of age — Penicillin is administered twice a day at a dose of 250 mg.

- Over five years of age — Offer the family the option to discontinue penicillin if the child has received the second dose of the pneumococcal polysaccharide vaccine (PPSV23) and has not had a severe pneumococcal infection or surgical splenectomy.

Patients with penicillin allergies should receive prophylactic erythromycin BID.

MANAGEMENT IN VARIANT SICKLE CELL SYNDROMES — SCD represents a variety of syndromes, which result from inheritance of the sickle cell gene as a homozygote (hemoglobin SS) or as a compound heterozygote with other mutant beta globin genes, such as Hemoglobin SC disease and sickle cell-beta thalassemia. (See "Variant sickle cell syndromes".)

Hemoglobin SS — SCD manifestations including susceptibility to serious infections are the most severe in patients with hemoglobin SS (Hb SS). In these patients, it is imperative that preventive measures to reduce bacterial infections are implemented and that prompt evaluation and treatment with empiric antibiotics are initiated for all febrile episodes. (See 'Prevention of infection' above and 'Acute management' above.)

Hemoglobin SC — Compared to those with Hb SS, patients with Hemoglobin SC (Hb SC) disease are less likely to develop invasive bacterial infection [13,48,49], because they maintain some splenic function during early childhood [50]. In addition, patients with Hb SC who develop bacteremia are less likely to develop sepsis and septic shock [13,49]. Although there are case reports of fatal bacterial infection in children with Hb SC disease [51], the risk of death due to overwhelming sepsis is significantly lower than that of patients with Hb SS.

As a result, in our center, patients with Hb SC are not routinely prescribed twice-daily prophylactic penicillin [49]. Patients and families are counseled to seek medical therapy for any febrile episode with a temperature above 101.5ºF (38.5ºC). The decision to initiate antibiotic therapy is based upon the clinical evaluation of the patient and the use of similar criteria utilized for treating children without hemoglobinopathies. However, in many centers, the evaluation of children with Hb SC and fever includes obtaining a blood culture and administration of empiric parenteral antibiotics. In general, these patients do not require admission for uncomplicated fever [18].

Sickle cell-beta thalassemia — Among patients with sickle cell-beta thalassemia, severity of the disease varies with the production of Hb A, and management varies accordingly:

- Patients with sickle cell-beta (0) thalassemia do not produce any Hb A. Their clinical course is similar to patients with Hb SS disease. They also develop functional asplenia early in childhood, thus, they have a similar risk of invasive bacterial infection as patients with Hb SS. As a result, they are treated in the same manner as those with Hb SS disease with prophylactic penicillin, immunizations, and empiric antibiotic therapy when they are febrile. (See 'Prevention of infection' above and 'Acute management' above.)

- Patients with sickle cell-beta (+) thalassemia produce variable amounts of hemoglobin A and in general have less severe SCD complications, although limited data are available regarding their risk of infection [49]. In general, they are treated in a similar manner to those with Hb SC. In our center, patients with Hb SC are not routinely prescribed twice daily prophylactic penicillin [49]. Patients and families are counseled to seek medical therapy for any febrile episode with a temperature above 101.5ºF (38.5ºC). The decision to initiate antibiotic therapy is based upon the clinical evaluation of the patient and the use of similar criteria utilized for treating children without hemoglobinopathies. However, in many centers, the evaluation of children with Hb SC and fever includes obtaining a blood culture and administration of empiric parenteral antibiotics. In general, these patients do not require admission for uncomplicated fever [18].

SUMMARY AND RECOMMENDATIONS — Fever is a common presenting feature of many clinical manifestations of sickle cell disease (SCD). In particular, fever can be the first indication of a serious and sometimes life-threatening infection in patients with SCD.

- Children with SCD are more susceptible to invasive bacterial infections, particularly encapsulated organisms (eg, S. pneumoniae and H. influenzae) because they have functional asplenia. (See 'Rationale for management approach' above.)

- Despite preventive measures to reduce the incidence of bacterial infections, such as immunizations and prophylactic antibiotics, children with SCD remain at risk for invasive bacterial infection. In the United States, the most common bacterial agents include S. pneumoniae, Salmonella, E. coli, and S. aureus. In other parts of the world, S. pneumoniae is less frequently isolated, even in countries where universal pneumococcal vaccination is not available. (See 'Rationale for management approach' above and 'Empiric antibiotic therapy' above.)

Management of febrile episode

- Patients with SCD and fever over 101.5ºF (38.5ºC) by history or measurement should be promptly evaluated by medical personnel knowledgeable about SCD. A brief history and physical examination focused upon identifying signs of systemic or localized infection, hemodynamic instability, and other manifestations of SCD such as acute chest syndrome should be performed. (See 'Acute management' above.)
- Laboratory tests should be obtained promptly and include blood culture, complete blood count, and reticulocyte count. If there is a clinical suspicion for meningitis, cerebral spinal fluid is obtained for culture. If symptoms suggest a urinary tract infection a urinalysis and culture should be obtained. A type and crossmatch is obtained if extreme pallor, severe pulmonary or neurologic symptoms, or significant acute increase in spleen size are present. (See 'Acute management' above.)
- After the initial laboratory tests are obtained, we recommend prompt administration of empiric parenteral antibiotics in all patients with SCD and fever (Grade 1C). Selected antibiotics should be active against bacterial pathogens that are commonly found in the local community. (See 'Acute management' above.)
- For empiric parenteral antibiotics, the following regimen is most commonly used in the United States:

- Parenteral ceftriaxone as a single dose of 50 to 75 mg/kg, (maximum dose 2 g), the dose of which is increased (dose 75 to 100 mg/kg, maximum dose 2 g) in regions with a high prevalence of antibiotic resistant S. pneumoniae.
- In patients who are hemodynamically unstable or suspected to have meningitis, vancomycin is added (dose 15 mg/kg IV, maximum dose 1 g).
- For patients who are allergic to cephalosporins, clindamycin can be used (dose of 10 to 15 mg/kg, maximum dose 1.6 g). Most patients requiring this therapy should be admitted for observation due to the shorter half-life of this antibiotic.

- The identification of a localized infection does not alter the need for empiric parenteral antibiotics. (See 'Acute management' above.)
- Further evaluation is obtained only after antibiotics are given and if clinically indicated (eg, chest radiography). (See 'Further evaluation' above.)
- Patients who are more likely to have invasive bacterial infection should be hospitalized. We recommend that patients with SCD be admitted for inpatient care if they have several of the following risk factors for invasive bacterial infection (Grade 1C): (See 'Decision about admission' above.)

- Age less than two years with hemoglobin SS or sickle beta (0) thalassemia
- Temperature greater than 40 degrees C (104 degrees F)
- White cell count >30,000/microL or <5000/microL
- Hemoglobin is ≥2 grams/dL below steady state value
- Previous invasive bacterial infection particularly with Streptococcus pneumoniae.
- Indwelling central venous line
- Signs of systemic toxicity, meningitis, or hemodynamic instability
- Other complications of SCD (eg, acute chest syndrome, splenic sequestration) are present that would benefit from inpatient management

- In addition, other indications for hospitalization are treatment with either vancomycin or clindamycin (because of their shorter half life), concern about inability to contact the family or ability to reliably return if the culture becomes positive or the patient's condition worsens, and if other complications of SCD are present (eg, pain requiring parenteral opioid to control) that require inpatient management. (See 'Decision about admission' above.)

- Inpatient management includes initiation of hemodynamic monitoring, oxygen saturation monitoring, supportive care (if needed), continuation of empiric antibiotic therapy, and readjustment of antibiotics when culture results are available. (See 'Inpatient management' above.)
- Patients can be managed as an outpatient if they do not have any of the above criteria for admission, they are clinically stable, there is a specific plan for next day follow-up, and there is a method of immediate recall if there is documented bacteremia. (See 'Outpatient management' above.)

Measures to reduce infection — Preventive measures to reduce infection in children with SCD include immunizations and prophylactic penicillin.

- Children with all SCD genotypes should receive all routinely recommended childhood vaccines. (See 'Immunization' above and "Standard immunizations for children and adolescents".)
- In the United States, all children with SCD below five years of age should receive BOTH the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine. (Grade 1A). (See 'Pneumococcal vaccination' above.)
- We recommend that children with SCD receive annual influenza vaccine starting at six months of age (Grade 1A). (See 'Other vaccinations' above and "Seasonal influenza vaccination in children", section on 'Indications'.)
- In the United States, we recommend that all children with Hb SS and sickle cell-beta (0) thalassemia below five years of age receive twice daily prophylactic oral penicillin because of the high prevalence of invasive pneumococcal infection in these patients. (Grade 1B). Prophylactic penicillin can be omitted in children with Hb SC and sickle cell-beta (+) thalassemia as these patients are at a lower risk for invasive pneumococcal infection. (Grade 1B). (See 'Prophylactic penicillin' above.)

Kawasaki disease: Clinical features and diagnosis

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INTRODUCTION — Kawasaki disease (KD, also called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood [1]. KD also occurs rarely in adults. It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 11 days without therapy [2]. However, complications such as coronary artery aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality. (See "Cardiovascular sequelae of Kawasaki disease".)

The clinical manifestations and diagnosis of KD are discussed in this review. The epidemiology, etiology, treatment, and complications, including cardiac sequelae, of Kawasaki disease are presented separately. Incomplete (atypical) KD and unique features in infants and adults are also reviewed separately. (See "Kawasaki disease: Epidemiology and etiology" and "Kawasaki disease: Initial treatment and prognosis" and "Cardiovascular sequelae of Kawasaki disease" and "Incomplete (atypical) Kawasaki disease" and "Kawasaki disease: Complications".)

CLINICAL MANIFESTATIONS — The clinical features of KD reflect widespread inflammation of medium- and small-sized blood vessels. Diagnosis is based upon evidence of systemic inflammation, as evidenced by fever, in association with signs of mucocutaneous inflammation. The characteristic bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, rash, extremity changes, and lymphadenopathy typically develop after a brief nonspecific prodrome of respiratory or gastrointestinal symptoms [3-7]. These clinical signs are the basis for the diagnostic criteria for KD (table 1) [8].

Mucous membrane findings are seen in approximately 90 percent of cases of KD, polymorphous rash in 70 to 90 percent, extremity changes in 50 to 85 percent, ocular changes in >75 percent, and cervical lymphadenopathy in 25 to 70 percent [7,9-11].

These findings are often not present at the same time. As an example, some patients have only developed fever and cervical lymphadenopathy by the time of admission (so-called KD with isolated cervical lymphadenopathy, KDiL) [12]. In one case series, these patients tended to be older and to have a more severe course, with increased risk of coronary artery disease and lack of response to intravenous immune globulin. Thus, repeated histories and physical examinations are important both for making a timely diagnosis of KD in children who fail to meet diagnostic criteria, as well as for appropriate consideration of alternative diagnoses. (See 'Diagnosis' below.)

Fever — Fever is the most consistent manifestation of KD. It reflects elevated levels of proinflammatory cytokines, such as tumor necrosis factor and interleukin-6, which are thought to mediate the underlying vascular inflammation [13]. Fever is minimally responsive to antipyretic agents, and it typically remains above 38.5ºC during most of the illness. The diagnosis of KD should be considered in all children with prolonged unexplained fever ≥five days. (See "Incomplete (atypical) Kawasaki disease".)

Conjunctivitis — Bilateral nonexudative conjunctivitis is present in more than 90 percent of patients. A predominantly bulbar injection typically begins within days of the onset of fever, and the eyes often have a brilliant erythema, which spares the limbus (picture 1). Children also are frequently photophobic, and anterior uveitis may develop [11,14]. Slit-lamp examination may be helpful in ambiguous cases; the presence of uveitis provides further evidence for the diagnosis of KD, since it is more commonly seen in KD than in other diseases with similar presentations. (See "Uveitis: Etiology; clinical manifestations; and diagnosis".)

Mucositis — Mucositis often becomes evident as KD progresses. Cracked, red lips (picture 2) and a strawberry tongue (picture 3) are characteristic; the latter is a result of sloughing of filiform papillae and denuding of the inflamed glossal tissue. Discrete oral lesions, such as vesicles or ulcers, and tonsillar exudate, are suggestive of a disease process other than KD [6].

Rash — The cutaneous manifestations of KD are polymorphous. The rash typically begins as perineal erythema and desquamation, followed by macular, morbilliform, or targetoid skin lesions of the trunk and extremities. Vesicular or bullous lesions are rare, but KD may trigger a psoriasiform eruption in children not previously recognized to have psoriasis [15-18].

Extremity changes — Changes in the extremities are generally the last manifestation to appear. Children develop an indurated edema of the dorsum of their hands and feet, and a diffuse erythema of their palms and soles (picture 2).

The convalescent phase of KD is often characterized by sheet-like desquamation that begins in the periungual region of the hands and feet (picture 4), and by linear nail creases (Beau's lines). The prevalence of periungual desquamation in patients with KD has been reported to vary from 98 to 68 percent [19]. The lowest rate was documented in a retrospective review of patients treated at a tertiary center in the United States from 2003 to 2007. Factors that might have contributed to this lower prevalence than was seen in earlier reports include uniform treatment with high dose IVIG, and ethnic differences from Asian case series [3,4,20,21].

Arthritis has been reported in 7.5 to 25 percent of patients [22,23]. The prevalence of arthritis was 7.5 percent in a retrospective Canadian study of 414 consecutive patients diagnosed with KD [22]. The large joints (ie, knee, ankle, and hip) were primarily involved. Oligoarticular involvement (arthritis of four or fewer joints) occurred in 16 patients and polyarticular involvement (arthritis of five or more joints) in 15 patients. Patients with arthritis were more likely to have increased levels of inflammatory markers (C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) and neutrophils. Otherwise, there were no differences in clinical features, response to therapy, or clinical outcome between patients with or without arthritis.

Lymphadenopathy — Cervical lymphadenopathy is the least consistent feature of KD, absent in as many as half to three-quarters of children with the disease [10]. When present, lymphadenopathy tends to involve primarily the anterior cervical nodes overlying the sternocleidomastoid muscles [24]. Diffuse lymphadenopathy or other signs of reticuloendothelial involvement (eg, splenomegaly) should prompt a search for alternative diagnoses.

Cardiovascular findings — Cardiac manifestations during the first week to 10 days of illness may include tachycardia out of proportion to the degree of fever, gallop sounds, and muffled heart tones [2]. Severely ill patients, particularly young infants, may develop fusiform aneurysms of the brachial arteries that are easily palpable or visible in the axillae. In addition, young infants may have cold, pale, or cyanotic digits of the hands

and feet with reduced blood perfusion. Gangrene may, in rare cases, cause loss of fingers or toes during this acute period. Cardiovascular findings are not part of the classical diagnostic criteria.

Other findings — The following nonspecific symptoms commonly occur in children within the first 10 days before diagnosis of KD, but are not included in the diagnostic criteria [5]:

- Diarrhea, vomiting, or abdominal pain — 61 percent
- Irritability — 50 percent
- Vomiting alone — 44 percent
- Cough or rhinorrhea — 35 percent
- Decreased intake — 37 percent
- Weakness — 19 percent
- Joint pain — 15 percent

LABORATORY FINDINGS — No laboratory studies are included among the diagnostic criteria for typical KD. However, certain findings may support the diagnosis of KD, particularly in ambiguous cases [1] (see 'Diagnosis' below and "Incomplete (atypical) Kawasaki disease", section on 'Laboratory tests'):

- Systemic inflammation is characteristic of KD. Typical manifestations include elevation of acute phase reactants (eg, C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]), leukocytosis, and a left-shift in the white blood cell count. Platelet counts generally rise by the second week of illness and may reach 1,000,000/mm3 (reactive thrombocytosis) in the most severe cases.
- Children with KD often present with a normocytic, normochromic anemia. Hemoglobin concentrations more than two standard deviations below the mean for age are noted in one-half of patients within the first two weeks of illness (table 2).
- Urinary microscopy commonly reveals white blood cells [25]. Pyuria is often of urethral origin and therefore may be missed on urinalyses obtained by bladder tap or catheterization [26]. In addition, white cells are mononuclear, and are not detected by dipstick tests for leukocyte esterase. Thus, children with suspected KD should have a clean voided or bagged urine specimen collected for microscopic examination.
- In one retrospective series of 259 patients, 45 percent had at least one abnormal liver function test [27]. In a case-control series approximately 30 percent of 280 patients with KD had mild to moderate elevation of transaminases (eg, serum alanine aminotransferase >50 U/L) because of intrahepatic congestion [6]. In addition, a minority of children develop obstructive jaundice from hydrops of the gallbladder.
- Cerebrospinal fluid (CSF) may display a mononuclear pleocytosis without hypoglycorrhachia or elevation of CSF protein. In a retrospective review, 46 of 520 children with KD underwent lumbar puncture [28]. In this subset of patients, 39 percent had elevated CSF white cell counts. The median count was 22.5 cells/mm3 with 6 percent neutrophils and 92 percent mononuclear cells, although cell counts as high as 320/mm3 with up to 79 percent neutrophils were reported. In a small case series of 10 children with KD, elevated CSF inflammatory cytokines (ie, IL-6 and sTNFR1) were reported in addition to CSF pleocytosis [29].
- Similarly, arthrocentesis of involved joints typically demonstrates a pleocytosis, with 125,000 to 300,000 white cells/mm3, primarily neutrophils [30].
- Children with KD develop significant perturbations in serum lipid profiles, including elevated triglycerides and low density lipoproteins, and depressed high density lipoproteins [2,31-33]. A return to normal may take years in untreated children, but generally occurs within weeks or months following IVIG therapy.
- Hyponatremia (serum sodium <135 mEq/L) may be seen and is associated with an increased risk of coronary artery aneurysms [34].

DIAGNOSIS — Guidelines for the diagnosis of KD were established by Tomisaku Kawasaki in 1967. Diagnosis of KD according to these criteria requires the presence of fever lasting ≥five days, combined with at least four of the five following physical findings, without an alternative explanation (table 1) [1,35]:

- Bilateral bulbar conjunctival injection (picture 1)
- Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue (picture 2)

- Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase) (picture 2)
- Polymorphous rash
- Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter)

Redness or crust formation at the site of Bacille Calmette-Guerin (BCG) inoculation is also suggested as a useful sign in several diagnostic guidelines [2,8]. In one series of 15,524 patients with KD and a history of BCG vaccination, 50 percent had this finding, compared with none of the 53 children admitted with respiratory syncytial virus or rotavirus infection who served as the control group [36].

As with all clinical criteria, these are imperfect guidelines with less than 100 percent sensitivity and specificity. Children who do not meet the criteria may have an incomplete or atypical form of KD; algorithms published in 2004 form the basis for identifying such cases [2]. In addition, Dr. Kawasaki published his guidelines before cardiac involvement was recognized in this disease, so they were never intended to identify children at risk for developing coronary artery abnormalities. Thus, it is not surprising that at least 10 percent of children who develop coronary artery aneurysms never meet criteria for KD [37]. (See "Incomplete (atypical) Kawasaki disease".)

Conversely, some patients who manifest five or six signs of KD may have other conditions. One study of patients referred for possible KD found that the standard clinical diagnostic criteria for KD were fulfilled in 18 of 39 patients (46 percent) in whom other diagnoses were established [6]. (See 'Differential diagnosis' below.)

Delayed diagnosis — Treatment with IVIG within the first 10 days of illness reduces the prevalence of coronary artery aneurysms fivefold compared with children not treated with IVIG [38,39]. Thus, it is desirable to diagnose KD as soon as possible after the criteria are met (ie, not before the fifth day of illness), in order to initiate treatment and reduce the risk of coronary artery lesions. However, timely identification is challenging because the diagnosis is based upon nonspecific clinical signs and there is no definitive diagnostic test.

In a retrospective study of 562 patients diagnosed with KD at eight North American centers, 92 cases (16 percent) were diagnosed after the first 10 days of illness (ie, late diagnosis) [40]. Predictors of a delay in diagnosis of KD included age below six months, clinical presentation of incomplete KD, greater distance from a tertiary center, and variability between clinical centers. In contrast, socioeconomic status was not associated with a delay in diagnosis.

These findings suggest that practice variation in confirming a diagnosis of KD may in part contribute to a delayed diagnosis. The results of this study underscore the need for a high index of suspicion of KD, especially in young infants and patients who present with incomplete KD, in order to identify and treat patients in a timely manner. (See "Incomplete (atypical) Kawasaki disease".)

DIFFERENTIAL DIAGNOSIS — KD is most commonly confused with infectious exanthems of childhood [2,41,42].

Infectious diseases and other mimics of KD may have the following clinical features not commonly found in KD [2]:

- Exudative conjunctivitis
- Exudative pharyngitis
- Discrete intraoral lesions
- Bullous or vesicular rash
- Generalized lymphadenopathy

The presence of any of these findings and/or the absence of fever should suggest a diagnosis other than KD. Of note, concurrent infections are common in patients with KD, found in up to 40 percent of patients in one study [43]. In this review of 129 consecutive children seen with KD in Toronto, infection at the time of diagnosis did not affect response to therapy or outcome. However, another series found that concomitant viral infection was associated with a higher frequency of coronary artery dilatation [44]. In any event, diagnosis of an infectious condition does not preclude a concurrent diagnosis of KD.

The differential diagnosis of KD includes (table 3):

- Measles, echovirus, adenovirus, and Epstein-Barr virus. These viral illnesses may share many of the signs of mucocutaneous inflammation, but they typically have less evidence of systemic inflammation and generally lack the extremity changes seen in KD. (See "Clinical presentation and diagnosis of measles" and "Clinical manifestations and diagnosis of enterovirus infections" and "Epidemiology and clinical manifestations of adenovirus infection" and "Clinical manifestations and treatment of Epstein-Barr virus infection".)
- Toxin-mediated illnesses, especially group A streptococcal infections (eg, scarlet fever and toxic shock syndrome). These usually lack the ocular and articular involvement typical of KD, though patients with staphylococcal toxic shock syndrome occasionally may have conjunctival hemorrhage. (See "Group A streptococcal (Streptococcus pyogenes) bacteremia in children" and "Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome" and "Staphylococcal toxic shock syndrome".)
- Rocky Mountain spotted fever and leptospirosis. Headache and gastrointestinal complaints typically are prominent features of these infections. (See "Clinical manifestations and diagnosis of Rocky Mountain spotted fever" and "Microbiology, epidemiology, clinical manifestations, and diagnosis of leptospirosis".)
- Drug reactions such as Stevens-Johnson syndrome or serum sickness. These may mimic KD, but with subtle differences in the ocular and mucosal manifestations. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Clinical manifestations; pathogenesis; and diagnosis".)
- Systemic onset juvenile idiopathic arthritis. Children with this condition generally lack the conjunctival and oral findings of KD. Lymphadenopathy also is generalized, unlike in KD. (See "Systemic onset juvenile idiopathic arthritis: Clinical manifestations and diagnosis".)
- Mercury hypersensitivity reaction (acrodynia). In particular, this shares certain clinical features with KD, including fever, rash, swelling of the palms and feet, desquamation, and photophobia. However, treatment of a child with possible KD should not be delayed while awaiting mercury levels, unless there is a convincing history of exposure to mercury, because of the rarity of acrodynia in the developed world. (See "Epidemiology and toxicity of mercury", section on 'Acrodynia'.)

SUMMARY

- Kawasaki disease (KD, also called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood. KD also occurs rarely in adults. It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 11 days without therapy. (See 'Introduction' above.)
- Kawasaki disease is characterized by systemic inflammation manifested by fever and mucocutaneous involvement, including bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, rash, extremity changes, and lymphadenopathy (table 1). These findings are often not present at the same time. Thus, repeated histories and physical examinations are important in making a timely diagnosis of KD in children with fever and signs of mucocutaneous inflammation. (See 'Clinical manifestations' above.)
- No laboratory studies are included among the diagnostic criteria for typical KD. However, certain findings may support the diagnosis of KD in ambiguous cases. (See 'Laboratory findings' above.)
- The diagnosis of KD according to classical criteria requires the presence of fever ≥five days, combined with at least four of the other five signs of mucocutaneous inflammation, without any other explanation (table 1). Incomplete KD, representing 20 to 60 percent of cases, is identified on the basis of additional clinical and laboratory features supportive of the diagnosis. (See 'Diagnosis' above and "Incomplete (atypical) Kawasaki disease".)
- KD is most commonly confused with infectious exanthems of childhood. The presence of clinical features not commonly found in KD, including exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and/or generalized lymphadenopathy, suggest another diagnosis (table 3). Nonetheless, KD is sufficiently pleomorphic that none of these findings can definitively exclude the diagnosis. In addition, many children with KD also have concurrent infections. (See 'Differential diagnosis' above.)

Evaluation of the child with joint pain or swelling

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INTRODUCTION — Joint pain and swelling are common manifestations of many musculoskeletal and rheumatologic diseases. As a result, the differential diagnosis of childhood joint pain and swelling is large and includes both benign and serious conditions. The assessment of a child with joint pain and/or swelling needs to differentiate between conditions of varying severity, especially those that require urgent medical intervention.

The evaluation of a child with joint pain or swelling will be reviewed here. Although there is overlap among the causes of limping, hip pain, and joint swelling and pain, the causes and approaches to assessing a child with limp and/or hip pain are discussed separately. (See "Approach to the child with a limp" and "Overview of the causes of limp in children" and "Overview of hip pain in childhood".)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of childhood joint pain or swelling is broad, ranging from benign to serious conditions, some of which can have devastating consequences (eg, septic arthritis) (table 1). The categories of possible disease that may present with joint pain and/or swelling are included in the following mnemonic, ARTHRITIS:

- Avascular necrosis and epiphyseal disorders. (See "Overview of hip pain in childhood", section on 'Legg-Calvé-Perthes' and "Slipped capital femoral epiphysis", section on 'Osteonecrosis'.)
- Reactive and postinfectious arthritis (see "Clinical manifestations and diagnosis of acute rheumatic fever")
- Trauma: Accidental and nonaccidental, including hypermobility associated with microtrauma
- Hematologic: Leukemia, bleeding diatheses, and hemoglobinopathies
- Rickets, metabolic and endocrine disorders (see "Overview of rickets in children")
- Infection: septic arthritis and osteomyelitis, as well as other types of infections such as Lyme arthritis and Parvovirus-associated arthritis. (see "Bacterial arthritis: Clinical features and diagnosis in infants and children" and "Bacterial arthritis: Epidemiology, pathogenesis, and microbiology in infants and children" and "Clinical features of hematogenous osteomyelitis in children" and "Musculoskeletal manifestations of Lyme disease" and "Specific viruses that cause arthritis" and "Clinical manifestations and pathogenesis of human parvovirus B19 infection")
- Tumor: Musculoskeletal neoplasia (eg, osteosarcoma), lymphoma, and neuroblastoma (see "Osteosarcoma: Epidemiology, pathogenesis, clinical presentation, diagnosis, and histology")
- Idiopathic pain syndromes, such as complex regional pain syndrome type 1 and fibromyalgia. (see "Clinical manifestations and diagnosis of fibromyalgia in children and adolescents" and "Complex regional pain syndrome in children")
- Systemic rheumatologic diseases (see "Systemic lupus erythematosus in children" and "Classification of juvenile arthritis (JRA/JIA)")

Note that the group of diseases incorporated under the grouping of juvenile idiopathic arthritis (JIA) does not appear on this differential diagnosis list. The diagnosis of JIA requires the exclusion of all the above diagnoses.

HISTORY — A thorough history and physical examination are the initial steps in determining the diagnosis of a child with joint pain and/or swelling. The history needs to differentiate between benign and pathologic conditions, especially those that require urgent medical attention, and helps direct a focus for the physical examination and diagnostic studies.

The important elements of the history include:

- Pain characterization including the site, number of joints involved, severity, frequency, duration and pattern of pain. The characterization of swelling is also important and includes many of the same elements as those for pain as well as the presence of associated findings of warmth and discoloration.
- Presence of precipitating factors, such as a history of trauma.
- Review of systems focusing on the presence of fever, rash, weight loss, abdominal pain, and ocular abnormalities.
- Other medical conditions associated with arthritis or arthralgias. These include celiac disease, inflammatory bowel disease, chronic lung or cardiac disease with hypoxia, uveitis, psoriasis, and cystic fibrosis.
- Family history. Psoriasis, hypermobility syndromes, inflammatory bowel disease, spondyloarthropathies, uveitis and bony dysplasias are important to ask about in close relatives, as these conditions have a genetic basis and may be associated with arthritis in the child. The likelihood that joint pain is due to an autoimmune condition is increased if multiple members of the patient's family have suffered from autoimmune diseases and/or immune deficiency syndromes. The health and medical history of the patient's siblings may also be informative.

Pain, swelling, and stiffness characterization — Pain and swelling are characterized by their location, severity, frequency, duration, and factors that either exacerbate or relieve the finding (table 2). Joint stiffness is also a common feature, but like pain is subjective and may be difficult to quantify.

The following questions help to characterize the child's joint pain and swelling:

- How severe is the pain, swelling, or stiffness?
- What is the location of the pain, stiffness or swelling?
- How many joints are involved?
- When and for how long have the joint(s) been painful, stiff, or swollen?
- How quickly did the pain, swelling, or stiffness appear?
- What makes the pain, swelling, or stiffness better or worse?

Severity — Although the severity or intensity of pain or stiffness should be assessed, one must be careful not to equate severity of pain or stiffness with severity of illness because the perception of pain is subjective. However, pain severe enough to cause the child to refuse to put any weight on the affected limb is a "red flag" for serious illness, such as bacterial infection of the joint or bone (eg, septic arthritis and osteomyelitis) or malignancy (eg, leukemia and osteosarcoma). In contrast, juvenile idiopathic arthritis (JIA), Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, Osgood-Schlatter disease, and transient synovitis are often associated with limping, but the pain is generally not severe enough for a child to refuse to bear weight. (See "Approach to the child with a limp".)

Young children and infants may have difficulty articulating the presence of pain and may not complain of joint pain even when there are obvious signs of joint inflammation and swelling [1]. In cases that involve the lower extremities, the young child may manifest pain as a refusal to walk or walking with a limp, and in those that involve the upper extremities, the patient may limit the movement and use of the involved arm.

In an adolescent who complains of excruciating pain, often accompanied by inability to walk, but does not seemed to be particularly bothered by the problem ("la belle indifference"), a pain disorder such as complex regional pain syndrome type 1 (CRPS) or fibromyalgia may be the likely diagnosis. (See "Complex regional pain syndrome in children" and "Clinical manifestations and diagnosis of fibromyalgia in children and adolescents".)

Pain that wakes a child in the middle of the night is generally severe and is a useful diagnostic clue, as it is more commonly seen in patients with bony pain due to relatively benign tumors such as osteoid osteoma, or malignancies, such as leukemia. Although other benign conditions such as growing pains also occur typically at night, these children are always entirely well during the day. (See "Growing pains".)

Significant joint symptoms are likely to interfere with daily activities, such as walking long distances, participating in sports or physical education, and playing instruments. Involvement of the small hand joints may interfere with writing, the ability to button clothes, and opening jars and bottles.

Location and number of involved joints — Determining the site(s) of the pain/swelling is important to develop a rational list of differential diagnoses, and to direct subsequent evaluation and treatment.

It may be challenging to have children localize pain accurately, especially younger children. Children should be asked to tell or to point to the painful area(s). For the nonverbal child, family members are asked what led them to think that the child has a joint problem and whether they noted any unusual warmth or swelling of the joint(s).

There is overlap between causes of monoarticular and polyarticular pain and swelling (table 1). However, it is important to determine the number of involved joints because infection is a relatively common cause of acute pain and swelling in a single joint, which can result in cartilage destruction within a few days if not treated. As a result, patients with monoarticular involvement need to be assessed urgently to ensure that therapy can be initiated as quickly as possible in those suspected of having a bacterial infection as the cause of their symptoms.

- Single joint involvement — Bacterial infections (eg, septic arthritis and osteomyelitis) and significant trauma (eg, fracture or hemarthroses) are important causes of pain in a single joint that must be considered without delay, as discussed above. Other common causes of monoarticular pain and/or swelling include osteonecrosis (ie, Legg-Perthes disease), oligoarticular JIA, Lyme arthritis, and some cases of reactive arthritis.
- Multiple joint involvement — As bacterial infection and significant trauma rarely affect multiple joints, there is less urgency to evaluate a child with polyarticular involvement [2]. Causes of multiple joint pain and/or swelling include connective tissue disorders such as systemic lupus erythematosus (SLE), JIA, and inflammatory bowel disease associated arthritis.

Frequency, duration, and pattern — Pain and swelling can be characterized based upon their frequency, duration, and pattern:

- Persistent, intermittent and migratory pain/swelling — Persistent pain is characteristic of inflammation of the joint space commonly seen in patients with arthritis that is due to infection or a rheumatologic disorder, or bony pain due to a neoplastic process.

  Intermittent pain, particularly associated with activity, is more likely due to a mechanical problem (eg, meniscal or ligamentous injury of the knee, and rotator cuff impingement disorder in the shoulder). In addition, recurrent pain and swelling of one or two large joints followed by spontaneous resolution, particularly in the knees, is characteristic of Lyme arthritis.

  Migratory joint pain is pain that lasts for several days in one or more joints and then resolves, while other, previously unaffected, joints become painful. It can be seen in patients with acute rheumatic fever or post-streptococcal reactive arthritis, Henoch-Schönlein purpura, and childhood leukemia or lymphoma. (See "Clinical manifestations and diagnosis of acute rheumatic fever" and "Clinical manifestations and diagnosis of Henoch-Schönlein purpura" and "Overview of the presentation and classification of acute lymphoblastic leukemia in children".)
- Time of day — Diurnal variation is an important distinguishing feature of many different causes of joint pain that aids in identifying the underlying diagnosis. Joint pain due to arthritis, such as JIA, is usually worse at the beginning of the day and improves throughout the day with movement and activity, In contrast, pain due to trauma or mechanical causes (eg, hypermobility, torn meniscus, patellofemoral syndrome or Legg-Calve-Perthes disease) is usually mild or nonexistent in the morning and worsens with activity, or may only occur after increased physical activity. Growing pains typically occur in a well child, with pain that may affect the joint usually beginning at the end of the day and into the middle of the night, but not during the daytime [3]. Although bone tumors can cause nocturnal pain, the child also has pain during the day. (See "Overview of hip pain in childhood", section on 'Legg-Calvé-Perthes' and "Growing pains" and "Clinical presentation, staging, and prognostic factors of the Ewing sarcoma family of tumors" and "Osteosarcoma: Epidemiology, pathogenesis, clinical presentation, diagnosis, and histology".)
- Acuity of onset — Rapid onset of findings within one or two days is often associated with septic arthritis, osteomyelitis and vasculitis (such as Henoch Schönlein Purpura), whereas many of the other causes of childhood joint pain and swelling are more insidious.

Other joint symptoms — The presence of a warm or red joint indicates inflammation of the joint (arthritis). These findings increase the concern for an infectious or inflammatory cause for joint pain and swelling. Locking or "giving way" of the joint are suggestive of a mechanical joint disorder.

Precipitating factors — The following factors may be associated with the initiation and/or worsening of joint symptoms. Their presence may be helpful in determining the possible cause of joint symptoms.

Antecedent trauma — Trauma may be the direct cause of joint pain, as with fractures or ligamentous injuries, or indirect, as with some cases of osteomyelitis. Judging the degree of trauma, and determining the temporal relation between the trauma and the child's presentation are important in deciding whether trauma can be the cause or a contributing factor to a child's joint symptoms. In a significant traumatic injury, the precipitating event is usually associated with the immediate onset of pain, swelling, and sometimes bruising. In some cases, however, an episode of minor trauma may simply bring to attention a preexisting, but as yet undiagnosed and unrelated, condition.

Antecedent infection — Recent infections, especially with enteric pathogens (Salmonella, Shigella, Yersinia and Campylobacter), viruses (eg, parvovirus B19 and varicella), Group A Streptococcus, and immunization (eg, rubella immunization), may be associated with reactive arthritis, a common cause of acute arthritis in children [4]. As an example, the arthritis of acute rheumatic fever (ARF), a sequel of a group A streptococcal pharyngeal infection, typically occurs two weeks after the precipitating infection. (See "Clinical manifestations and diagnosis of acute rheumatic fever".)

Reactive arthritis is broadly defined as an arthritis which developed soon after or during an infection elsewhere in the body, but in which the microorganisms cannot be recovered from the joints. In the In the most restricted definition, reactive arthritis has been used to refer to the triad of postinfectious arthritis, urethritis, and conjunctivitis, formerly called Reiter syndrome. (See "Reactive arthritis (formerly Reiter syndrome)".)

Inactivity — Joint pain or stiffness that is worsened by periods of inactivity (called articular or inactivity gelling) is typical of chronic inflammatory arthritis, such as seen in some cases of JIA or SLE. An important question to ask is whether the child appears stiff in the morning with gradual resolution or improvement during the day's activity. Some parents will volunteer that their child "looks like an old man" after getting up in the morning. Very young children may simply be irritable upon awakening and ask to be carried until they feel better. Affected children may have similar complaints/findings later in the day after a nap, a period of inactivity (such as a long car ride), or even sitting at a desk in class.

Increased physical activity — Children with mechanical causes of joint pain, such as hypermobility syndrome, patellofemoral syndrome, and osteochondroses, will often have pain that is significantly worse or only occurs after increased physical activity. Growing pains are also often reported to be more frequent after an active day. (See "Clinical manifestations and treatment of the hypermobility syndrome" and "Approach to the young athlete with chronic knee pain or injury", section on 'Patellofemoral dysfunction' and "Overview of the causes of limp in children", section on 'Apophysitis (formerly osteochondrosis)' and "Growing pains".)

Associated symptoms

Fever — The presence of fever narrows the differential diagnosis significantly. If there has been a history of fever it is important to ascertain the timing and pattern of fever, and the height of elevated temperature.

Fever may precede or present at the same time as joint symptoms in children whose disease is due to bacterial infection. High fever (temperature greater than 38º C) in a patient with monoarticular disease is typical of a bacterial infection of the joint or bone. However, subacute or partially treated infection may not be accompanied by significant fever. Fever may also have been present during an antecedent illness that preceded the development of reactive arthritis. (See 'Antecedent infection' above and "Reactive arthritis (formerly Reiter syndrome)".)

Fever is also associated with noninfectious diseases including JIA, Kawasaki disease, vasculitis, and SLE. In some conditions, the pattern of fever may be an important clue to the diagnosis as demonstrated in the following examples:

- Systemic JIA is associated with a quotidian fever pattern. A daily spike of high fever often occurs in the afternoon or evening with a return to normal temperature between spikes. (See "Systemic onset juvenile idiopathic arthritis: Clinical manifestations and diagnosis", section on 'Fever'.)
- Periodic fever syndromes, such as familial Mediterranean fever, have a characteristic pattern of intermittent episodes of fever. These last for a few days or longer, resolve spontaneously, and give way to weeks of normal temperature. During the febrile episodes, patients may have joint pain and swelling. (See "Periodic fever syndromes and other autoinflammatory diseases: An overview".)
- The fever in patients with SLE has a gradual onset and is typically low-grade and intermittent. (See "Systemic lupus erythematosus in children".)

Review of systems — A thorough review of systems detects the presence of other symptoms that may aid in the identification of the correct diagnosis. Clinical features, such as rash, weight loss, abdominal pain, and eye abnormalities, in combination with joint findings are suggestive of specific diseases based upon pattern recognition (table 3).

PHYSICAL EXAMINATION — Abnormalities detected by the physical examination are important clues to the diagnosis and help differentiate severe conditions requiring urgent medical intervention from more benign disorders.

In addition to a thorough general examination, a complete musculoskeletal examination includes:

- General appearance including measurement of growth parameters and vital signs.
- Special attention to the heart, lung, skin, and eyes, as these organ systems are often affected in children with joint pain or swelling. In many cases, abnormalities of these organs may suggest an underlying etiology.
- Screen of the entire musculoskeletal system with a focused examination of the painful or swollen joint(s).
- Evaluation of motor strength (both proximal and distal) as neuromuscular conditions and inflammatory myopathies may be accompanied by joint symptoms.

Performing a meticulous pediatric musculoskeletal examination, especially in young children, requires a patient and persistent approach. It may even take more than one session to complete if the child is fractious. Without a thorough and systematic examination, however, subtle signs of critical importance to the diagnosis of the condition may be missed.

General appearance — A general inspection of the patient should determine whether the child is ill or well appearing. Height and weight measurements are compared to reference ranges and prior values. A change in the patient's growth curve or recent weight loss may be indicative of a serious pathologic disorder, such as systemic-onset or polyarticular JIA, systemic lupus erythematosus, inflammatory bowel disease, or a malignancy (eg, leukemia). On the other hand, persistent complaints associated with weight gain may be a sign of a pain syndrome, such as fibromyalgia.

Vital signs include determination of blood pressure, which may be elevated in SLE or a primary vasculitis, and temperature. (See 'Fever' above.)

Musculoskeletal screening — The pGALS (Pediatric Gait Arms Legs Spine) examination is a simple screen for musculoskeletal abnormalities that can be performed in minutes (figure 1 and figure 2 and figure 3 and figure 4) [5,6]. It is a screen that uses simple physical maneuvers, including observation of the gait, to assess for musculoskeletal abnormalities.

Focused joint examination — If an affected joint is extremely painful, its assessment should be reserved until the end to encourage cooperation with the rest of the evaluation.

The joint examination begins with inspection and proceeds to palpation and estimation of active and passive range of motion (table 4).

Inspection — Observation is the first step in joint examination. If joint pain is asymmetrical, compare both extremities looking for differences in size and shape. Does the child hold an affected joint in a particular position

of comfort? If a joint appears bigger than the corresponding contralateral articulation, further assessment will need to determine if joint effusion, synovial thickening, edema of the soft tissue overlying the joint, bony overgrowth, or some combination of these abnormalities has led to the increase in joint size. (See 'Palpation' below.)

Even if only a single joint is painful, the entire extremity should be examined to detect the presence of muscle atrophy, discrepancies of length, and/or generalized asymmetry. If there is a leg length discrepancy, measure the leg lengths carefully from the anterior superior iliac spine to the medial malleolus to distinguish an apparent difference due to a pelvic tilt from a true difference in length. Alternatively, a pelvic tilt in the standing position may be observed from behind, and correcting the tilt by placing a lift under ("blocking up") the shorter leg should give an accurate estimate of leg length discrepancy.

The skin overlying the joint should be inspected for evidence of scars, bruises, and discoloration, which could be caused by a rash or inflammation.

Palpation — The initial step in palpation is to detect any changes in the temperature of the skin overlying the affected joint. Increased warmth of the affected joint compared to the unaffected side could indicate inflammation due to infection or rheumatologic disorder. Extremities affected by complex regional pain syndrome (CRPS) Type 1 can be either cooler or warmer than the unaffected side.

Palpation includes assessment for the presence and location of tenderness. Joint tenderness may be secondary to disorders of the bone, such as osteomyelitis, bone tumor, or Osgood-Schlatter disease; synovial disease, such as arthritis; or abnormalities of the ligaments, tendons, and menisci. Palpation of the "entheses" (points of insertion of ligament, tendon or joint capsule into bone) is of particular importance in determining the subtype of JIA and occasionally in other musculoskeletal and rheumatic diseases. Inflammation at these points of insertion is referred to as "enthesitis".

If osteomyelitis is suspected, careful palpation of the bone should start away from the painful area and move towards it slowly. In a febrile child, severe pain in a localized area of bone ("point tenderness") is indicative of possible osteomyelitis. In a non-febrile child, there is a wide differential diagnosis for point bone tenderness, including fracture, periostitis, benign or malignant neoplasia, and enthesitis.

If swelling is present, palpation may help determine the nature of the enlargement. A cystic or fluctuant quality to the swelling suggests a fluid collection that may be indicative of a joint effusion, ganglion, meniscal cyst, bursal swelling, or abscess. A doughy or rubbery consistency suggests synovial thickening, whereas, a hard, bony feel may indicate osseous overgrowth (eg, bone tumor or exostosis). (See "Overview of benign bone tumors in children and adolescents".)

Range of motion — Range of motion (ROM) is an important part of the examination of a child with joint pain; however, if there is severe pain, particularly if there is a history of trauma and/or an obvious deformity, it is prudent to splint the involved joint and proceed to obtain radiographs to rule out a fracture or dislocation. (See 'Diagnostic studies' below.)

In the absence of severe pain, deformity, and/or a history of significant trauma, joint function is assessed with the following questions in mind:

- Is the ROM limited, and if so, to what degree? Keep in mind that while most joints are limited in movement to flexion and extension, a few joints move in other planes resulting in a greater ROM. These include the hips, shoulders, spine, wrists, and ankles. Active and passive range of motion should be noted in abduction and with internal and external rotation of the hips and shoulders.

  Of note, one of the biggest mistakes that nonspecialists make when testing passive ROM is not pushing the joint to the limits of its range of motion. Frequently in arthritis and other inflammatory conditions, there may be very subtle abnormalities that are missed when this is not done. As an example, in the knee, where loss of the normal few degrees of "relaxed passive extension" may be the only indication of knee pathology, a few degrees of motion may be the sole distinguishing feature between an arthritic joint and a normal one. To demonstrate this finding, while the child lies supine and relaxed with the legs extended, the feet are gently lifted off the bed by the examiner. If there is asymmetry of the

expected 5 to 10 degrees hyperextension of the knees, pathology is generally found in the side that has "lost" relaxed passive extension.

- Is there excessive joint mobility [7]? Excessive mobility of the joint, which may be associated with joint pain, can be seen in benign hypermobility syndrome and in pathologic joint laxity syndromes such as Ehlers Danlos or Marfan's syndrome. (See "Clinical manifestations and treatment of the hypermobility syndrome" and "Genetics, clinical features, and diagnosis of Marfan syndrome and related disorders".)
- Is there pain with motion? If palpation and movement of the painful joint do not reproduce or exacerbate the pain, then referred pain should be suspected. As an example, knee pain may arise from a problem at the hip. If the hip and knee are normal on examination, consider an even more proximal site, such as the spine or retroperitoneum. For example, pyomyositis of the psoas (psoas abscess) typically presents with hip pain and flexion deformity [2].
- Is muscle strength normal? Muscle weakness, especially proximal weakness, may be an indication of myopathy, such as dermatomyositis or muscular dystrophy. The inflammatory myopathies in particular may be associated with joint symptoms as well as muscle pain and weakness.

Specific joints — There are separate topics that review the pediatric evaluation of pain and injury of specific joints.

- Neck (see "Approach to the young athlete with neck pain or injury")
- Foot and ankle (see "Evaluation of foot and ankle pain in the young athlete")
- Knee (see "Approach to the young athlete with acute knee pain or injury" and "Approach to the young athlete with chronic knee pain or injury")
- Hip (see "Overview of hip pain in childhood")

DIAGNOSTIC STUDIES — Diagnostic studies should be done judiciously and chosen on the basis of likely diagnoses [8]. In fact, most rheumatologic disorders affecting children are diagnosed based upon the history and physical examination. Diagnostic studies may help to exclude other conditions or support one's clinical impression, but rarely do they reveal a previously unsuspected diagnosis. A particular danger for the inexperienced clinician is finding and dealing with irrelevant or inconsequential "abnormalities" as a result of performing an overenthusiastic battery of investigations. The addition of selective imaging and laboratory testing to a complete and thorough history and physical examination may help to establish the cause of joint abnormalities. However, some of the most common rheumatic diseases of children, such as JIA, may have few or no associated laboratory abnormalities. If the cause remains elusive despite a comprehensive evaluation, or if a disease or disorder requiring a specialist's expertise is discovered or suspected, referral to a pediatric rheumatologist or orthopedist is often a more efficient approach than performing numerous imaging and laboratory studies.

Joint aspiration — The possibility of septic arthritis should be considered carefully in a child with an acute monoarthritis, and if there is any suspicion or uncertainty, joint aspiration and examination of the synovial fluid should be performed to either make the diagnosis or rule it out.

For most children with joint swelling and pain, however, even when only one joint is affected, joint aspiration is usually not necessary. Unlike the situation in adults, in whom other illnesses, such as gout, make arthrocentesis a more important diagnostic tool, joint aspirations rarely add useful information in children.

If joint aspiration is required, older children usually can tolerate it with the use of local anesthetic. Younger children and those requiring aspiration of a shoulder or hip may require procedural sedation or general anesthesia. Hip joint aspiration should be performed with ultrasonographic guidance by someone skilled in this procedure. (See "Joint aspiration or injection in children: Indications, technique, and complications".)

The following testing is performed routinely on synovial fluid, although Gram stain and culture are undoubtedly the most useful:

- Cell count and differential — High white cell count is indicative of an inflammatory process, such as JIA or septic arthritis
- Gram stain
- Glucose
- Protein

- Microbiology (aerobic and anaerobic bacterial cultures)

Examination of the joint fluid for crystals is rarely informative in children. Gouty arthritis is very rare before puberty, even in children with Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency) [9].

Imaging — A plain radiograph of the affected joint should be performed to rule out fractures, periostitis, avascular necrosis, bone tumors, and bone dysplasias. Simultaneous imaging of the contralateral joint allows for comparison of growth and development; unilateral acceleration may be a sign of chronic inflammation.

In patients with hip involvement, ultrasonography is particularly useful in detecting joint effusion.

Computerized axial tomography (CT) scans and magnetic resonance imaging (MRI) scans are generally reserved for evaluating noninflammatory conditions and should be discussed with the appropriate radiologist prior to ordering the study. MRI may be useful in differentiating infectious arthritis from recent-onset JIA [10].

Technetium bone scans can be helpful in differentiating septic arthritis from osteomyelitis when the clinical examination does not separate the two [11]. It is also used for detecting unsuspected skeletal trauma and tumors, such as osteoid osteoma. Perhaps the most common use of these scans is attempting to localize symptoms in a non-acute situation when the source or location of the patient's pain remains unclear after the clinical examination. In fact, imaging is seldom as useful as the examination of an experienced practitioner, since bone scans primarily detect abnormal tracer uptake by osteoblasts, a type of cell not affected by potential causes of joint symptoms. (See "Overview of benign bone tumors in children and adolescents" and "Diagnostic imaging of joint pain", section on 'Bone scan'.)

Laboratory testing — The following laboratory tests should be considered in any child with acute or chronic joint pain without an immediately obvious cause:

- Complete blood count and differential to detect abnormalities of blood cell lines that may be associated with SLE, systemic JIA, bacterial and viral infections, and leukemia [12].
- Acute-phase reactants (erythrocyte sedimentation rate or C reactive protein). When elevated, these tests are nonspecific markers of inflammation. However, many children with inflammatory diseases, such as JIA, may have normal acute phase reactants values.
- Serum chemistries, especially liver and kidney function tests. (Abnormal values may be indicative of a possible systemic disorder, such as SLE or vasculitis).
- Serum lactate dehydrogenase (LDH) (elevated levels may be indicative of the presence of malignant neoplasm [12,13]) and creatine kinase (elevated levels may be indicative of myositis).
- Urinalysis to detect urinary abnormalities that may be associated with some rheumatologic disorders such as SLE and Henoch-Schönlein purpura.

Further evaluation is dependent upon whether the joint symptoms are acute or chronic.

Acute joint pain — Acute joint pain, either as a solitary manifestation or when accompanied by systemic symptoms, may be directly or indirectly related to an infectious process; therefore, the following tests may be helpful:

- Cultures of the throat, blood, joint fluid, stool, and/or urine
- Serologic testing for Lyme disease for children who live in or have visited an endemic area, since one of the most common late or chronic manifestations of Lyme disease is an acute pauciarthritis
- Antistreptolysin-O (ASO) titer or similar studies looking for evidence of a recent streptococcal infection

Chronic joint pain — Chronic joint pain is unlikely to be related to an infectious process, the primary exceptions being the arthritis of Lyme disease or tuberculosis.

The following tests should be considered in children with chronic as opposed to acute symptoms [14,15]:

- Quantitative immunoglobulins to detect immune deficiencies

- Serologic testing for Lyme disease
- Antinuclear antibody (ANA)
- Rheumatoid factor (RF)
- HLA-B27 (presence is associated with juvenile ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease, and reactive arthritis)

However, many of these tests, especially ANA and RF, are generally not useful because they have a high false positive rate [16] and are often negative in children with rheumatologic disorders, such as JIA. It is important to avoid the pitfall of eliminating rheumatologic conditions as a possible diagnosis based upon negative results of these tests, when the majority of children with JIA will have normal and/or negative ANA and/or RF [17].

SUMMARY

- The differential diagnosis for joint pain and swelling is broad, ranging from benign to serious conditions, some of which can have devastating consequences (table 1).
- A complete history may differentiate between benign and pathologic conditions, especially those that require immediate medical attention, and helps direct the physical examination and work-up.
- The important elements of the history include characterization of the pain and/or swelling (ie, site, severity, frequency and duration of symptoms, and the number of joints involved) (table 2), presence of other joint findings (instability, warmth and redness) and precipitating factors (antecedent infection or trauma, and level of activity), review of other associated non-musculoskeletal symptoms (eg, fever and rash) (table 3), and the presence of other medical conditions associated with arthritis. (See 'History' above.)
- Abnormalities detected by the physical examination may be important clues to the diagnosis and help differentiate severe conditions requiring urgent medical intervention from more benign disorders. A thorough physical examination includes general inspection including measurement of growth parameters and vital signs, screening of the entire musculoskeletal system (figure 1) as well as a focused examination of the affected joint(s) (table 4), and evaluation of motor strength to detect any neuromuscular conditions that may be accompanied by joint symptoms. (See 'Physical examination' above.)
- Selective imaging and laboratory testing are directed by the history and physical examination. (See 'Diagnostic studies' above.)
- If the cause of joint pain or swelling remains elusive despite a comprehensive evaluation, or if a disease or disorder requiring a specialist's expertise is discovered or suspected, referral to a pediatric rheumatologist or orthopedist may be necessary.

Varicella-zoster infection in the newborn

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INTRODUCTION — Varicella-zoster virus (VZV) is the virus responsible for varicella (chickenpox) and herpes zoster ("shingles"). VZV is a member of the herpesvirus family, along with herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus (HHV) -6, -7, and -8.

Varicella usually is a mild, self-limited illness in healthy children. Rarely, varicella affects the pregnant or postpartum woman, causing problems for the fetus or newborn. Nosocomial acquisition of VZV also can occur in newborns. (See "Clinical features of varicella-zoster virus infection: Chickenpox" and "Varicella-zoster virus infection in pregnancy".)

CONGENITAL VARICELLA SYNDROME — Most cases of congenital varicella syndrome occur in infants whose mothers were infected between 8 and 20 weeks gestation. However, the overall risk of infection is quite small compared to numerous other viruses acquired during pregnancy. The risk appears to be approximately 2 percent if the infection occurs before 20 weeks and less than 1 percent if it occurs before 13 weeks [1,2]. Intrauterine growth restriction commonly occurs. (See "Varicella-zoster virus infection in pregnancy".)

Characteristic findings of affected infants include some or all of the following in order of the frequency of occurrence [3]:

- Cicatricial skin lesions, which may be depressed and pigmented in a dermatomal distribution.
- Ocular defects, such as cataracts, chorioretinitis, Horner syndrome, microophthalmos, and nystagmus. (See "Cataract in children".)
- Limb abnormalities, which often include hypoplasia of bone and muscle.
- Central nervous system abnormalities, such as cortical atrophy, seizures, and intellectual disability (mental retardation).

NEONATAL VARICELLA — Neonatal varicella is a serious illness associated with a mortality rate up to 25 percent. Newborns born to mothers who are exposed to VZV or have clinical disease manifestations within two weeks of delivery are at the greatest risk for infection. Nosocomial acquisition of VZV also can occur.

The risk of infection and the case fatality rate are significantly increased when symptoms of maternal infection occur less than five days prior to delivery [4]. This interval allows insufficient time for the development of maternal IgG and passive transfer of antibody protection to the fetus. Postnatally acquired varicella that occurs between 10 and 28 days after birth usually is mild [5]. However, because of their relative immunologic immaturity, newborns are at greater risk for acquiring severe disease than are older infants or children [6].

Premature infants are at increased risk for nosocomial acquisition of VZV compared to infants born at term because active transfer of maternal IgG antibodies occurs primarily during the third trimester of pregnancy [7]. Postnatal age also is a risk factor because antibody levels decline with age [8,9]. In one report of VZV exposure in a Neonatal Intensive Care Unit (NICU), seronegativity occurred frequently in infants older than two months of age [8].

Clinical features — The clinical picture of neonatal varicella is variable, ranging from a mild illness resembling chickenpox in older children to a disseminated infection similar to manifestations seen in immunocompromised hosts. Fever may develop within the first days after birth, followed by a vesicular eruption. In mild cases, the lesions heal within 7 to 10 days. However, disseminated disease may ensue, with varicella pneumonia, hepatitis, and meningoencephalitis being the most common visceral manifestations. Reports of neonatal herpes zoster in babies born to mothers with varicella during pregnancy are rare [10,11]. Administration of varicella-zoster

immune globulin (ie, VariZIG) within one day of age to infants born to women with active varicella infection at delivery may ameliorate neonatal disease.

DIAGNOSIS — The diagnosis of varicella usually is made clinically based upon the characteristic appearance of skin lesions. VZV may be cultured from vesicular fluid, but the virus takes several weeks to grow, unlike HSV, which can be recovered in 48 to 72 hours. Other rapid diagnostic studies include direct fluorescent antigen (DFA) and polymerase chain reaction (PCR). PCR is a highly sensitive and specific test that detects VZV from either vesicular swabs or scrappings, scabs from crusted lesions, tissue from biopsy samples, and cerebral spinal fluid [12].

Serologic tests may help to document acute infection in confusing cases or indicate immunity. IgM antibody may be detected as soon as three days after VZV symptoms appear, and IgG may be detected as early as seven days after varicella symptoms appear. Other diagnostic tests include fluorescent anti-membrane antibody (FAMA), latex agglutination (LA), enzyme-linked immunosorbent assay (ELISA), and complement-enhanced neutralization, are available. All of these tests are more sensitive than is the older complement fixation (CF) assay. Although PCR is the most sensitive, LA and DFA provide the most rapid results. Prenatal diagnosis of fetal varicella infection is possible. (See "Varicella-zoster virus infection in pregnancy".)

MANAGEMENT OF EXPOSURE — Management of newborns who are exposed to VZV by maternal infection or contact with affected individuals includes isolation and postexposure prophylaxis. The specific intervention depends upon the timing of exposure, the mother's serologic status, and gestational age. Varicella vaccination, which is used for prevention in older children and adults, has not been tested for this purpose in newborns. (See "Prevention and control of varicella in hospitals".)

Postexposure prophylaxis

Varicella-zoster immune globulin — Varicella-zoster immune globulin (VZIG) was discontinued in the United States in 2005 and has been replaced by VariZIG.

VariZIG — VariZIG is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies [13]. (See "Post-exposure prophylaxis against varicella-zoster virus infection", section on 'VariZIG'.)

Postexposure prophylaxis has been shown to either prevent varicella in exposed neonates, ameliorate the course, or delay the disease in patients in whom the infection was not fully prevented [14].

The Advisory Committee on Immunization Practices (ACIP) recommends administration of VariZIG to newborns who have had a significant exposure to VZV that are the same circumstances used in the past for VZIG [12,13]:

- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (five days before or two days after).
- Premature infants born at >28 weeks of gestation who are exposed during the neonatal period and whose mothers do not have signs of immunity.
- Premature infants born at <28 weeks of gestation or who weigh <1000 grams at birth and were exposed during the neonatal period, regardless of maternal history of varicella or vaccination.

VariZIG should be administered within 96 hours because its efficacy after this time interval is not known [13]. The recommended dose is 125 units (1 vial) intramuscularly. VariZIG is lyophilized and must be reconstituted for intramuscular administration.

In the United States, VariZIG is available under an Investigational New Drug Application Expanded Access protocol and may be obtained by contacting the distributor of this product, FFF Enterprises, at 800-843-7477 and faxing a completed release form. The release form can be accessed from the manufacturer's website: (http://www.fffenterprises.com/Products/VariZIGINDProtocolPre.aspx, last accessed October 29, 2009) [13].

If VariZIG cannot be administered within 96 hours of exposure, then intravenous immunoglobulin (IVIG) should be considered. If IVIG is unavailable, some experts would recommend prophylaxis with acyclovir [12]. (See "Post-exposure prophylaxis against varicella-zoster virus infection", section on 'Passive immunization'.)

Isolation — Isolation for the mother and infant depends upon whether there is active disease or the timing of exposure.

- Active disease — A mother with active VZV lesions must be isolated. The infant is isolated from the mother until she is not infectious. If the onset of maternal disease occurred within 5 days before or 2 days after delivery, the infant should be treated with VariZIG.

Any infant who develops varicella in the nursery or NICU is also isolated.

- Active disease 21 days before delivery — A mother who has active varicella within 21 days of delivery that resolves before hospitalization does not need to be isolated. However, the newborn should stay in the mother's room and be isolated from other infants. The infant should have passively acquired maternal antibody and therefore does not need to receive varicella-zoster immune globulin.
- Maternal exposure 6 to 21 days before hospitalization — A seronegative mother exposed to VZV 6 to 21 days before hospital admission should be isolated from other patients and the nursery because she may develop varicella while hospitalized. This calculation takes into account the incubation period of varicella, which is 8 to 21 days plus a possible period of infectivity three days before lesions appear. Her infant, if born at term, should be isolated with the mother. The mother and infant should be cared for only by staff with immunity to VZV. Both should be discharged as soon as possible.
- Maternal exposure within 6 days of hospitalization — If a seronegative mother was exposed within 6 days of admission and discharged before 48 hours, isolation is not needed because varicella would not be expected to develop during the hospital stay.

Nursery exposure — An infant who develops varicella in the nursery or NICU should be isolated. The more common situation is nursery exposure by a visitor or hospital worker who is infectious. In the newborn nursery, exposed infants typically are discharged before they would be infectious.

Postnatally acquired varicella in infants older than 10 days of age usually is mild. Thus, some clinicians favor providing routine newborn care without administration of VariZIG or determination of maternal immune status. However, administration of VariZIG may be considered for an infant exposed during the first month after birth [6]. In this case, one approach is to give VariZIG only if maternal serology is negative.

Isolation may be required for the rare infant who remains hospitalized longer than eight days and whose mother is seronegative. (See "Prevention and control of varicella in hospitals".)

NICU exposure — Exposed infants in the NICU usually are cohorted. They are isolated from new patients admitted between 8 and 21 days after exposure. VariZIG should be given to all NICU patients with seronegative mothers and to all preterm infants <28 weeks gestation or ≤1000g birth weight regardless of maternal immune status [12,15]. Infants who received VariZIG should be isolated from new patients for 28 days [10].

TREATMENT

Acyclovir — Acyclovir reduces the risk of mortality in severe varicella. Newborns with severe infection should be treated with acyclovir (30 mg/kg per day in 3 divided doses IV) for 10 days [16,17]. To be effective, antiviral treatment must be started as soon as possible after the onset of symptoms because most viral replication has stopped by 72 hours after appearance of the rash.

Fever control — Fever control rarely is needed in varicella because temperature elevations usually are mild. The use of aspirin should be avoided because of the increased risk of developing Reye syndrome [18]. Use of acetaminophen may prolong the illness [19]. Nonsteroidal antiinflammatory agents have not been recommended in this condition because of a proposed association with necrotizing group A streptococcal infections, although this association was not supported by a case-control study [20]. If temperature elevation persists, the patient should be evaluated for secondary complications.

Breastfeeding — Whether VZV is secreted in human milk is uncertain, although VZV DNA has been detected [21]. Breastfeeding is encouraged in newborns exposed to or infected with varicella because antibody in breast milk may be protective [22].

SUMMARY AND RECOMMENDATIONS — Varicella-zoster viral (VZV) infection in the newborn is due to either vertical transmission from the mother during pregnancy or delivery, or acquired after birth from the environment or infected care providers.

- Congenital varicella syndrome occurs in infants whose mothers are infected between 8 and 20 weeks gestation. Clinical manifestations vary and include Cicatricial skin lesions, ocular defects (eg, cataracts, chorioretinitis, Horner syndrome, microophthalmos, and nystagmus), and abnormalities of the limb (eg, hypoplasia of bone and muscle) and central nervous system (eg, cortical atrophy, seizures, and cognitive impairment). (See 'Congenital varicella syndrome' above and "Varicella-zoster virus infection in pregnancy", section on 'Congenital varicella syndrome'.)
- Neonatal varicella is a serious illness with a 25 percent mortality rate.
- Neonates born to mothers with VZV infection, or who were exposed within two weeks of delivery are at high risk for neonatal varicella. The risk and severity of illness increases when maternal infection occurs less than five days prior to delivery because there is insufficient time for the development and transfer of maternal antibody. (See 'Neonatal varicella' above.)
- The clinical manifestations of neonatal varicella vary from a mild illness similar to chickenpox in older children to a disseminated disease involving the liver, lung, and central nervous system. (See 'Clinical features' above.)
- The diagnosis of varicella usually is made clinically based upon the characteristic appearance of skin lesions. VZV infection is confirmed by detection of the virus in vesicular fluid culture, or by direct fluorescent antigen and polymerase chain reaction (PCR) in vesicular scrappings, swabs, and, for PCR, cerebral spinal fluid. (See 'Diagnosis' above.)
- Postexposure prophylaxis with VariZIG is recommended for infants born to symptomatic mothers around the time of delivery, preterm infants with gestational age (GA) >28 weeks born to mothers without immunity and preterm infants <28 weeks. (See 'VariZIG' above.)
- Mothers with active disease or a history of exposure 6 to 21 days must be isolated from other patients including her infant. The newborn is isolated from the mother until she is no longer infectious. Any infant who develops varicella is isolated. (See 'Isolation' above.)
- We recommend a 10-day course of acyclovir (30 mg/kg per day in 3 divided doses IV) to treat neonatal varicella. (See 'Acyclovir' above.)
- Breastfeeding is encouraged in infants exposed to or infected with varicella. (See 'Breastfeeding' above.)