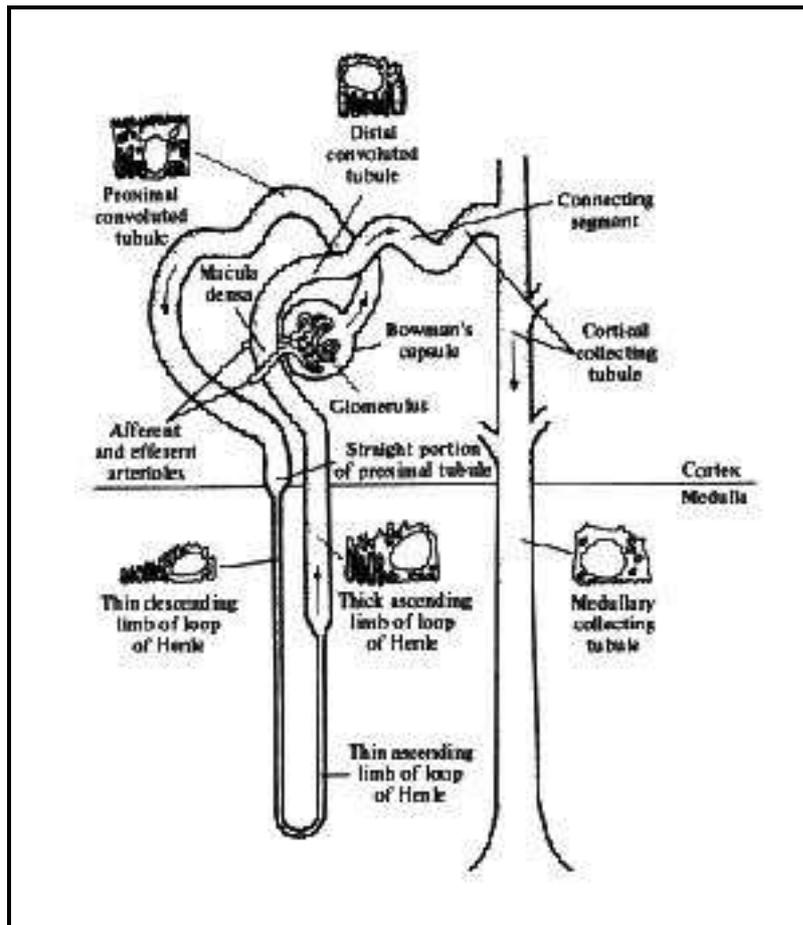


# Néphrologie pédiatrique à l'usage du 3<sup>o</sup> cycle ou des masters complémentaires

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## Table du contenu

- évaluation de la fonction rénale
- whats'new in pediatric nephrology and hypertension?
- Le bilan renal et les valeurs normales
- Introduction to renal function
- glomerular anatomy and function
- Water balance and regulation of plasma osmolality
- Maintenance fluid therapy in children, in newborns and clinical assessment of hypovolemia
- Les néphropathies héréditaires
- Evaluation de l'hématurie
- Nephrolithiase
- Diagnostic des malformations et des obstructions des voies urinaires
- L'insuffisance rénale aiguë
- Acute renal failure in the newborn
- Clinical presentation, evaluation and diagnosis of acute renal failure in children
- dialyse péritonéale
- Clinical manifestations and diagnosis of Henoch-Schönlein purpura
- Syndrome néphritique aigu
- Syndromes néphrotiques de l'enfant
- La biopsie rénale
- L'obstruction des voies urinaires
- L'infection urinaire
- Préhypertension et hypertension artérielle ; la décompensation cardiaque
- Vitamine et ostéodystrophie
- Reins polykystiques
- Remplacement rénal

## Evaluation de « la fonction rénale »

### **Introduction**

Le rein possède plusieurs fonctions :

- Co-gestion de l'équilibre hydro-électrolytique ;pour cette raison, certains aspects de la gestion des fluides et électrolytes seront traités ici.
- Co-gestion de la tension artérielle ; pour cette raison, l'abord de l'hypertension artérielle sera traité ici.
- Co-gestion de l'équilibre acido-basique ;
- Co-gestion de l'équilibre phospho-calcique ; pour cette raison, le métabolisme de la vitamine D sera traité ici.
- Co-gestion de l'hémopoïèse ;
- Co-gestion de la croissance.

Il est aussi la cible de malformations ou d'autres états malades.

Il intervient aussi dans la gestion et l'excrétion de médicaments.

## **What's new in nephrology and hypertension**

### **GLOMERULAR DISEASE AND VASCULITIS**

In the largest series of patients with idiopathic membranous nephropathy treated with rituximab, 10 of 50 consecutive patients achieved remission of proteinuria to less than 500 mg/day at one year [1].

Among patients with IgA nephropathy and baseline proteinuria greater than 1 g/day, a prospective controlled study showed that tonsillectomy plus steroid therapy increased the rate of remission of proteinuria and hematuria compared to steroid therapy alone [2].

Forty patients with lupus nephritis with concurrent diffuse proliferative and membranous lesions were randomly assigned to induction therapy with either intravenous cyclophosphamide or mycophenolate, tacrolimus and corticosteroids [3]. At six and nine months, there was a higher rate of complete remission (defined as proteinuria <0.4 g/day, normal urinary sediment and normal creatinine) in patients treated with combination therapy (50 and 65 percent) compared to those who received cyclophosphamide (5 and 15 percent).

### **HYPERTENSION**

A secondary analysis of the ONTARGET trial in patients with known atherosclerotic vascular disease or with diabetes and end organ damage revealed that, compared to ramipril alone, combined therapy with ramipril and telmisartan was associated with a significantly higher rate of a composite outcome of dialysis, doubling of the serum creatinine, and death at 4.5 years [4].

### **ACUTE AND CHRONIC KIDNEY DISEASE**

Among predialysis patients with chronic kidney disease, a retrospective study found that the use of oral calcitriol may be associated with improved survival [5].

A study of over 1700 patients found that even moderate chronic kidney disease (estimated GFR between 30 and 59 mL/min per 1.73 m<sup>2</sup>) is a major risk factor for the development of acute kidney injury during hospitalization [6].

Secondary analysis of the CHOIR trial has found that high doses of erythropoietin, rather than a higher target hemoglobin level, is associated with an increased risk of adverse events [7]. To achieve target hemoglobin levels, we suggest that the dose of epoetin-alpha NOT exceed 20,000 units per week in predialysis patients with chronic kidney disease.

Among 212 outpatients with estimated glomerular filtration rate between 45 and 60 mL/min per 1.73 m<sup>2</sup>, fewer than one percent had an increase in serum creatinine greater than 0.5 mg/dL within 48 to 96 hours following intravenous contrast administration for a nonemergent CT scan [8].

## **DIALYSIS**

Fibroblast growth factor 23 (FGF-23), an osteoblastic hormone involved in the regulation of phosphate and vitamin D, stimulates the renal excretion of phosphate and inhibits the synthesis of 1,25-dihydroxyvitamin D. Among patients initiating hemodialysis, a nested case control study found that increased FGF-23 levels are significantly associated with increased mortality [9]. Further study is required to better characterize the role of FGF-23 as a marker of increased mortality in this setting.

In a small randomized study of patients with end-stage renal disease, survival was found to be superior with hemofiltration compared with hemodialysis [10]. However, given the small number of patients in this trial, any possible survival benefit with hemofiltration must be confirmed in larger studies.

## **TRANSPLANTATION**

The addition of rituximab to a high dose intravenous immune globulin (IVIG) regimen was safe and effective in lowering panel reactive antibody levels and increasing kidney transplantation rates among highly sensitized patients [11].

An observational study found that sirolimus is associated with impaired spermatogenesis, resulting in a decreased fathered pregnancy rate [12]. Men who desire to father children should be informed of the risks and benefits associated with exposure to sirolimus.

## **GENETIC DISEASES**

Gene polymorphisms that involve the MYH9 gene, which encodes the podocyte protein, nonmyosin heavy chain IIA, are highly associated with nondiabetic end-stage renal disease and both HIV- and non-HIV-related focal and segmental glomerulosclerosis (FGS) [13,14]. The MYH9 alleles that confer risk are more commonly present in African Americans (60 percent of alleles) compared to European Americans (4 percent of alleles) and may explain both the increased risk of kidney failure and the heightened incidence of FGS among African Americans.

## **NEPHROLITHIASIS**

Some patients with idiopathic hypercalciuria have increased calcitriol levels, due possibly to a urinary phosphate leak. In some cases, the mechanism for the urinary phosphate leak may be mutations in the sodium-hydrogen exchanger regulator factor 1 (NHERF1), which interacts with both renal sodium phosphate transporters to facilitate normal phosphate regulation. This was shown in a study of 94 patients with nephrolithiasis or bone demineralization, of whom seven had mutations in NHERF1 [15]. All seven had low maximal reabsorption of phosphate, hypophosphatemia, and increased calcitriol levels. Further study is required to better clarify the increased risk of renal stone formation with abnormalities in NHERF1.

## **PEDIATRIC NEPHROLOGY**

The American Heart Association (AHA) has published a scientific statement outlining the indications for 24-hour ambulatory blood pressure monitoring (ABPM) and the necessary criteria for accurate and valid ABPM

in children and adolescents [16]. An analysis of longitudinal data from the National Childhood Blood Pressure database demonstrated 12 and 14 percent of female and male prehypertensive adolescents, respectively, became hypertensive over a two-year time period [17]. Prehypertension was defined as a systolic and/or diastolic blood pressure  $\geq$ 90th percentile but  $<$ 95th percentile for age, gender, and height, or BP exceeding 120/80 mmHg.

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## **Bilan rénal : quels sont les besoins potentiels pour le réaliser ?**

### **Analyse du Sang :**

Formule sanguine, plaquettes, fer, ferritine, réticulocytes, urée, créatinine,  $\beta_2$  microglobulines, ph, urates, calcium, phosphore, phosphatases alcalines, Mg plasmatique, Na, K, Cl, protéines sériques et électrophorèse  
fibrinogène, VS, CRP, ASL, IgA, G, M.

### **Analyse des Urines :**

réactions urinaires, sédiment urinaire, culture urinaire,  $\beta_2$  microglobulines, Ca, créatinine

### **Bilan immunologique :**

C3, C4, ( C3PA, C3C), Ci IgA, CiC, anticorps anti-membranes-glomérulaires, anticorps anti MBT  
IgA  
ANCA cyto , périnucléaire ( Wegener, P.N, GL rapidement progressive )  
C3 néphritic factor

### **Bilan en imagerie :**

Echographie, uroscan, scintigraphie anatomique et fonctionnelle.

En pratique courante trois examens ont un intérêt capital dans l'évaluation de la fonction rénale chez l'enfant :

#### **→La mesure de la filtration glomérulaire**

##### **La clearance de la créatinine**

Elle est la technique la plus employée. Elle doit être interprétée en valeur corrigée (ml/mn/1,73 m<sup>2</sup>). Valeurs normales en ml/mn/1,73 m<sup>2</sup> en fonction de l'âge :

- nouveau-né : 40
- 12 mois : 90
- 24 mois et au delà : 120

##### **Créatinémie**

En fait le **recueil d'urine** est parfois difficile chez l'enfant et la filtration glomérulaire peut être appréciée par la seule créatinémie.

### → L'étude du pouvoir de concentration rénale

La technique la plus aisée est le test au D.D.A.V.P (MINIRIN).

Les urines sont recueillies **toutes les heures pendant 5 heures**, après administration nasale de D.D.A.V.P., leur osmolarité est mesurée.

Le pouvoir de concentration normal est de :

- 700 mosm/kg avant 3 mois,
- 1000 mosm/kg après 12 Mois.

**Indications** : la mesure du pouvoir de concentration est un élément essentiel de surveillance des uropathies et des tubulopathies, le pouvoir de concentration est perturbé bien avant l'atteinte de la filtration glomérulaire.

### → L'évaluation des fonctions tubulaires

Tant proximales que distales : difficile et d'indication plus rare (mesure du taux de réabsorption des phosphates, mesure du pouvoir d'acidification des urines ).

On peut, notamment, utiliser le concept global de la fraction excrétrice d'une substance « x » :

$FEx = \text{Clearance } x / \text{Clearance créatinine}$

$$FEx = [Ux] [Pcr] / [Px] [Ucr]$$

Où U sont les concentrations urinaires de x et de créatinine, et P les concentrations plasmatiques de x et de créatinine.

L'avantage de ce concept est qu'il permet, à partir de valeurs sanguines et de valeurs sur un spot urinaire, d'arriver à des conclusions très utiles en clinique.

La *filtration glomérulaire* est basse chez le nouveau né, et encore moindre en cas de prématurité. A la naissance, elle est de  $\pm 20 \text{ ml/min/m}^2$  73 et va rapidement doubler dans les premières semaines, suite aux modifications hémodynamiques.

### ==> Il faut adapter les dosages médicamenteux en conséquence

De même, le *pouvoir de concentration* maximale des urines ( $\pm 650 \text{ mOsm/L}$ ) est moindre que chez l'adulte, et n'atteint sa maturité que vers l'âge de un an. Pour rappel, la pression osmotique du milieu intérieur est de  $\pm 293 \text{ mOsm/L}$

### ==> Le nourrisson est sensible à une charge osmotique trop grande → risque en cas de déshydratation ou d'un régime trop riche en protéines.

La *fraction excrétée du sodium* atteint rapidement la valeur normale de l'adulte. Chez le nourrisson, surtout prématuré, cette fonction immature peut nécessiter un apport sodé plus important. La maintenance de sodium chez un nouveau né est de l'ordre de  $3 \text{ meq/kg/jour}$ .

La fonction rénale atteint sa maturité "adulte" vers 2 ans.

La clearance des xénobiotiques, et donc de nombreux médicaments est différente chez l'enfant. Lorsqu'il s'agit d'une élimination rénale, la clearance de type adulte est atteinte avec la maturation rénale vers l'âge de 2 ans. La clearance peut toutefois aussi être liée au métabolisme hépatique (CYP) avec une clearance plus importante chez le jeune enfant. Il est donc insuffisant d'adapter la dose selon le poids, et tout médicament doit faire l'objet d'une étude pharmacocinétique pédiatrique spécifique.

### → Composition corporelle-Besoins en eau et électrolytes

Le nourrisson est constitué de 75% d'eau, et ce pourcentage diminue vers la proportion adulte (60%) vers l'âge de 1 an.

Son apport quotidien d'eau doit être de 10 à 15% (=100 à 150 cc/kg) de son poids (=100 à 150 cc/kg) , versus 2-4% chez l'adulte

Les pertes rénales sont de 50 %, le reste étant éliminé par les selles, la peau, les poumons. Les besoins augmentent donc en cas de diarrhée, T°, hyperventilation.

### Maintenance

- Maintenance calorique: 100 ml/kg/jour jusque 10 kg, ensuite 50cc/kg allant de 11 à 20 kg, puis 20 cc/kg au-delà de 20 gk ou 1500 cc/M2.
- La maintenance hydrique = maintenance calorique + 20 %.
- Maintenance Na+: 2-3 meq/kg/jour (NaCl)
- Maintenance K+: 1-2 meq/kg/jour (KCl)
- Maintenance Ca<sup>++</sup>: 50-100 mg/kg/jour (Gluconate de Ca) ;
- Maintenance en phosphore = ½ maintenance en calcium.
- Autres ions (Mg<sup>++</sup>, PO<sup>4--</sup>, oligoéléments à ajouter en cas de prolongation

**Dans une perfusion de maintenance, la concentration en K<sup>+</sup> ne pourra en aucun cas ( sauf en phase de réhydratation du diabète inaugural où il faudra parfois aller au-delà de 30 mEq/L ) dépasser 10 mEq/100 ml .**

- Pertes accrues de sodium par voie rénale : Addison, Hyperplasie congénitale des surrénales, pseudo-hypoaldostéronisme ou extra-rénales: : Sueur (mucoviscidose), brûlure cutanée, ichtyose, iléostomies, drainage d'ascite, diarrhée...
- Pertes accrues de K<sup>+</sup>: vomissements, anorexie, diurétiques, hyperaldostéronisme, syndrome de Bartter, déficience en Magnésium.
- Le calcium est présent dans les os. Il est aussi lié à l'albumine: en cas d'hypoalbuminémie, il faut se baser sur le Calcium ionisé. Hypocalcémies liées à un déficit d'absorption (déficit en vitamine D) ou des pertes accrues: hyperparathyroïdie, immobilisation, thiazides, hypercalciurie idiopathique, hypersensibilité à la vitamine D.

**Le volume circulant** est maintenu grâce à la pression osmotique, et plus particulièrement par la pression oncotique (= pression osmotique liée aux colloïdes) : Ces colloïdes, principalement l'albumine, ne passent normalement pas les membranes capillaires ni glomérulaires. La pression colloïde diminue en cas de pertes protéiques (rénale, digestive), en cas de vasoplégie dans le choc (fuite dans le milieu interstitiel) ou en cas de déficit de

synthèse (insuffisance hépatique, malnutrition). Le turnover aqueux est élevé chez le nouveau né et le nourrisson, qui sont très sensibles à la déshydratation: rapide oligoanurie, et rapide insuffisance rénale ne cas de maladie grave.

→ **Formules et mesures utiles pour évaluer la fonction rénale de l'enfant**

- GFR: filtration glomérulaire calculée: (formule de Schwartz) :  
< 2 ans:  $0.45 \times \text{Taille(cm)} / \text{créatine sanguine (mg/dl)}$  ; > 2ans:  $0.55 \times \text{Taille(cm)} / \text{créatinine sanguine (mg/dl)}$
- Clearance de la créatinine:  $(\text{Cr ur} \times \text{Volume(ml)}) / \text{Cr pl} \times 1440) \times 1,73/\text{SC}$  (! ne pas oublier l'adaptation selon Surface Corporelle)
- Surface corporelle:  $4 \times \text{poids(kg)} + 7 / \text{Poids} + 90$  ou selon abaques.
- TRP: Taux de réabsorption du phosphore:  $\text{P ur} \times \text{Cr pl} / \text{Cr ur} \times \text{P pl}$
- Aminoacidurie, glucosurie
- Calciurie de 24 heures: normalement < 4 mg/ kg
- Rapport Ca/Cr urinaire: < 0.3
- Débit urinaire normal : 1 à 2 ml/kg/heure
- Excrétion fractionnelle du Na:  $(\text{Na ur} \times \text{Cr pl} / \text{Na pl} \times \text{Cr ur}) \times 100$  : nl < 1%
- Rétention sodée: Na urinaire < 10 meq/L: hyperaldostéronisme, hypovolémie, .
- Fuite sodée urinaire > 40 meq/L

→ **Modifications du volume plasmatique, du volume extracellulaire et de l'eau totale de l'organisme chez l'enfant à différents âges**

	0 - 1 mois	1 - 12 mois	1 - 10 ans	10 - 16 ans
<u>Eau totale</u> D2O : % du PC	75	64	62	62
<u>Volume extracellulaire</u> - Thiocyanate (% du PC) - Inuline (% du PC)	39 33	33 25 - 30	30 19	29 16
<u>Volume plasmatique</u> ( ml / kg)	50	50	48	47

**Valeurs normales de la créatinine plasmatique et de la créatinurie**

Age	créatinine µmol/l	plasmatique	créatinurie µmol :kg x j
Nouveau- né	50 – 88		62 - 88
2 semaines	30 – 58		62 - 88
2 ans	20 – 35		108 - 188
8 ans	30 – 60		132 - 212
Puberté	30 – 70		177 - 265
Adulte H.	64 – 108		177 - 230
Adulte F.	47 – 88		124 - 195

**Percentile 95 pour la concentration urinaire des protéines**

Age ( années)	Protéinurie		
	µg / ml	µg / mg créatinine	mg / mmol créatinine
< 2	148	0.492	55.5
2 – 13	100	0.178	20.1
> 13	148	0.178	20.1

→ **Etude de la fonction rénale globale**

- RU, SU, CU 3X
- ADDIS
- PROTEINURIE / 24H
- CLEARANCE CREATININE / 24 H
- Na, K, Ca, P sanguins
- URINE MATIN :osmolarité  
                  densité  
                  pH  
                  Ca  
                  Creatinine

→ **CLEARANCE EAU LIBRE** = capacité rénale d'évacuer une charge d'eau

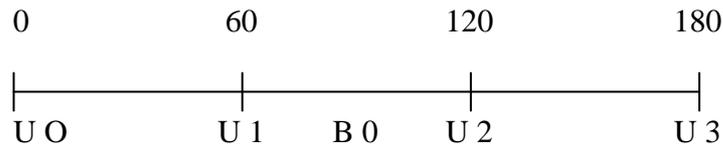
1. Poids  
   Taille  
   Sc  
   TA
2. 20cc / kg eau à boire ou IV en 30 à 45 min
3. après 30 min → B 0  
      U 0  
      puis perfusion NaCl 0,45 % ( 1000 ml / 1,73 m<sup>2</sup>:/ H ) pendant 2 heures
4. 60'            B 1  
   120'           B 2
5. Obtenir 5 échantillons urinaires pendant 2 heures : U 1 → U 5

B = Na<sup>+</sup>  
      K<sup>+</sup>  
      osmolarité  
      créatinine

U = Na  
      K  
      Cl  
      osmolarité  
      créatinine  
      volume miction

→ **CLEARANCE DE LA CREATININE ET DE L'UREE**

1. Peser et mesurer l'enfant  
Prendre la P.A.
2. Donner 10-20 cc / kg en 30', puis faire boire selon diurèse (c'est à dire boissons = diurèse )
3. Récolte pendant 3 heures



U 0 = urée  
créatinine  
calcium  
R.U.

Mesurer le volume d'urines et noter l'heure exacte de fin de test

Envoyer au labo U 1 + U 2 + U 3 pour volume + urée, créatinine, phosphates

B 0 = urée  
créatinine  
Ca  
phosphore  
Na  
K

→ **Excrétion urinaire normale de solutés**

<b>Substance</b>	<b>Excretion urinaire mg,mmol,µmol / kg x j</b>	<b>Concentration urinaire mmol / mmol créatinine</b>
Acides Aminés	1 - 5 mg	
Acidité titrable	1 - 2 mmol	
Acide urique	31 - 60 µmol	< 0,67
Ammonium	1 - 3 mmol	
Bicarbonates	0 si pH urinaire < 6,8	
Calcium	25 - 100 µmol	< 0,70
Chlore	variable selon régime	
Citrate	31 - 62 µmol	
Magnésium	< 0,18 mmol	< 1,9
Oxalate	< 6,6 µmol	< 0,085
Phosphore	50 - 65 µmol	
Potassium	variable selon régime	
Sodium	variable selon régime	
Rapport des conc. Na / K	souvent voisin de 2	

**→ Pouvoir de concentration des urines en fonction de l'âge**

<b>Age</b>	<b>Osmolalité mOsmol / kg H<sub>2</sub>O</b>	<b>Densité maximale</b>
Prématuré		
1 - 3 semaines	203 - 395	1004 - 1009
4 - 6 semaines	425 - 610	1010 - 1014
nné – terme		
1 - 3 semaines	350 - 430	1008 - 1010
4 - 6 semaines	480 - 630	1011 - 1015
2 mois	700 - 1200	1023 - 1040
2 ans - 12 ans	870 - 1300	1025 - 1043
Adulte	800 - 1400	1026 - 1046

→ **Diagnostic sémiologique d'une maladie rénale chez le nouveau né et le nourrisson**

- Antécédents familiaux dans les néphropathies héréditaires: syndrome néphrotique congénital, polykystose infantile....
- Antécédents obstétricaux: Oligamnios en cas de réduction du débit urinaire in utéro, hydramnios en cas de diabète insipide.. , placenta volumineux dans le syndrome néphrotique congénital, thromboses des veines rénales en cas de souffrance foetale aigüe....
- Masse unilatérale et hémi-hypertrophie dans la tumeur de Wilms
- Uropathies malformatives: examen systématique néonatal , échographies anténatales (hydronéphroses, reins uniques, petits reins....)
- Examen clinique : miction, force du jet, recherche d'un globe vésical, d'une masse rénale, oedèmes, TA
- Exagération de la perte de poids "physiologique": trouble du pouvoir de concentration ?
- T°, sepsis: infection urinaire sur uropathie malformative ?
- Cholestase: parfois liée à une infection urinaire
- Etude du débit urinaire au moindre doute . Oligurie si  $< 1\text{ml/kg/h}$  . Polyurie si  $> 4\text{ml/kg/h}$ .
- Tout enfant hospitalisé doit être pesé chaque jour, et son débit urinaire évalué.

→ **Répercussions d'une maladie rénale chronique sur la croissance**

La retard de croissance est bien entendu une caractéristique propre aux affections rénales pédiatriques. Il faut toujours tracer la courbe de croissance d'un nourrisson / enfant, tant lorsqu'il va bien qu'en cas de maladie. L'absence de données anthropométriques antérieures rend l'interprétation des points actuels difficile. Une maladie rénale chronique, surtout au stade d'insuffisance rénale (cfr chapitre insuffisance rénale chronique) ou encore en cas de tubulopathie, interfère avec la croissance. Qui plus est, une malnutrition protéino-calorique accompagne la plupart des maladies chroniques. La recherche des causes néphrologiques suivantes de retard de croissance font partie du bilan d'un retard de croissance chez l'enfant.

- L'acidose tubulaire distale
- Le rachitisme hypophosphorémique vitaminorésistant
- Le syndrome de Bartter
- Le syndrome de Toni Debré Fanconi: tubulopathie complexe: Phosphore, K<sup>+</sup>, acides aminés, Bicarbonate...,
- Cystinose
- Syndrome néphrotique
- Toute néphropathie au stade d'insuffisance rénale

## **The renal functions**

The kidney normally performs a number of essential functions:

- It participates in the maintenance of the constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of some of the waste products of metabolism (such as urea, creatinine, and uric acid) and by specifically adjusting the urinary excretion of water and electrolytes to match net intake and endogenous production. As will be seen, the kidney is able to regulate individually the excretion of water and solutes such as sodium, potassium, and hydrogen, largely by changes in tubular reabsorption or secretion.
- It secretes hormones that participate in the regulation of systemic and renal hemodynamics (renin, angiotensin II, prostaglandins, nitric oxide, endothelin, and bradykinin), red blood cell production (erythropoietin), and calcium, phosphorus, and bone metabolism (1,25-dihydroxyvitamin D3 or calcitriol).
- It performs such miscellaneous functions as catabolism of peptide hormones [1,2] and synthesis of glucose (gluconeogenesis) in fasting condition [3,4] .

This chapter will review briefly the morphology of the kidney and the basic processes of reabsorption and secretion. The regulation of renal hemodynamics, the specific functions of the different nephron segments, and the relationships between hormones and the kidney will then be discussed in the ensuing chapters.

**RENAL MORPHOLOGY** — The basic unit of the kidney is the nephron, with each kidney in humans containing approximately 1.0 to 1.3 million nephrons. Each nephron consists of a glomerulus, which is a tuft of capillaries interposed between two arterioles (the afferent and efferent arterioles), and a series of tubules lined by a continuous layer of epithelial cells (show figure 1). The glomeruli are located in the outer part of the kidney, called the cortex, whereas the tubules are present in both the cortex and the inner part of the kidney, the medulla (show figure 1 and show figure 2).

The initial step in the excretory function of the nephron is the formation of an ultrafiltrate of plasma across the glomerulus. This fluid then passes through the tubules and is modified in two ways: by reabsorption and by secretion. Reabsorption refers to the removal of a substance from the filtrate, whereas secretion refers to the addition of a substance to the filtrate. As will be seen, the different tubular segments make varying contributions to these processes.

Fluid filtered across the glomerulus enters Bowman's space and then the proximal tubule (show figure 1). The proximal tubule is composed anatomically of an initial convoluted segment and a later straight segment, the pars recta, which enters the outer medulla. The loop of Henle begins abruptly at the end of the pars recta. It generally includes a thin descending limb and thin and thick segments of the ascending limb. The hairpin configuration of the loop of Henle plays a major role in the excretion of a hyperosmotic urine.

It is important to note that the length of the loops of Henle is not uniform (show figure 3). Approximately 40 percent of nephrons have short loops which penetrate only the outer medulla or may even turn around in the cortex; these short loops lack a thin ascending limb [5] . The remaining 60 percent have long loops that course through the medulla and may extend down to the papilla (the innermost portion of the medulla). The length of the loops is largely determined by the cortical location of the glomerulus: glomeruli in the outer cortex (about 30 percent) have only short loops; those in the juxtamedullary region (about 10 percent) have only long loops; and those in the midcortex may have either short or long loops (show figure 3).

The thick ascending limb also has a cortical segment which returns to the region of the parent glomerulus. It is in this area, where the tubule approaches the afferent glomerular arteriole, that the specialized tubular cells of the macula densa are located (show figure 4). The juxtaglomerular cells of the afferent arteriole and the macula densa compose the juxtaglomerular apparatus, which plays a central role in renin secretion.

After the macula densa, there are three cortical segments (show figure 3): the distal convoluted tubule, the connecting segment (previously considered part of the late distal tubule), and the cortical collecting tubule [6,7] . The connecting segments of many nephrons drain into a single collecting tubule. Fluid leaving the cortical collecting tubule flows into the medullary collecting tubule and then drains sequentially into the calyces, the renal pelvis, the ureters, and the bladder (show figure 2).

The segmental subdivision of the nephron is based upon different permeability and transport characteristics that translate into important differences in function [5] . In general, the proximal tubule and loop of Henle reabsorb the bulk of the filtered solutes and water, while the collecting tubules make the final small changes in urinary composition that permit solute and water excretion to vary appropriately with alterations in dietary intake.

There may also be significant heterogeneity within a given tubular segment, particularly in the proximal tubule and cortical collecting tubule. In the latter segment, for example, there are two cell types with very different functions: the principal cells reabsorb sodium and chloride and secrete potassium, in part under the influence of aldosterone; and the intercalated cells secrete hydrogen or bicarbonate and reabsorb potassium, but play no role in sodium balance [6]. (See "Chapter 5B: Collecting tubules").

**REABSORPTION AND SECRETION** — The rate of glomerular filtration averages 135 to 180 L/day in a normal adult. Since this represents a volume that is more than 10 times that of the extracellular fluid and approximately 60 times that of the plasma, it is evident that almost all of this fluid must be returned to the systemic circulation. This process is called tubular reabsorption and can occur either across the cell or via the paracellular route between the cells. With transcellular reabsorption, the substance to be reabsorbed is first transported from the tubular lumen into the cell, usually across the luminal aspect of the cell membrane; it then moves across the basolateral (or peritubular) aspect of the cell membrane into the interstitium and then the capillaries that surround the tubules (show figure 5). With paracellular reabsorption, the substance to be reabsorbed moves from the tubular lumen across the tight junction at the luminal surface of adjacent cells (see below) into the interstitium and then into the peritubular capillaries (show figure 5).

Most reabsorbed solutes are returned to the systemic circulation intact. However, some are metabolized within the cell, particularly low-molecular-weight proteins in the proximal tubule.

Solutes can also move in the opposite direction, from the peritubular capillary through the cell and into the urine. This process is called tubular secretion (Fig. 1-5).

Filtered solutes and water may be transported by one or both of these mechanisms. For example, Na<sup>+</sup>, Cl<sup>-</sup>, and H<sub>2</sub>O are reabsorbed; hydrogen ions are secreted; K<sup>+</sup> and uric acid are both reabsorbed and secreted; and filtered creatinine is excreted virtually unchanged, since it is not reabsorbed and only a small amount is normally added to the urine by secretion.

The transcellular reabsorption or secretion of almost all solutes is facilitated by protein carriers or ion-specific channels; these transport processes are essential since free diffusion of ions is limited by the lipid bilayer of the cell membrane. The spatial orientation of the

cells is also important because the luminal and basolateral aspects of the cell membrane, which are separated by the tight junction, have different functional characteristics.

As an example, filtered sodium enters the cell passively down a favorable electrochemical gradient, since the active Na<sup>+</sup>-K<sup>+</sup>-ATPase pump in the basolateral membrane maintains the cell Na<sup>+</sup> concentration at a low level and makes the cell interior electronegative. Sodium entry occurs by a variety of mechanisms at different nephron sites, such as Na<sup>+</sup>-H<sup>+</sup> exchange and Na<sup>+</sup>-glucose cotransport in the proximal tubule, a Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> carrier protein in the thick ascending limb of the loop of Henle, and through a Na<sup>+</sup> channel in the cortical collecting tubule and papillary collecting duct (show figure 6). The sodium that enters the cells is then returned to the systemic circulation by the Na<sup>+</sup>-K<sup>+</sup>-ATPase pump in the basolateral membrane [8] . Removal of this Na<sup>+</sup> from the cell maintains the cell Na<sup>+</sup> concentration at a low level, thereby promoting further diffusion of luminal Na<sup>+</sup> into the cell and continued Na<sup>+</sup> reabsorption.

This simple summary of the mechanism of Na<sup>+</sup> transport illustrates that reabsorption can involve both active and passive mechanisms. This is also true for tubular secretion. Potassium, for example, is secreted from the cortical collecting tubule cell into the lumen. The Na<sup>+</sup>-K<sup>+</sup>-ATPase pump in the basolateral membrane actively transports K<sup>+</sup> from the peritubular capillary into the cell; the ensuing rise in the cell K<sup>+</sup> concentration then promotes secretion into the lumen via K<sup>+</sup> channels in the luminal membrane.

The tubular cells perform these functions in an extremely efficient manner, reabsorbing almost all the filtrate to maintain the balance between intake and excretion. In an individual on a normal diet, more than 98 to 99 percent of the filtered H<sub>2</sub>O, Na<sup>+</sup>, Cl<sup>-</sup>, and HCO<sub>3</sub><sup>-</sup> is reabsorbed (show table 1). Although this process of filtration and almost complete reabsorption may seem inefficient, a high rate of filtration is required for the excretion of those waste products of metabolism (such as urea and creatinine) that enter the urine primarily by glomerular filtration.

**Role of the tight junction** — The tight junction is composed primarily of the zona occludens, which is a strand-like structure on the luminal membrane that brings adjacent cells into apposition at their luminal surface [9,10] . Within the kidney, the tight junction has two important effects on segmental function [9,11,12] .

- It serves as a relative barrier or gate to the passive diffusion of solutes and water between the cells.

- It serves as a boundary or fence between the luminal (or apical) and basolateral membranes.

It has been proposed that these two functions — paracellular gate and fence for polarity — are mediated by different kinds of molecular contacts between the tight junction strands: the gate function may be due to contact between strands on apposing cells, while the fence function may be due to contact between the particles forming the strands within a single cell [12].

The "leakiness" of the tight junction barrier to passive diffusion varies with the nephron segment. The barrier is relatively leaky in the proximal tubule, with as much as one-third of proximal Na<sup>+</sup> reabsorption occurring via this paracellular route. (See "Chapter 3A: Cell model for proximal transport"). This leakiness is important, because it allows the proximal tubule to efficiently reabsorb 55 to 60 percent of the filtrate (or over 90 L/day).

In comparison, the collecting tubule is a relatively "tight" epithelium with a thicker tight junction than the proximal tubule [9]. As a result, diffusion across the tight junction is limited. This relative impermeability to passive paracellular transport allows this segment to create and sustain very large transepithelial concentration gradients. As an example, the medullary collecting tubule is able to lower the urine pH to 4.5, which represents a H<sup>+</sup> concentration that is almost 1000 times greater than that in the plasma (where the pH is about 7.40). The proximal tubule, on the other hand, can only reduce the tubular fluid pH to about 6.8, which represents a H<sup>+</sup> concentration only four times higher than the plasma. (See "Chapter 11A: Renal hydrogen excretion").

The boundary function of the tight junction is thought to play an important role in the maintenance of the polarity of the two membranes preventing lateral movement of transporters or channels from one membrane to the other [9,11,12]. Membrane polarity is an essential component of reabsorption or secretion in the renal tubular cells, as each component of the cell membrane plays an important role [13]:

- Luminal membrane — The luminal (or apical) membrane contains the channels or carriers that allows filtered solutes to enter the cells or some cellular solutes to be secreted into the lumen (show figure 6).
- Basolateral membrane — The basolateral membrane performs two major functions. That part of the membrane adjacent to the luminal membrane (also called the lateral membrane) contains the components of the tight junction and the

cell adhesion molecules that participate in cell-cell contact and communication. The more distal part of this membrane (also called the basolateral or basal-lateral membrane) plays an essential role in ion transport and hormone responsiveness, as it contains the Na<sup>+</sup>-K<sup>+</sup>-ATPase pumps, hormone receptors, and solute carriers and channels.

- Basal membrane — The basal membrane contains the basement membrane receptors that allow the cell to be anchored to the basement membrane.

As an example of transcellular transport, filtered Na<sup>+</sup> enters the cells across the luminal membrane via specific transporters or channels; it is then returned to the systemic circulation by the Na<sup>+</sup>-K<sup>+</sup>-ATPase pump to the basolateral membrane. Disruption of this normal polarity, as with opening of the tight junctions due to ischemia, is associated with an impairment in Na<sup>+</sup> reabsorption [11] . This may be mediated in part by the translocation of functioning Na<sup>+</sup>-K<sup>+</sup>-ATPase pumps onto the luminal membrane [14] .

The signals that govern the initial insertion of a protein into the luminal or basolateral membrane are incompletely understood. One signal appears to be the presence of cassettes of unique amino acids (located within the sequences of the proteins themselves) that relay localization information to cellular sorting machinery. One such amino acid motif, contiguous leucines located in the cytoplasmic tail, helps direct the vasopressin V2 receptor to the basolateral membrane [15] .

Another mechanism may involve the type of membrane anchor: studies in kidney cells suggest that the presence of glycosylphosphatidylinositol (GPI) at the C-terminal end of the protein leads to specific insertion on the luminal membrane, perhaps because this membrane is rich in glycosphingolipids [16,17] . On the other hand, the localization of the Na<sup>+</sup>-K<sup>+</sup>-ATPase pump to the basolateral membrane may be mediated by specific attachment to basolateral cytoskeletal proteins, such as actin microfilaments and ankyrin [11,18] . Disruption of the actin microfilaments following ischemia impairs this tethering function, allowing Na<sup>+</sup>-K<sup>+</sup>-ATPase pumps to diffuse onto the luminal membrane through the now open tight junctions, thereby impairing net Na<sup>+</sup> reabsorption [11] .

The attachment to actin and fodrin also may promote the basolateral localization of Na<sup>+</sup>-K<sup>+</sup>-ATPase pumps by preventing their endocytic removal. Pumps that do get inserted into the luminal membrane are removed at a rate 40 times faster than those inserted into the basolateral membrane [19] .

Aberrant localization of membrane proteins may contribute to the development of multiple disorders, such as autosomal dominant polycystic kidney disease (ADPKD). ADPKD is in most cases caused by mutations in a membrane protein termed polycystin [20], which appears to be involved in cell adhesion [21]. Abnormal apical polarity of the Na<sup>+</sup>-K<sup>+</sup>-ATPase pumps in these patients may cause sodium secretion into and fluid accumulation in epithelial cysts [22]. In addition, abnormal epithelial proliferation within the cysts may be due to apical mislocation of epidermal growth factor receptors. The correlation between polycystin mutations and abnormal polarity is unclear, but may result from the dampened expression of fetal genes.

**Membrane recycling** — In addition to proper polarity, normal functioning of transporting epithelia requires the delivery of newly synthesized and recycled membrane components to precise locations in the cell membrane [23]. As an example, antidiuretic hormone combines with its receptor on the basolateral membrane of collecting tubular cells. This initiates a sequence of events in which preformed water channels (called aquaporin-2) in cytoplasmic vesicles are specifically inserted into the luminal membrane, thereby allowing the reabsorption of luminal water. (See "Chapter 6B: Antidiuretic hormone and water balance"). The hormone-receptor complex is internalized by endocytosis in clathrin-coated pits and then enters acidic endosomes where the hormone and receptor are split (show figure 7) [23]. The former is metabolized within the cell, while the receptor is returned to the basolateral membrane. Attenuation of the ADH effect is associated with endocytosis of only those areas of the luminal membrane that contain water channels, thereby restoring the relative water impermeability of the luminal membrane.

The signaling events that control membrane recycling are incompletely understood but activation of adenylyl cyclase appears to be involved [24]. (See "Chapter 6A: Mechanisms of hormone action"). In addition, the structure of aquaporin-2 helps dictate cellular distribution and recycling. Mutations of the aquaporin-2 gene can cause resistance to antidiuretic hormone (called nephrogenic diabetes insipidus). In the families reported thus far, the defect appears to involve misrouting rather than loss of function [25].

**Composition of urine** — The composition of the urine differs from that of the relatively constant extracellular fluid in two important ways. First, the quantity of solutes and water in the urine is highly variable, being dependent upon the intake of these substances. A normal subject, for example, appropriately excretes more Na<sup>+</sup> on a high-salt diet than on a low-salt diet. In both instances, the steady-state and therefore the extracellular volume are maintained as output equals intake. Similarly, the urine volume is greater after a water load than after

water restriction, resulting in a stable plasma Na<sup>+</sup> concentration†. (See "Chapter 8A: Effective circulating volume and the steady state"). This relation to intake means that there are no absolute "normal" values for urinary solute or water excretion. We can only describe a normal range which merely reflects the range of dietary intake, eg, 100 to 250 meq/day for Na<sup>+</sup>.

† These changes in Na<sup>+</sup> and water excretion are relatively precise, so that increasing Na<sup>+</sup> intake from 100 to 200 meq/day, for example, results in a parallel rise in Na<sup>+</sup> excretion. If, as depicted in Table 1, 26,000 meq of Na<sup>+</sup> is filtered per day, then a 100 meq increase in excretion represents a change involving less than 0.5 percent of the filtered load. This illustrates the high degree of efficiency required to maintain salt and water balance.

Second, ions compose 95 percent of the extracellular fluid solutes; in comparison, the urine has high concentrations of uncharged molecules, particularly urea. This allows urea and other metabolic end-products to be excreted, rather than accumulating in the body.

**Summary of nephron function** — The following chapters in Part Two will describe the roles of the different nephron segments in the regulation of solute and water homeostasis. These functions are summarized in Table 2 (show table 2). As can be seen, there are marked differences in segmental function, a finding consistent with the differences in segmental histology (show figure 1) and permeability and transport characteristics [5] . In addition, multiple sites participate in the regulation of the rates of excretion of the different substances in the filtrate. This diversity provides the flexibility that allows the kidney to maintain solute and water balance, even in the presence of major changes in dietary intake.

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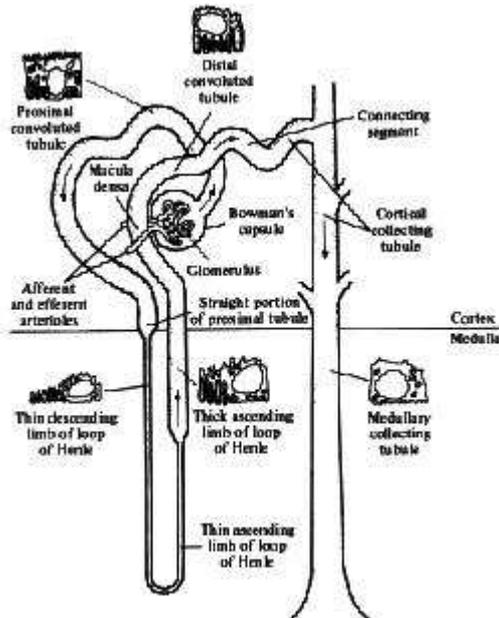
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## GRAPHICS

### Nephron anatomy

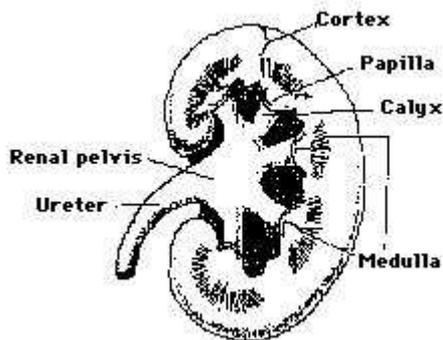
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Anatomic relationships of the component parts of the nephron. Adapted from Vander, R, *Renal Physiology*, 2d ed, McGraw-Hill, New York, 1980.

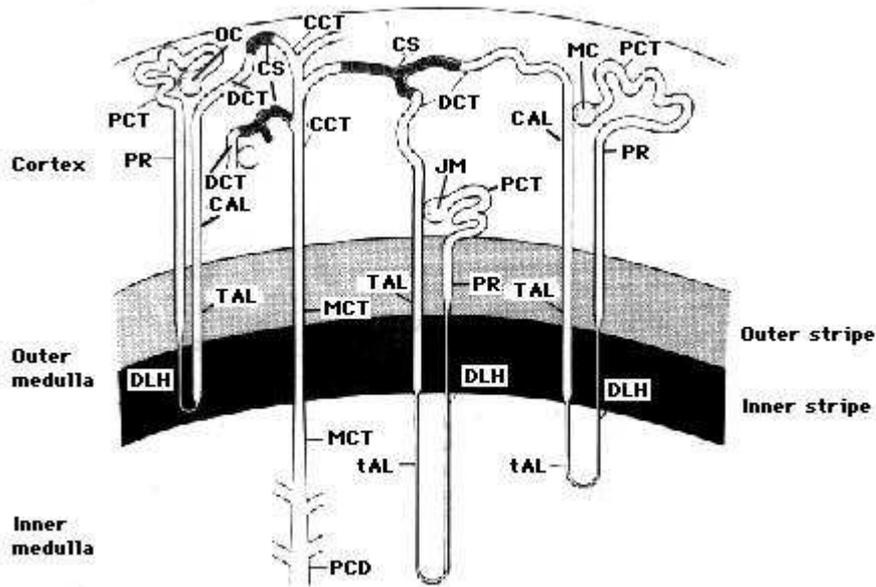
### Section of a human kidney

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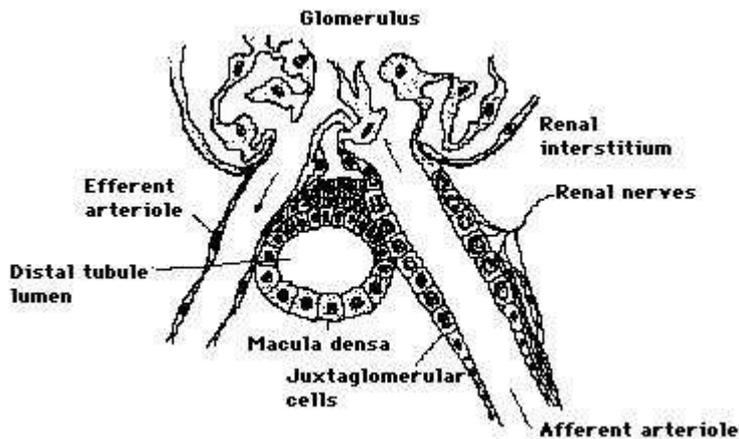
The outer portion (the cortex) contains all the glomeruli. The tubules are located in both the cortex and the medulla, with the collecting tubules forming a large portion of the inner medulla (the papilla). Urine leaving the collecting tubules drains sequentially into the calyces, renal pelvis, ureter, and then the bladder. Adapted from Vander R, *Renal Physiology*, 2d ed, McGraw-Hill, New York, 1980.

### Anatomic relations of the different nephron segments



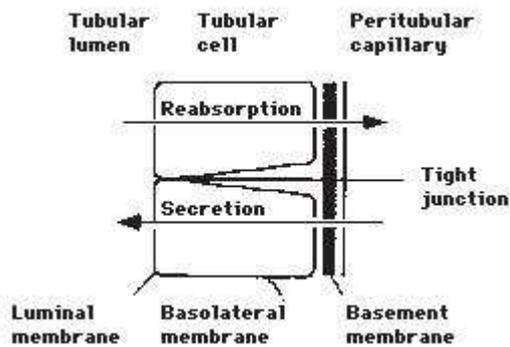
The anatomic relationships between the different nephron segments, according to the location of the glomeruli in the outer cortex (OC), midcortex (MC), or juxtamedullary area (JM). The major nephron segments are labelled as follows: PCT: proximal convoluted tubule; PR: pars recta, which ends in the S3 segment at the junction of the outer and inner stripes of the outer medulla; DLH: descending limb of the loop of Henle; TAL: thin ascending limb, which is not present in outer cortical nephrons that have short loops of Henle; TAL: thick ascending limb, which ends in the macula densa adjacent to the parent glomerulus; DCT: distal convoluted tubule; CS: connecting segment; CCT: cortical collecting tubule; MCT: medullary collecting tubule; and PCD: papillary collecting duct at the end of the medullary collecting tubule. Adapted from Jacobson, HR, *Am J Physiol* 1981; 241:F203.

### Anatomy of the juxtaglomerular apparatus

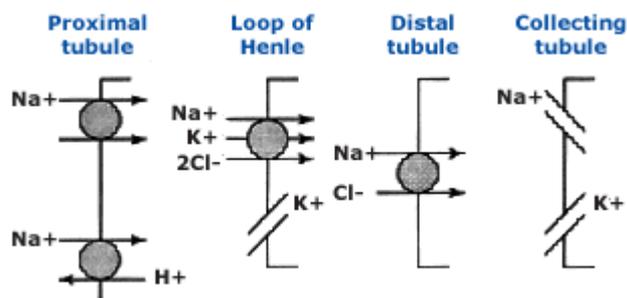


The juxtaglomerular cells in the wall of the afferent arteriole secrete renin into the lumen of the afferent arteriole and the renal lymph. Stretch receptors in the afferent arteriole, the sympathetic nerves ending in the juxtaglomerular cells, and the composition of the tubular fluid reaching the macula densa all contribute to the regulation of renin secretion. Adapted from Davis JO, *Am J Med* 1973; 55:333.

### Schematic representation of reabsorption and secretion in the nephron



### Sodium entry into different tubule segments



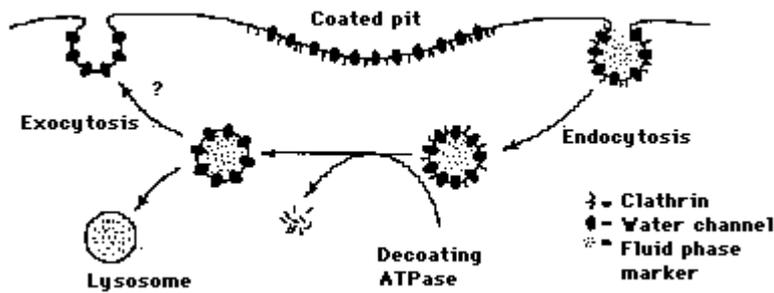
Major mechanisms of passive  $\text{Na}^+$  entry into the cells across the luminal (apical) membrane in the different nephron segments. With the exception of the selective  $\text{Na}^+$  channels in the collecting tubules,  $\text{Na}^+$  reabsorption in the more proximal segments is linked to the reabsorption or secretion of other solutes. *Adapted from Rose, BD, Kidney Int 1991; 39:336.*

### Solute reabsorption by the kidney

Substance	Filtered	Excreted	Percent net reabsorption
Water	180 liters	0.5-3.0 liters	98-99
$\text{Na}^+$	26,000 meq	100-250 meq	>99
$\text{Cl}^-$	21,000 meq	100-250	99
$\text{HCO}_3^-$	4,800 meq	0	~100
$\text{K}^+$	800 meq	40-120 meq	80-95
Urea	54 grams	27-32 grams	40-50

Summary of the net daily reabsorptive work performed by the kidney. These values are for a normal adult man on a typical Western diet. The glomerular filtration rate and therefore the filtered load of solutes and water is approximately 25 percent lower in women.

### Water channel recycling



Proposed pathways of recycling of luminal membrane water channels in principal cells in the collecting tubule. Water channels are concentrated in clathrin-coated pits at the cell surface and are endocytosed in coated vesicles. These vesicles are rapidly decoated; the water channels may escape degradation and be recycled to the luminal membrane in the presence of ADH. Adapted from Brown, D, *Kidney Int* 1989; 256:F1.

Nephron segment	Major functions
Glomerulus	Forms an ultrafiltrate of plasma
Proximal tubule	Reabsorbs isosmotically 60 to 65 percent of the filtered NaCl and H <sub>2</sub> O Reabsorbs 90 percent of the filtered HCO <sub>3</sub> <sup>-</sup> Major site of ammonia production in the nephron Reabsorbs almost all of filtered glucose and amino acids Reabsorbs K <sup>+</sup> , phosphate, calcium, magnesium, urea, and uric acid Secretes organic anions (such as urate) and cations (such as creatine); this pathway is also used for excretion of protein-bound drugs and toxins
Loop of Henle	Reabsorbs 25 to 35 percent of filtered NaCl Countercurrent multiplier as NaCl reabsorbed in excess of water Major site of active regulation of magnesium excretion
Distal tubule	Reabsorbs about 5 percent of filtered NaCl but almost no water Major site, with connecting segment, of active regulation of calcium excretion
Connecting segment and cortical collecting tubule	Principal cells reabsorb Na <sup>+</sup> and Cl <sup>-</sup> and secrete K <sup>+</sup> under the influence of aldosterone Intercalated cells secrete H <sup>+</sup> , reabsorb K <sup>+</sup> , and, in metabolic alkalosis, secrete HCO <sub>3</sub> <sup>-</sup> Reabsorb water in the presence of antidiuretic hormone
Medullary collecting tubule	Site of final modification of the urine Reabsorb NaCl, the concentration of which can be reduced to less than 1 meq/L Reabsorb water and urea relative to the amount of antidiuretic hormone present, allowing a concentrated or dilute urine to be excreted Secrete H <sup>+</sup> and NH <sub>3</sub> ; urine pH can be reduced to as low as 4.5 to 5.0 Can contribute to potassium balance by reabsorption or secretion of K <sup>+</sup>

Contribution of the different nephron segments to solute and water homeostasis.

## **Glomerular anatomy and function**

The blood flow to the kidneys averages 20 percent of the cardiac output. In terms of flow per 100 g weight, the renal blood flow (RBF) is four times greater than that to the liver or exercising muscle and eight times that of coronary blood flow. Blood enters the kidney through the renal arteries and passes through serial branches (interlobar, arcuate, interlobular) before entering the glomeruli via the afferent arterioles. The portion of the plasma not filtered across the glomerular capillary wall then leaves the glomeruli via the efferent arterioles and enters the postglomerular capillaries. In the cortex, these capillaries run in apposition to the adjacent tubules, although not necessarily to the tubule segments from the same glomerulus [1]. In addition, branches from the efferent arterioles of the juxtamedullary glomeruli enter the medulla and form the vasa recta capillaries ([show figure 1](#)). Blood returns to the systemic circulation through veins similar to the arteries in name and location.

The renal circulation affects urine formation in the following ways:

1. The rate of glomerular filtration is an important determinant of solute and water excretion.
2. The peritubular capillaries in the cortex return reabsorbed solutes and water to the systemic circulation and can modulate the degree of proximal tubular reabsorption and secretion.
3. The vasa recta capillaries in the medulla return reabsorbed salt and water to the systemic circulation and participate in the countercurrent mechanism, permitting the conservation of water by the excretion of a hyperosmotic urine.

The remainder of this chapter will review glomerular function, the factors responsible for the regulation of the glomerular filtration rate (GFR) and renal plasma flow, and the clinical methods used to measure these parameters.

**GLOMERULAR ANATOMY AND FUNCTION** — The glomerulus consists of a tuft of capillaries that is interposed between the afferent and efferent arterioles. Each glomerulus is enclosed within an epithelial cell capsule (Bowman's capsule) that is continuous both with the epithelial cells that surround the glomerular capillaries and with the cells of the proximal convoluted tubule ([show figure 2](#)) [2]. Thus, the glomerular capillary wall, through which the filtrate must pass, consists of three layers: the fenestrated endothelial cell, the glomerular basement membrane (GBM), and the epithelial cell. The epithelial cells are attached to the GBM by discrete foot processes. The pores between the foot processes (slit pores) are closed by a thin membrane called the slit diaphragm, which functions as a modified adherens junction ([show figure 2](#)) [3].

The GBM is a fusion product of basement membrane material produced by the glomerular epithelial and endothelial cells [4,5]. The GBM performs a variety of functions including maintenance of normal glomerular architecture, anchoring adjacent cells, and acting as a barrier to the filtration of macromolecules. It consists of the following major constituents [4]:

- Type IV collagen, which forms cords that provide the basic superstructure of the GBM
- The spaces between the cords are filled by a variety of substances including laminin, nidogen, and heparan sulfate proteoglycans [6]. Laminin and nidogen form a tight complex, one of the

major functions of which is cell adhesion to the GBM. In comparison, anionic heparan sulfate proteoglycans is largely responsible for the charge barrier to the filtration of anionic macromolecules (see below)

An abnormality in type IV collagen is responsible for the disorder hereditary nephritis (Alport's syndrome), which is a progressive form of glomerular disease (at least in males) that is often associated with hearing loss and lenticular abnormalities. The primary defect in almost all patients appears to reside in the noncollagenous domain of type IV collagen, involving the gene coding for the alpha-5 chain which is located on the X chromosome, the COL4A5 gene [7,8]. Abnormalities in the alpha-3 and alpha-4 chains of type IV collagen may also cause hereditary nephritis, which is not surprising since the alpha-3, -4, and -5 chains combine to form a novel collagen that is expressed in the glomerulus and a few other tissues [9].

**Filtration barrier and protein excretion** — One of the major functions of the glomerulus is to allow the filtration of small solutes (such as sodium and urea) and water, while restricting the passage of larger molecules (show figure 3). Solute up to the size of inulin (mol wt 5200) are freely filtered. On the other hand, myoglobin (mol wt 17,000) is filtered less completely than inulin, while albumin (mol wt 69,000) is filtered only to a minor degree. Filtration is also limited for ions or drugs which are bound to albumin, such as roughly 40 percent of the circulating calcium.

This difference in filtration of solutes is important physiologically. The free filtration of sodium, potassium, and urea, for example, allows the kidney to maintain the steady state by excreting the load derived from dietary intake and endogenous metabolism. On the other hand, the restricted filtration of larger proteins prevents such potential problems as negative nitrogen balance, the development of hypoalbuminemia, and infection due to the loss of immunoglobulin gamma (IgG).

**Size selectivity** — As illustrated in figure 3, the GBM is size and charge selective, as smaller and cationic molecules are more likely to be filtered. Both the GBM and the slit diaphragms between the foot processes of the epithelial cell contribute to size-selectivity [10,11].

The size limitation in the GBM represents functional pores in the spaces between the tightly packed cords of type IV collagen [12]. In addition, the cellular components of the glomerular capillary wall are also important determinants of glomerular permeability [13]. This is illustrated by the following observations:

- Macromolecules that pass through the GBM often accumulate below the slit diaphragms rather than passing into the urinary space.
- In vitro studies of isolated GBM indicate that the GBM is much more permeable to macromolecules than the intact glomerulus; the net effect is that the glomerular cells may be responsible for as much as 90 percent of the barrier to filtration [14].
- Increased protein filtration in glomerular diseases may primarily occur in areas of focal foot process detachment [15].

Specific proteins have been identified that play an important role in glomerular morphology and function. Podocalyxin is an anionic protein that lines the sides of the epithelial cell foot processes and is probably

responsible, by electrostatic repulsion, for maintaining the separation of adjacent foot processes [16]. Mice that lack podocalyxin fail to form foot processes and slit diaphragms, have tight and adherens junctions in the epithelial cells, and are anuric presumably due to a lack of glomerular filtration [17]. On the other hand, a mutation in the gene for nephrin, a protein specifically located at the slit diaphragm, results in congenital nephrotic syndrome [18].

Most of the pores in the glomerular capillary wall are relatively small (mean radius about 42 Å)† [19]: they partially restrict the filtration of albumin (mean radius 36 Å), but allow the passage of smaller solutes and water [20]. The endothelial cells, in comparison, do not contribute to size-selectivity, since the endothelial fenestrae are relatively wide open and do not begin to restrict the passage of neutral macromolecules until their radius is larger than 375 Å [21]. These cells do, however, contribute to charge selectivity.

†The data in Figure 3 used dextrans of different sizes. However, dextrans are long and pliable and may underestimate the impermeability to round macromolecules such as albumin. Studies using ficoll, which behaves as an ideal solid sphere, have estimated the pore radius to be 42 Å [19].

There is also a much less numerous second population (less than 0.5 percent) of larger pores that permit the passage of macromolecules (including IgG) as large as 70 Å [20]. In normal subjects, however, only a very small amount of filtrate passes through these pores.

**Charge selectivity** — Molecular charge is a second major determinant of filtration across the GBM [10,11,22]. As illustrated in figure 3, cationic and neutral dextrans are filtered to a greater degree than anionic dextran sulfates of similar molecular sizes. This inhibitory effect of charge is due in part to electrostatic repulsion by anionic sites both in the endothelial fenestrae and in the GBM. The negative charge is primarily composed of heparan sulfate proteoglycans† (which are produced by the glomerular epithelial and endothelial cells) [2,23].

Albumin is a polyanion in the physiologic pH range. As with dextran sulfate, albumin filtration is only about 5 percent that of neutral dextran of the same molecular radius. Thus, charge as well as size limits the filtration of albumin. However, the importance of charge selectivity may not be as great as previously thought [24,25].

Dextran infusions have also been used in humans both to assess normal function and to determine the mechanism of the increase in protein excretion that typically occurs in glomerular diseases [22,26]. As illustrated in figure 4, for example, there is an increased number of larger pores as evidenced by a selective elevation in the clearance of neutral dextrans that are larger than 52 Å in diameter (show figure 4). Tunnels and cavities in the glomerular basement membrane appear to be the pathways for protein leakage [27].

The net effect of loss of size selectivity is enhanced excretion of IgG (radius about 55 Å) as well as albumin [28]. This pattern has been demonstrated in most glomerular diseases, including membranous nephropathy, minimal change disease, focal glomerulosclerosis, and diabetic nephropathy [22,28,29]. In these conditions, however, the size defect can account for all of the increase in albumin excretion in only about one-half of cases, suggesting a concurrent defect in charge-selectivity which may be most prominent in minimal change disease [26].

Figure 4 also illustrates an important clinical difference between the filtration of larger proteins and that of smaller solutes and water ([show figure 4](#)). The reduced clearance of smaller molecules in most proteinuric states reflects a decrease in surface area (due to fewer functioning pores) induced by the glomerular disease. At the same time, there is increased clearance of large proteins due to an enhanced number of larger pores (which still represent a very small fraction of the total number of pores) and perhaps partial loss of the charge barrier (which does not affect the filtration of smaller molecules).

**OTHER FUNCTIONS** — The glomerular cells also have synthetic, phagocytic, and endocrine functions. The epithelial cells, for example, are thought to be responsible for the synthesis of the GBM and for the removal of circulating macromolecules that are able to pass through the GBM and enter the subepithelial space [2,30]. The endothelial cells, on the other hand, regulate vasomotor tone, in part via the release of prostacyclin, endothelin, and nitric oxide. They may also play an important role in inflammatory disorders involving the glomerulus by expressing adhesion molecules that promote the accumulation of inflammatory cells [31].

The mesangium, in comparison, is composed of two different types of cells. One is the mesangial cell, which has microfilaments similar to smooth muscle cells [32,33]. After glomerular injury or depopulation of resident mesangial cells, new mesangial cells may originate from cells that normally reside in the juxtaglomerular apparatus [34]. These cells do not appear to be macrophages or smooth muscle or endothelial cells, or to excrete renin.

The intrinsic mesangial cells can respond to angiotensin II (which is locally produced by the endothelial cells in the afferent arteriole) and can synthesize prostaglandins, both of which play an important role in the regulation of glomerular hemodynamics (see below and Chap. 6) [35]. These cells also may be involved in immune-mediated glomerular diseases. They can both release a number of cytokines (including interleukin-1, interleukin-6, chemokines, and epidermal growth factor) and proliferate in response to cytokines (such as platelet-derived growth factor and epidermal growth factor) [32,36,37]. These actions can contribute to the hypercellularity, mesangial matrix expansion, and glomerular injury that are often seen in these disorders.

The second cell type in the mesangium consists of circulating macrophages and monocytes that move into and out of the mesangium. These cells may have a primary phagocytic function, removing those macromolecules that enter the capillary wall but are unable to cross the basement membrane and move into the urinary space; they may also contribute to local inflammation in immune-mediated glomerular diseases [38]. Macromolecule entry into and subsequent removal from the mesangium can occur because most of the mesangium is separated from the capillary lumen only by the relatively permeable fenestrated endothelium, not by basement membrane ([show figure 2](#)).

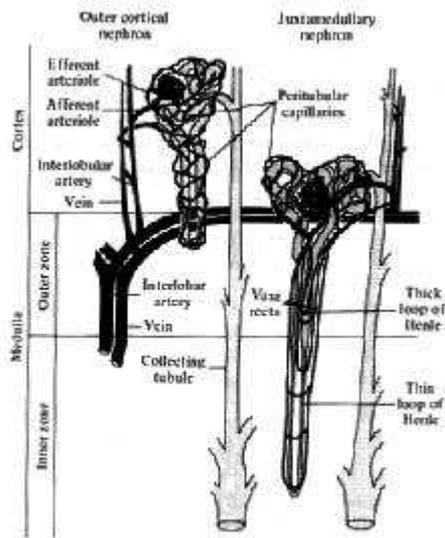
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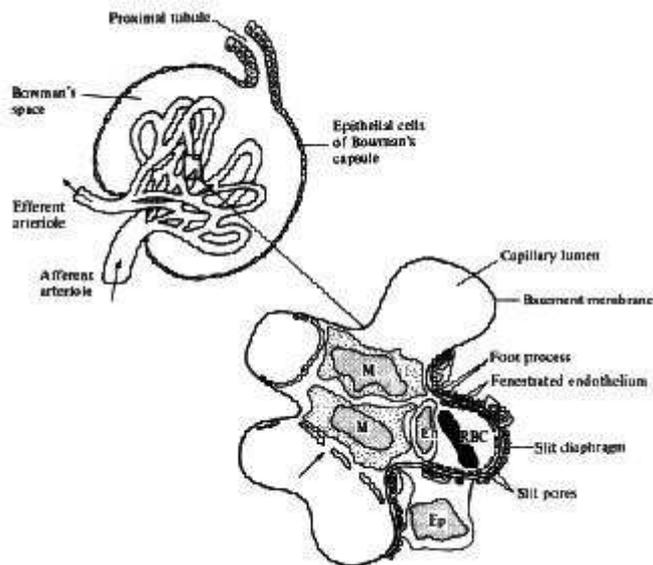
## GRAPHICS

### Anatomy of the renal circulation



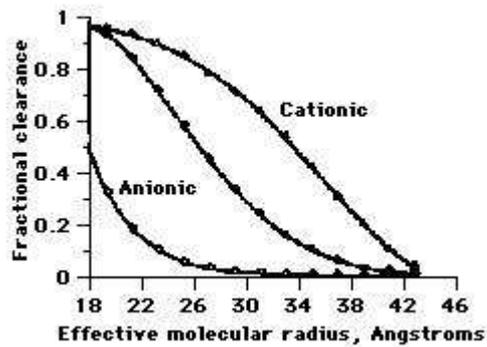
Comparison of the anatomy and blood supplies of outer cortical and juxtamedullary nephrons. Note that the efferent arterioles from the juxtamedullary nephrons not only form peritubular capillaries around the convoluted tubules but also enter the medulla and form the vasa recta capillaries. *Adapted from Pitts, RF, Physiology of the Kidney and Body Fluids, 3d ed, copyright, 1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission.*

### Anatomy of the glomerulus



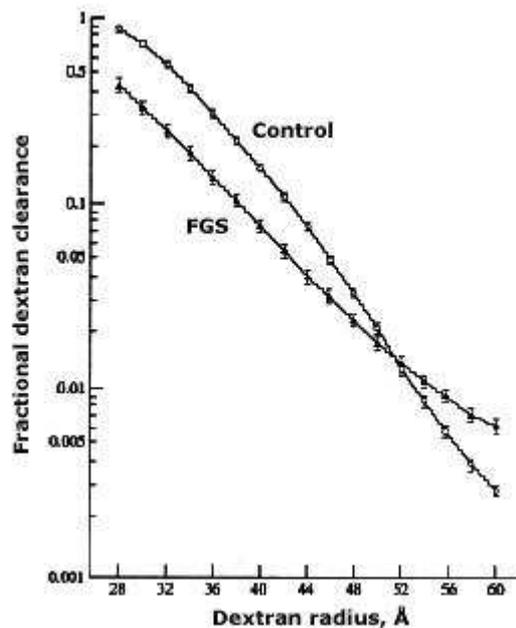
The bottom drawing is a diagram of part of a capillary tuft with the mesangial cells (M) in the middle surrounded by capillaries. The capillary wall has three layers composed of the fenestrated endothelial cells (En), the basement membrane, and the epithelial cells (Ep) which attach to the basement membrane by discrete foot processes. Between the foot processes are slit pores which are closed by a thin membrane, the slit diaphragm. The glomerular basement membrane surrounds the capillary loops, but most of the mesangium is separated from the capillary lumen only by the relatively permeable fenestrated endothelium (arrow). *Adapted from Vander, R, Renal Physiology, 2d ed, McGraw-Hill, New York, 1980, and Latta, H, in Handbook of Physiology, sec 8, Renal Physiology, vol I, Orloff, J, Berliner, RW, Geiger, R, (Eds), American Physiological Society, Washington, DC, 1973*

### Size and charge determinants of glomerular permeability



Fractional clearances (the ratio of the filtration of a substance to that of inulin, which is freely filtered) of anionic, neutral (middle curve), and cationic dextrans as a function of effective molecular radius. Both molecular size and charge are important determinants of filtration, as smaller or cationic dextrans are more easily filtered. As a reference, the effective molecular radius of albumin (which is anionic in the physiologic pH range) is 36 Å. *Reproduced with permission from the American Society for Clinical Investigation Bohrer MP, et al, J Clin Invest 1978; 61:72.*

### Mechanism of proteinuria in FGS



Dextran sieving profiles in patients with heavy proteinuria and the nephrotic syndrome due to focal glomerulosclerosis (FGS). A fractional dextran clearance of 1 represents complete filtration. Patients with FGS have decreased clearance of smaller dextrans but increased clearance of dextrans with a radius above 52 Å, suggesting an increased number of larger pores. *Data from Guasch, A, Hashimoto, H, Sibley, RK, et al, Am J Physiol 1991; 260:F728.*

## **Water balance and regulation of plasma osmolality**

Hypoosmolality and hyperosmolality can produce serious neurologic symptoms and death, primarily due to water movement into and out of the brain, respectively [1-5]. To prevent this, the plasma osmolality (Posm), which is primarily determined by the plasma Na<sup>+</sup> concentration, is normally maintained within narrow limits by appropriate variations in water intake and water excretion. This regulatory system is governed by osmoreceptors in the hypothalamus that influence both thirst and the secretion of antidiuretic hormone (ADH).

Although it may seem that regulation of the plasma Na<sup>+</sup> concentration must have something to do with Na<sup>+</sup> balance, osmoregulation is almost entirely mediated by changes in water balance. Thus, the effectors for osmoregulation (ADH and thirst, affecting water excretion and water intake) are very different from those involved in volume regulation (renin-angiotensin-aldosterone system and atrial natriuretic peptide, affecting Na<sup>+</sup> excretion) (show table 1). This chapter will describe the sources of water intake, the sites of water loss from the body, and the roles of ADH, thirst, and renal water excretion in the maintenance of the Posm.

### **WATER BALANCE**

**Obligatory water output** — In the steady state, water intake (including that generated from endogenous metabolism) must equal water output (show table 2). Much of the water output involves obligatory losses in the urine, stool, and, by evaporation, from the moist surfaces of the skin and respiratory tract. The evaporative losses play an important role in thermoregulation; the heat required for evaporation, 0.58 kcal/1.0 mL of water, normally accounts for 20 to 25 percent of the heat lost from the body, with the remainder occurring by radiation and convection [6]. The net effect is the elimination of the heat produced by body metabolism, thereby preventing the development of hyperthermia.

In contrast to these insensible losses, sweat can be called a sensible loss. Sweat is a hypotonic fluid (Na<sup>+</sup> concentration equals 30 to 65 meq/L) secreted by the sweat glands in the skin. It also contributes to thermoregulation, as the secretion and subsequent evaporation of sweat result in the loss of heat from the body. In the basal state, sweat production is low, but it can increase markedly in the presence of high external temperatures or when endogenous heat production is enhanced, as with exercise, fever, or hyperthyroidism [6]. As an example, a subject exercising in a hot, dry climate can lose as much as 1500 mL/h as sweat [7].

The obligatory renal water loss is directly related to solute excretion. If a subject has to excrete 800 mosmol of solute per day (mostly Na<sup>+</sup> and K<sup>+</sup> salts and urea) to remain in the steady state, and the maximum U<sub>osm</sub> is 1200 mosmol/kg, then the excretion of the 800 mosmol will require a minimum urine volume of 670 mL/day.

Only small amounts of water are normally lost in the stool, averaging 100 to 200 mL/day. However, gastrointestinal losses are increased to a variable degree in patients with vomiting or diarrhea. The effect of these losses on the plasma Na<sup>+</sup> concentration depends on the sum of the Na<sup>+</sup> and K<sup>+</sup> concentrations in the fluid that is lost.

**Water intake** — To maintain water balance, water must be taken in (or generated) to replace these losses (show table 1). Net water intake is derived from three sources: (1) ingested water; (2) water contained in foods, e.g., meat is roughly 70 percent water and certain fruits and vegetables are almost 100 percent water; and (3) water produced from the oxidation of carbohydrates, proteins, and fats. If the latter two sources account for 1200 mL/day and the obligatory water loss (from the skin, gastrointestinal tract, and in the urine) is 1600 mL/day, then at least 400 mL must be ingested by drinking to maintain balance. Humans drink more than this minimum requirement for social and cultural reasons, and the extra water is excreted in the urine.

**REGULATION OF PLASMA OSMOLALITY** — The normal plasma osmolality ( $P_{osm}$ ) is 275 to 290 mosmol/kg. It usually is held within narrow limits as variations of only 1 to 2 percent initiate mechanisms to return the  $P_{osm}$  to normal. These alterations in osmolality are sensed by receptor cells in the hypothalamus which affect water intake (via thirst) and water excretion (via ADH, which increases water reabsorption in the collecting tubules)†.

† The physiology of the release and actions of ADH are discussed in detail in Chap. 8.

In terms of water balance, a water load decreases the  $P_{osm}$ , and water loss (as with exercise on a hot day) increases the  $P_{osm}$ . In both of these settings, there is a parallel change in the plasma  $Na^+$  concentration. These alterations in water balance must be differentiated from conditions of isosmotic fluid loss (such as bleeding or some cases of diarrhea), in which solute and water may be lost proportionately, producing no direct change in the  $P_{osm}$  or the plasma  $Na^+$  concentration.

The body responds to a water load by suppressing ADH secretion, resulting in decreased collecting tubule water reabsorption and excretion of the excess water. The peak diuresis is delayed for 90 to 120 min, the time necessary for the metabolism of previously circulating ADH. As will be seen, the kidneys can excrete up to 10 to 20 liters of water per day, well above any normal level of water intake. Therefore, water retention resulting in hyposmolality and hyponatremia occurs, with rare exceptions, only in patients with an impairment in renal water excretion.

The correction of a water deficit (hyperosmolality) requires the intake and retention of exogenous water. This is achieved by increases in thirst and ADH release, which are induced by the elevation in the  $P_{osm}$ . In contrast to the response to hyposmolality, in which renal water excretion is of primary importance, increased thirst is the major defense against hyperosmolality and hypernatremia. Although the kidney can minimize water excretion via the effect of ADH, a water deficit can be corrected only by increased dietary intake.

An example of the efficiency of the thirst mechanism occurs in patients with complete central diabetes insipidus who, because they secrete little or no ADH, may excrete more than 10 liters of urine per day. Despite this, the  $P_{osm}$  remains near normal because the thirst mechanism augments water intake to match output. Thus, symptomatic hypernatremia generally will not occur in a patient with a normal thirst mechanism and access to water.

Excretion of a water load generally occurs so rapidly that there is little change in volume and no activation of the volume regulatory pathways. There are, however, settings in which both the volume and osmoregulatory

systems come into play. As an example, the intake of NaCl without water (as with a large quantity of potato chips) results in an elevation in the Posm and, due to the rise in extracellular Na<sup>+</sup> stores, expansion of the effective circulating volume. The latter change promotes the renal excretion of the excess Na<sup>+</sup>, via a response that is mediated at least in part by a reduction in the release of aldosterone and an increase in that of atrial natriuretic peptide. ADH secretion and thirst also are stimulated (by the rise in Posm); the ensuing increment in water intake both lowers the Posm toward normal and further expands the volume, thereby enhancing the stimulus to renal Na<sup>+</sup> excretion. The end result is that the urine has a high osmolality and a relatively high concentration of Na<sup>+</sup>, a composition that is similar to net intake.

In comparison, an infusion of isotonic saline causes volume expansion, but does not change the Posm. Consequently, ADH release and thirst are not directly affected, and the steady state is restored by the volume regulatory pathways.

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## GRAPHICS

### Differences between osmoregulation and volume regulation

	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	Effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotic sinus Afferent glomerular arteriole Atria
Effectors	Antidiuretic hormone	Sympathetic nervous system Renin-angiotensin-aldosteron Natriuretic peptides Pressure natriuresis Antidiuretic hormone
What is affected	Water excretion (via ADH) Water intake (via thirst)	Sodium excretion

## **Maintenance fluid therapy in children**

**INTRODUCTION** — Fluid therapy maintains the normal volume and composition of body fluids and, if needed, corrects any existing abnormalities. In children, the most common clinical abnormality requiring fluid therapy is hypovolemia, primarily due to vomiting and diarrhea from gastroenteritis. Thus, it is useful clinically to divide fluid therapy into two potential components: provision of volume for homeostatic needs (maintenance therapy) and provision of fluid for deficit requirements (repletion therapy).

Maintenance therapy replaces the ongoing losses of water and electrolytes occurring via normal physiologic processes.

Repletion therapy replaces the water and electrolyte deficits that have accrued via some perturbation in normal processes. Repletion returns the patient to a normal volume and electrolyte status. Thus, in a patient who is hypovolemic, fluid therapy will include both repletion and maintenance therapy.

Maintenance fluid therapy, including alterations in maintenance requirements, will be reviewed here. Assessment of hypovolemia and treatment of dehydration are discussed elsewhere.

**MAINTENANCE WATER NEEDS** — Daily water needs are based upon insensible losses from the respiratory tract and skin, and sensible losses from urine and stool [1]. Water requirements are estimated in direct relation to caloric energy expenditures, with approximately 100 mL of exogenous water needed for every 100 kcal/kg of energy expended.

The most widely utilized method for calculation of water needs is based upon the estimated caloric expenditures of hospitalized children at bed rest [2]. Caloric expenditure varies directly with body weight, with the rate changing over three broad weight ranges (show figure 1).

Weight less than 10 kg — 100 kcal/kg

Weight from 10 to 20 kg — 1000 kcal for first 10 kg of body weight plus 50 kcal/kg for any increment of weight above 10 kg

Weight from 20 to 80 kg — 1500 kcal for first 20 kg of body weight plus 20 kcal/kg for any increment of weight above 20 kg.

**Calculation** — The above caloric groupings are also directly applied to determine water maintenance requirements. Two methods of calculation are currently popular, one based upon a volume calculated for needs over 24 hours, and the other upon a volume that would be delivered on an hourly basis.

Both methods assume that urinary losses are isosmotic to plasma. Since the kidney can both concentrate and dilute the urine, normal children generally tolerate fluid intakes

below or above these calculated values, but these calculations serve as a starting point for a presumptive maintenance fluid volume.

**Method 1** — Maintenance fluid volume for a 24-hour period:

Weight less than 10 kg — 100 mL/kg

Weight >10 kg to 20 kg — 1000 mL for first 10 kg of body weight plus 50 mL/kg for any increment of weight over 10 kg

Weight >20 kg to 80 kg — 1500 mL for first 20 kg of body weight plus 20 mL/kg for any increment of weight over 20 kg, up to a maximum of 2400 mL daily

**Method 2** — Maintenance fluid needed on an hourly basis:

Weight less than 10 kg — 4 mL/kg per hour

Weight >10 kg to 20 kg — 40 mL/hour for first 10 kg of body weight plus 2 mL/kg per hour for any increment of weight over 10 kg

Weight >20 kg to 80 kg — 60 mL/hour for first 20 kg of body weight plus 1 mL/kg per hour for any increment of weight over 20 kg, to a maximum of 100 mL/hour, up to a maximum of 2400 mL daily

At body weights above 80 kg, the contribution of water to total body weight falls, so that these methods would significantly overestimate the fluid requirements, and total maintenance needs are generally capped near 2.5 liters daily.

The total daily volume of fluid prescribed by the hourly format is a bit lower than the daily format, but the difference is almost always of no clinical significance. For example, the maintenance needs for a 12-kg child are calculated using both methods:

Utilizing the 24-hour method, the maintenance needs would be 1100 mL for 24 hours (1000 mL for the first 10 kg, plus 100 mL for the next 2 kg [50 mL/kg per day for each kg of body weight between 10 and 20 kg]).

Utilizing the hourly method, the maintenance needs would be slightly lower at 44 mL per hour or 1056 mL for 24 hours (40 mL/hour for the first 10 kg of body weight, plus 4 mL/hour for the next 2 kg [2 mL/kg per hour for each kg of body weight between 10 and 20 kg]).

**Sensible and insensible water loss** — As mentioned above, daily water needs are based upon insensible losses from the respiratory tract and from the skin, and sensible losses from water losses in urine and stool output [1].

Under normal physiological conditions, insensible losses account for approximately 45 mL per 100 kcal of energy expended. • Skin losses, due to evaporation from convection and conduction, account for two-thirds of the insensible losses (30 mL per 100 kcal), and increase with higher core body temperature.

Respiratory losses account for one-third of insensible losses (15 mL per 100 kcal), and result from the warming and humidification of inspired air.

Since water loss from stool is negligible in healthy children, sensible water losses are primarily due to the daily urine output (55 mL per 100 kcal). An obligate urine water loss

is required to excrete the daily solute load that ensues from dietary intake and cellular metabolism. The daily water maintenance requirements, as calculated above, assume a normal dietary solute load and a urine that is isosmotic to plasma (approximately 290 mosmol/L). The minimal obligate urine volume is 25 mL for every 100 kcal of energy expended and requires maximal stimulation of antidiuretic hormone (ADH) release, with a urine osmolality (U<sub>osm</sub>) that can reach 1200 to 1400 mosmol/L.

Thus, individuals who do not receive their calculated maintenance water therapy, or who have increased losses, can still maintain water balance by limiting urinary water loss via increased release of ADH. In that condition, the stimulus to ADH release is initial negative water balance, which raises the plasma osmolality and trigger osmoreceptors. If ongoing, water deprivation may also trigger baroreceptors that sense intravascular or atrial stretch as effective intravascular volume falls (show figure 1).

**Variability in maintenance water needs** — Insensible or sensible water losses can vary with a number of clinical scenarios, often as a function of fluid intake, physical exertion, and complicating disease states (show table 2). As examples:

Premature infants have increased insensible skin fluid losses due to an increased surface area for mass and a thinner dermis. The losses are accentuated if the infant is cared for in an open radiant heater or has received phototherapy.

Patients with a colostomy or ileostomy will have increased stool losses due to their inability to reabsorb intestinal fluid that is usually presented to more distal regions of the digestive tract.

Patients with oliguric renal failure will have decreased water losses and are at risk of actual volume overload.

Patients on ventilators with pre-humidified air will have decreased water losses from respiration.

In such patients, the daily fluid intake must be appropriately adjusted to maintain balance. Unreplaced water losses will lead to both hypernatremia and volume depletion, while water intake in excess of excretory capacity will lead to both hyponatremia and volume expansion.

When prescribing fluid therapy, it is always important for the clinician to look at net volume balance as a dynamic interplay between input and output (ie, an accounting ledger of gains and losses). Often clinicians may focus on specific parameters such as urine flow, with a common misperception that urine output exceeding 0.5 to 1 ml/kg/hour corresponds to good renal output. However, the appropriateness of any urine volume over any unit of time directly corresponds to the patient's volume and solute balance in real time and the concomitant exogenous provision or loss of fluid or solute. Thus, in the normovolemic patient given a large volume of fluid there should follow a large volume diuresis. In

contrast, the hypovolemic patient given a similar large volume of fluid should have limited output until the volume depletion is corrected.

**MAINTENANCE ELECTROLYTE NEEDS** — Maintenance electrolyte requirements, like water requirements, are estimated based upon caloric energy expenditure.

Sodium and chloride — 2 to 3 meq/100 mL of water per day

Potassium — 1 to 2 meq/100 mL of water per day

The majority of the maintenance electrolyte losses is from the urine, with a lesser contribution from sweat and stool losses. As is the case with water balance, the maintenance electrolyte intake must be considered based on specific clinical context, especially when an abnormal physiologic condition is ongoing. For example, sodium and potassium intake may need to be reduced in patients with oliguric renal failure to prevent volume expansion and hyperkalemia; conversely, their intake may need to be increased in patients with diarrhea or burns to prevent volume depletion and hypokalemia.

**MAINTENANCE PARENTERAL THERAPY** — Based upon the above estimations, the standard commercially available parenteral solution of one-quarter isotonic or normal saline with 20 meq/L potassium will meet the usual electrolyte maintenance needs of a healthy, normovolemic child, assuming that a maintenance volume of fluid is administered. The above solution is often given along with 5 percent dextrose, which provides approximately 20 percent of daily caloric needs assuming a maintenance fluid rate.

In a 15-kg child, for example, maintenance water intake is approximately 1250 mL/day (100 mL/kg for the first 10 kg [1000 mL] plus 50 mL/kg for the remaining 5 kg [250 mL]).

This volume of one-quarter isotonic saline with 20 meq/L of potassium will provide:

Sodium intake of 47 meq/day (3.1 meq/kg)

Potassium intake of 25 meq/day (1.67 meq/kg).

**Hospitalized children and hypotonic fluids** — In hospitalized patients, the ongoing administration of hypotonic maintenance fluids may result in hyponatremia [3-5]. In such cases, hyponatremia is often caused by the intake of electrolyte-free water that cannot be excreted due primarily to persistent ADH secretion that is "inappropriate," or not triggered by usual osmotic or volume parameters [6]. In children, inappropriate ADH secretion may occur post-operatively, with certain central nervous system or pulmonary infections, after the provision of certain medications, or in response to pain or anxiety. [5-7].

The risk for hyponatremia in hospitalized children provided hypotonic maintenance fluids was illustrated in a systematic review of the literature that included three observational

studies, two unmasked randomized trials, and one unrandomized trial [5]. In this analysis, four of the studies were conducted in surgical patients and one study in patients hospitalized with gastroenteritis. This review concluded that such children when given hypotonic parenteral fluids were at increased risk of dropping serum sodium levels below 136 mEq/L.

In another review of hyponatremia as a complication of hypotonic fluid therapy in hospitalized children, the authors concluded that, in the majority of cases, hyponatremia resulted from one of the following situations [7]:

Elevated plasma ADH, due either to appropriate stimuli from hypovolemia or due to the syndrome of inappropriate ADH secretion, preventing excretion of free water even in the face of low serum sodium concentrations.

Administration of 1.5 to 3 times the recommended "maintenance" fluid needs in the face of a clinical situation favoring persistent ADH secretion.

These findings suggest that the administration of hypotonic solutions at higher-than-recommended volumes does lead to hyponatremia in patients with elevated ADH levels. The authors noted that the use of an isotonic solution for maintenance therapy would prevent most of these cases of hyponatremia but has its own inherent risks in certain patient populations, for instance children with cardiopulmonary or renal disease who may not tolerate increased sodium loads. In addition, the use of isotonic saline as maintenance therapy leads to excess intravenous sodium chloride intake [8].

A retrospective review reviewed the serum sodium status of 145 patients admitted postoperatively to a pediatric intensive care unit [9]. Hypotonic fluid was given to 116 patients (80 percent) and 29 (20 percent) received isotonic fluids.

Hyponatremia (defined as a serum sodium less than 130 mEq/L) was detected in 16 patients (11 percent). Thirteen patients had moderate hyponatremia (serum sodium between 125 and 129 mEq/L) and three had severe hyponatremia (serum sodium less than 125 mEq/L). Patients were asymptomatic and there were no acute neurologic sequelae or deaths attributed to hyponatremia.

There was no difference in the likelihood of developing hyponatremia between patients who received hypotonic fluids compared to those given isotonic fluids.

In addition, there were 11 patients with hypernatremia (serum sodium equal to or greater than 145 mEq/L), all of whom received isotonic fluids.

These reports underscore why an assessment of the patient's clinical condition and volume state must be performed before parenteral fluid therapy is begun and why reassessment must occur as fluid therapy is ongoing [8]. For children who are thought to be volume-depleted, initial therapy should be directed at repletion of the estimated deficit with an

isotonic solution [6]. Volume repletion will remove the hypovolemia-induced stimulus to ADH release, thereby improving the ability to excrete free water.

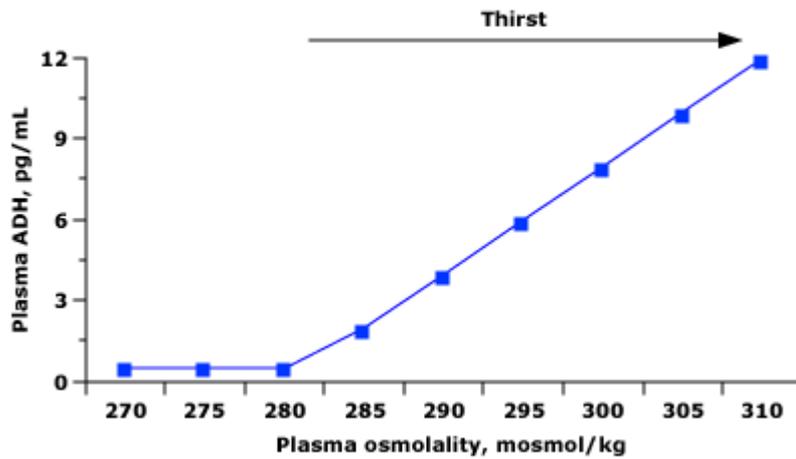
Once the patient is thought to be euvolemic, the fluid used with any further maintenance therapy must be chosen with careful consideration of the patient's ability to excrete free water. In hospitalized children, the likelihood of persistent inappropriate ADH secretion exists due to a variety of disease states, pain, or anxiety. As an example, in a retrospective review of 103 children admitted with acute illness, 80 patients had elevated serum ADH and renin levels during their hospitalization [10]. In children with ADH release, free water provision must be judicious and free water restriction may actually be needed to prevent or treat hyponatremia.

A detailed discussion of the clinical manifestations, assessment, and treatment of volume depletion in children is presented elsewhere.

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**GRAPHICS**      Osmotic regulation of ADH release and thirst



Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH. *Data from Robertson, GL, Aycinena, P, Zerbe, RL, Am J Med 1982; 72:339.*

**Factors affecting water maintenance needs**

Source	Increased water needs	Decreased water needs
Skin	Burns Fever Phototherapy Prematurity Radiant heater Sweat	Enclosed incubator Mist tent
Lungs	Tachypnea Tracheostomy	Humidified air
Gastrointestinal tract	Diarrhea Emesis Ileostomy Nasogastric suction	
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain Increased activity	Sedation Hypothyroidism

## **Fluid and electrolyte therapy in newborns**

**INTRODUCTION** — Water and electrolyte homeostasis in newborn infants is influenced by physiologic adaptations following birth and developmental effects on the distribution of total body water and water loss. Fluid and electrolyte therapy must account for these factors in determining maintenance requirements and correction of any abnormalities.

**DISTRIBUTION OF BODY WATER** — Total body water is composed of extracellular fluid (ECF), which includes intravascular and interstitial fluid, and intracellular fluid. The distribution between these compartments changes with increasing gestational age [ 1] . Compared to an infant born at 27 weeks, a newborn term infant has a total body water that comprises a smaller fraction of body weight (75 versus 80 percent) and an ECF volume that is a smaller fraction of total body water (45 versus 70 percent) [ 2] .

Infants normally lose weight during the first week after birth. This weight loss is greater in preterm than term infants (approximately 10 to 15 versus 5 percent) and is associated with a diuresis. The postnatal diuresis is approximately 1 to 3 mL/kg per hour in term infants and is greater in preterm infants. Physiologic weight loss results primarily from an isotonic reduction in extracellular water, although the mechanism for this process is uncertain [ 1] .

**SOURCES OF WATER LOSS** — Water loss can occur through the kidneys, skin, and lungs. The absolute and relative amounts of water loss through these routes change with development. Excessive loss of other fluids, such as stool, gastric drainage, or thoracostomy output, can lead to water and electrolyte disturbances.

**Renal** — A urine volume of approximately 45 mL/kg per day, or 2 mL/kg per hour, allows excretion of a normal solute load, typically in a dilute urine. Changes in urinary water and electrolytes occur with changes in blood flow and maturation of renal function. The proportion of cardiac output directed to the kidneys increases during gestation and after birth. This proportion is 2 percent during the first week after birth at term, 8.8 percent at five weeks of age, and 9.6 percent at one year [ 3] . In contrast, approximately 16 percent of cardiac output in adults goes to the kidneys [ 4] .

Compared to term infants, aspects of renal function are reduced in preterm infants and can result in water and electrolyte imbalance. These factors include:

- Glomerular filtration
- Tubular reabsorption of sodium and bicarbonate and secretion of potassium and hydrogen
- Capacity to concentrate or dilute urine

Factors that contribute to immaturity have been suggested by studies in animals. As an example, transport proteins play an important role in tubular function. These include:

- The Na-H exchanger and Na-glucose cotransporter on the luminal membrane, which permit filtered sodium and glucose to be reabsorbed and hydrogen to be

secreted (resulting in bicarbonate reabsorption) [ 5]

- The Na-K-ATPase pump on the peritubular membrane, which returns reabsorbed sodium to the systemic circulation [ 6]
- The ADH-sensitive aquaporin 2 water channel, which allows a concentrated urine to be formed [ 7]

These transport proteins are at relatively low levels at birth and gradually increase to adult levels [ 8] . The reduced levels of these proteins limit the ability of immature infants to vary sodium excretion and to retain water. Depending upon intake, the impairment in sodium handling can lead to hyponatremia, hypernatremia, or volume depletion or expansion, whereas the impairment in water reabsorption increases the risk of excessive water loss and hypernatremia.

**Skin** — Evaporation through the skin can result in large insensible water losses in newborns. These may be excessive in extremely low birth weight (ELBW) infants with very thin skin. As the skin matures with increasing gestational and postnatal age, evaporative loss is reduced, becoming less significant after 28 weeks gestation and one week after birth. As an example, insensible water loss in an infant born at 24 weeks gestation may be approximately 200 mL/kg per day compared to 20 mL/kg per day for a term infant. Water loss also may be excessive in conditions in which skin integrity is compromised (eg, epidermolysis bullosa, abdominal wall defect).

Radiant warmers increase evaporative water loss by approximately 50 percent [ 9] . Use of humidification and plastic wrap may minimize this loss [ 10] . Phototherapy also increases transepidermal water loss [ 11,12] .

**Respiratory** — With the typical ambient humidity in the nursery, approximately one-half of insensible losses in term infants is caused by water loss through the respiratory system [ 13,14] . Respiratory water loss increases with decreasing gestational age, although transepidermal loss increases even more [ 14] . Thus, in preterm infants, skin water loss is greater than respiratory loss. Respiratory loss also increases with increasing respiratory rate.

**Effect of antenatal glucocorticoids** — Antenatal administration of glucocorticoids to promote lung maturation in preterm infants also results in maturation of the skin and kidneys. ( See "Antenatal use of glucocorticoids in women at risk for preterm delivery"). In one report, water and sodium homeostasis during the first week after birth were compared in ELBW infants exposed and not exposed to antenatal glucocorticoids [ 15] . Exposed infants had lower insensible water loss, less hypernatremia, and an earlier diuresis and natriuresis than unexposed infants. These changes were thought to result from enhanced epithelial cell maturation that improved the barrier function of the skin. In experimental studies, glucocorticoid exposure resulted in maturation of ion channels in the proximal renal tubular epithelium [ 16,17] .

In another report, exposure to antenatal glucocorticoids prevented the nonoliguric hyperkalemia that frequently occurs in ELBW infants [ 18] . The mechanism is uncertain but may be related to enhanced stabilization of cell membranes and upregulation of Na-K-ATPase activity, leading to a decrease in the movement of

potassium from intracellular to extracellular compartments.

**MONITORING** — Careful monitoring is essential to maintaining the correct balance of fluid and electrolytes in newborns. It consists of performing serial physical examinations, measuring body weight, monitoring intake and output, and performing laboratory studies.

**Physical examination** — Physical examination should include signs of cardiovascular stability (heart rate, blood pressure, capillary refill), state of hydration (skin turgor, mucus membrane status, fullness of the anterior fontanelle), and the presence or absence of edema. Body weight should be measured at least daily.

Volume overload is suggested by excessive weight gain, edema, and increased blood pressure. Inadequate fluid administration may be accompanied by weight loss, tachycardia, poor capillary refill, and, in severe cases, hypotension. Volume deficits can occur when third spacing takes place, such as with sepsis or ileus. In this case, body weight may be increased rather than decreased.

**Intake and output** — For the first few days after birth, fluid intake and output of urine and stool should be followed closely, especially in preterm infants or those with acute illness. Urine specific gravity may also be a helpful indicator of fluid status.

On the average, approximately 50 percent of administered fluid is excreted as urine and the remainder is lost through the skin and respiratory tract. With increased fluid administration, the urine becomes more dilute and accounts for the excretion of more than one-half of water intake [ 19] . In contrast, fluid restriction usually results in urine output that is concentrated and less than one-half of intake.

**Serum electrolyte concentrations** — For most newborns receiving parenteral fluids, serum electrolyte concentrations should be measured daily or every other day. The specific monitoring schedule depends upon gestational and postnatal age, as well as the infant's clinical condition. Because the newborn ELBW infant has very high insensible water losses, serum sodium concentration should be measured every four to six hours during the first few days to avoid inadequate or excessive administration of free water [ 20] .

**Effect of pH on potassium** — Potassium is primarily an intracellular cation. The distribution of potassium between intracellular and extracellular compartments depends in part upon the pH of each compartment. As a result, the serum concentration of potassium does not necessarily reflect the amount of total body potassium. On average, the serum potassium concentration will rise by 0.6 meq/L (range 0.2 to 1.7 meq/L) for every 0.1 unit reduction in extracellular pH [ 21] .

However, this effect is minimal or absent in patients with organic acidoses, such as lactic acidosis or ketoacidosis [ 21,22] . Hyperkalemia can occur with these disorders but it is not caused by the acidosis. It may, for example, be caused by excess tissue breakdown and reduced urinary excretion in lactic acidosis resulting from severe hypotension. ( See "Potassium balance in acid-base disorders").

**FLUID REQUIREMENTS** — Calculation of fluid and electrolyte requirements must account for maintenance requirements and ongoing losses, as well as replacement of deficits. Maintenance fluid requirements are those needed for neutral water balance

after accounting for obligatory losses (eg, urine and stool) and insensible losses (eg, skin and lungs) ( show table 1). Requirements will be influenced by factors that include the gestational and postnatal age, ambient temperature and humidity, renal function, and ventilator dependence (which affects respiratory losses). During the first few days, physiologic weight loss should be anticipated.

Excessive loss of other fluids, such as ileostomy or gastric drainage, thoracostomy output, polyuria caused by osmotic diuresis, or repeated removal of cerebrospinal fluid must also be measured and replaced. Deficits associated with cardiovascular changes require prompt correction with a bolus infusion of normal saline (10 to 20 mL/kg); in severe cases, this may need to be repeated. Once hemodynamic stability has been restored, the remaining deficit may be corrected over one to two days, depending upon severity.

**ELECTROLYTE REQUIREMENTS** — Maintenance requirements for sodium, potassium, and chloride are approximately 1 to 2 meq/kg per day. For infants receiving intravenous fluids, these electrolytes generally are not given during the first 24 hours after birth. Sodium and chloride are not needed because their content in body fluids is relatively high [ 1] . Urine flow should be adequate before potassium is added.

In addition to maintenance requirements, electrolyte deficits should be replaced. Depending upon the volume of fluid output, electrolyte losses from gastric or ileostomy drainage can be large. As examples, gastric output is approximately 130 to 140 meq/L Na, 10 to 15 meq/L K, and 140 meq/L Cl, and small bowel output is approximately 100 to 140 meq/L Na, 10 to 30 meq/L K, 50 to 60 meq/L Cl, and 40 to 75 meq/L HCO<sub>3</sub>.

**DISORDERS OF SODIUM, WATER, AND POTASSIUM BALANCE** — Electrolyte disorders include abnormalities of the serum concentration of sodium or potassium. These disorders can occur with normal, decreased, or increased ECF volume.

**Hyponatremia** — The etiology and approach to hyponatremia vary with the postnatal age.

**Early newborn period** — In the early newborn period, hyponatremia, defined as a serum sodium concentration of 128 meq/L or less, most often reflects excess total body water with normal total body sodium. This may result from increased maternal free water intake or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH may accompany pneumonia or meningitis, pneumothorax, or severe intraventricular hemorrhage [ 23] .

Hyponatremia due to these causes is treated by fluid restriction, which usually results in a slow return to normal levels. However, if neurologic signs such as seizures or lethargy develop or if the serum sodium concentration is extremely low (<120 meq/L), urgent correction is needed. Hypertonic saline (3 percent, 6 mL/kg ), infused over one hour, should be given to increase the serum sodium concentration to 120 to 125 meq/L and eliminate seizures [ 24] . This approach typically increases the serum sodium concentration by approximately 5 meq/L. Further correction of hyponatremia should be accomplished slowly, over one to two days.

Correction of hyponatremia should be based on calculations of the sodium deficit, which is equal to the product of the volume of distribution of the serum sodium

concentration times the sodium deficit per liter (ie, 140 minus the serum sodium concentration). The volume of distribution of the serum sodium concentration is the total body water because of rapid osmotic equilibration between the ECF and intracellular fluid. As noted above, the total body water is 75 percent in normal term infants and increases with immaturity. However, most clinicians use a volume of distribution of 60 percent to minimize the likelihood of overly rapid correction.

**Later newborn period** — In contrast, the later onset of hyponatremia is typically caused by negative sodium balance. It is seen most often in preterm infants, who have excessive renal losses [ 25] . Causes include low sodium intake (since the ability to conserve sodium is impaired), diuretic therapy, and mineralocorticoid deficiency caused by congenital adrenal hyperplasia. Patients with the latter disorder, most often caused by 21-hydroxylase deficiency, can present with hyponatremia, hyperkalemia, metabolic acidosis, and shock. ( See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to CYP21A2 (21-hydroxylase) deficiency"). Management includes repletion of the sodium deficit.

Hyponatremia occasionally is factitious. This condition usually is caused by hyperglycemia, which is associated with a decline in serum sodium of 1.6 meq/L for each 100 mg/dL (5.5 mmol/L) increase in glucose concentration. Treatment consists of gradual correction of the hyperglycemia.

**Hypernatremia** — Hypernatremia is defined as a serum sodium concentration of 150 meq/L or more. The disorder is seen most often in ELBW infants. It usually results from high rates of insensible water loss and urine output and is associated with reduced ECF volume. Therapy consists of administration of free water at a rate that repairs the deficit and accounts for maintenance requirements.

The ability to excrete a sodium load is reduced in newborns, especially those born preterm. As a result, excessive sodium administration can result in hypernatremia. One setting in which this can occur is in infants treated with sodium bicarbonate during resuscitation.

In fullterm infants, hypernatremia usually results from fluid loss because of inadequate breastfeeding postpartum. This was illustrated in a retrospective study of 3718 infants (<29 days of age) admitted to a tertiary care center between 1997 and 2001 [ 26] . Two percent of the infants were admitted with a diagnosis of breastfeeding-associated hypernatremic hypovolemia due to inadequate milk intake was 1.9 percent. Three-quarters of these 70 infants had >10 percent weight loss.

In developed countries, most fullterm newborn infants with prompt access to medical care are at low risk for long-term complications. As an example, in a study that compared fullterm newborn infants who were rehospitalized within 15 days of age with dehydration (defined as weight loss  $\geq$  12 percent of birth weight) and hypernatremia to matched controls, there were no difference in neurodevelopmental outcome [ 27] . In this cohort, there were no episodes of shock, gangrene, or respiratory failure. Infants with hypernatremia were more likely to have been exclusively breastfed. These reassuring results are contrasted by a retrospective study from rural Turkey of 116 breastfed infants admitted with severe hypernatremic dehydration [ 28] . In this cohort, the average weight loss from birth was 21.5 percent, and the mean serum sodium upon admission was 166 mEq/L. Six infants died during the hospitalization. Of the 90 infants

who were discharged and had known outcomes, three subsequently died at home and 16 had severe impairment and microcephaly at 12 or more months of age. ( See "Breastfeeding in the perinatal period" section on Weight loss).

An unusual cause of hypernatremia in newborns is diabetes insipidus, which is sometimes associated with hypoxic-ischemic encephalopathy or central nervous system malformations. Affected patients typically manifest polyuria and polydipsia.

Treatment of hypernatremia associated with deficient ECF volume consists of increasing free water administration. Rapid correction of the hypernatremia (generally defined as more than 0.5 meq/L per h) should be avoided since this may result in cerebral edema and seizures [ 29] . If hypernatremia is caused by excessive sodium intake, sodium administration should be reduced and, if necessary, water intake increased.

**Hypokalemia** — Hypokalemia, defined as a serum potassium concentration <3.0 meq/L, usually results from excessive losses of potassium. Contributing factors include chronic diuretic use, renal tubular defects, or significant output from a nasogastric tube or ileostomy.

Hypokalemia usually is asymptomatic. However, it can cause weakness and paralysis, ileus, urinary retention, and conduction defects detected on the electrocardiogram (eg, ST segment depression, low voltage T waves, and U waves).

In most cases, treatment consists of increasing the daily potassium intake by 1 to 2 meq/kg. In severe or symptomatic hypokalemia, KCl (0.5 to 1 meq/kg) is infused intravenously over one hour with continuous ECG monitoring to detect arrhythmias.

**Hyperkalemia** — Hyperkalemia is defined as a serum potassium concentration >6 meq/L. This abnormality may result from multiple causes, including decreased potassium clearance (eg, renal failure, certain forms of congenital adrenal hyperplasia), increased potassium release caused by bleeding or tissue destruction (eg, intraventricular hemorrhage, cephalohematoma, hemolysis, bowel infarction), and inadvertent excessive administration of potassium (eg, supplementation for hypokalemia associated with diuretic therapy).

Hyperkalemia occurs frequently in ELBW infants [ 30-32] . The mechanism may be an exaggerated shift from intracellular to extracellular potassium after birth [ 30] . As noted above, antenatal glucocorticoids may be protective [ 18] .

Depending upon severity and the rate of onset, hyperkalemia can be asymptomatic or so severe as to constitute a medical emergency. Signs include arrhythmias and cardiovascular instability. ECG findings associated with hyperkalemia consist of peaked T waves, flattened P waves, increased PR interval, and widening of the QRS. Bradycardia, supraventricular or ventricular tachycardia, and ventricular fibrillation may occur.

When the diagnosis is made, administration of any fluid that contains potassium should be discontinued immediately. Treatment is aimed at three factors:

- Reversal of the effect of hyperkalemia on the cell membrane by infusion of 10

percent calcium gluconate (100 mg/kg per dose IV).

- Promotion of potassium movement from the ECF into the cells by one of the three following interventions:
  - Administration of intravenous glucose and insulin (0.05 units/kg human regular insulin with 2 ml/kg 10 percent dextrose in water), followed by a continuous infusion of insulin (0.1 units/kg per hour with 2 to 4 ml/kg per hour 10 percent dextrose in water).
  - Administration of intravenous sodium bicarbonate (in a dose of 1 to 2 milliequivalent per kilogram over 30 to 60 minutes).
  - Administration of beta agonists, such as albuterol, via nebulization.
- Increasing urinary excretion with intravenous administration of furosemide (1 mg/kg per dose) in infants with adequate renal function.

Peritoneal dialysis can be considered in infants with oliguria or anuria.

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## GRAPHICS

### Fluid requirements (mL/kg per day) in newborns

Birth weight (g)	Days 1-2	Day 3	> Day 3
<1000	90-120	140	150
1001-1250	80-100	120	150
1251-1500	80	100	150
1501-2000	65-80	100	150
>2000	65-80	100	150

These are intended as guidelines and should be adjusted according to the infant's clinical status. *Courtesy of Peter M Haney, MD*

### Normal water balance

Source	Water intake, mL/day		Source	Water output, mL/day	
	Obligatory	Elective		Obligatory	Elective
Ingested water	400	1000	Urine	500	1000
Water content of food	850		Skin	500	
Water of oxidation	350		Resp tract	400	
			Stool	200	
Total	1600	1000		1600	1000

Typical daily water balance in a normal human, assuming a low rate of sweat production. When exercise and/or hot weather stimulates sweat production, water losses from the skin can increase markedly, occasionally exceeding 5 L/day. In this setting, the ensuing rise in plasma osmolality stimulates thirst, resulting in an appropriate increase in water intake.

## **Clinical assessment and diagnosis of hypovolemia (dehydration) in children**

**INTRODUCTION** — Fluid therapy is intended to maintain the normal volume and composition of body fluids and, if needed, to correct any existing abnormalities. In children, the most common abnormality is hypovolemia.

Volume depletion occurs when fluid is lost from the extracellular space at a rate that exceeds intake. The most common sites for extracellular fluid loss are:

- Gastrointestinal tract (eg, diarrhea, vomiting, bleeding)
- Skin (eg, fever, burns)
- Urine (eg, glucosuria, diuretic therapy, diabetes insipidus)

In addition, hypovolemia can result from prolonged inadequate intake without excessive losses.

Children are at increased risk for hypovolemia for the following reasons:

- There is a higher frequency of gastroenteritis (diarrhea and vomiting) in children compared to adults.
- Children, especially young children, have a higher surface area-to-volume ratio with proportionally higher insensible losses that are accentuated in disease states (eg, fever or burns).
- Young children are unable to communicate their need for fluids or cannot independently access fluids to replenish volume losses.

Volume depletion reduces the effective circulating volume (ECV), compromising tissue and organ perfusion. If severe hypovolemia is not corrected in a timely fashion, ischemic end-organ damage occurs, leading to serious morbidity and, in patients in shock, death. ( See "Hypovolemic shock in children: Initial evaluation and management").

The clinical assessment and diagnosis of hypovolemia will be reviewed here. Repletion therapy for hypovolemia is discussed elsewhere. ( See "Treatment of hypovolemia (dehydration) in children").

**VOLUME DEPLETION VERSUS DEHYDRATION** — The terms volume depletion (hypovolemia) and dehydration are often used interchangeably. However, these terms differentiate physiologic conditions resulting from different types of fluid loss [ 1] . ( See "Dehydration is not synonymous with hypovolemia").

- Volume depletion refers to any condition in which the effective circulating volume is reduced. It can be produced by salt and water loss (as with vomiting, diarrhea, diuretics, bleeding, or third space sequestration) or by water loss alone (as with insensible water losses or diabetes insipidus).

- Dehydration refers to water loss alone. The clinical manifestation of dehydration is often hypernatremia. The elevation in serum sodium concentration, and therefore serum osmolality, pulls water out of the cells into the extracellular fluid ( see "Type of fluid lost" below).

However, much of the clinical literature does not differentiate between the two terms and uses them interchangeably. Thus, we will follow this convention and use the terms hypovolemia, volume depletion, and dehydration interchangeably as referring to all types of fluid deficits.

**CLINICAL ASSESSMENT** — When assessing a child with hypovolemia, the clinician needs to address two issues:

- The degree of extracellular fluid volume depletion
- The type of fluid lost (extracellular fluid or both intracellular and extracellular fluid)

**Degree of dehydration** — Fluid repletion guidelines for children with gastroenteritis by the American Academy of Pediatrics, Centers for Disease Control, and the World Health Organization are based upon the degree of volume depletion. As a result, it is important to be as accurate as possible when assessing the degree of dehydration [ 2,3] . Severe hypovolemia requires rapid isotonic fluid resuscitation, although oral rehydration may be sufficient for mild to moderate hypovolemia. ( See "Treatment of hypovolemia (dehydration) in children" and see "Prevention and treatment of viral gastroenteritis in children").

Volume depletion is most objectively measured as a change in weight from baseline. Acute loss of body weight reflects the loss of fluid, not lean body mass; thus, a 2 kg weight loss should reflect the loss of two liters of fluid.

In most cases, however, a previous recent weight is not available. As a result, a number of findings on physical examination as well as pertinent history are used to help assess the severity of hypovolemia. These include the pulse, blood pressure, skin turgor, systemic signs, and changes in urine output ( show table 1).

- Mild dehydration (3 to 5 percent volume loss) — A history of fluid losses may be the sole finding as clinical signs may be absent or minimal. Such patients may have a reduction in urine output.
- Moderate dehydration (6 to 9 percent volume loss) — Signs and symptoms are now apparent and can include the following: tachycardia, a fall in blood pressure especially with orthostatic changes, decreased skin turgor, dry mucous membranes, irritability, decreased peripheral perfusion with a delay in capillary refill between two and three seconds, and deep respirations with or without an increase in respiratory rate. There may be a history of reduction in urine output and decreased tearing and, in infants, an open fontanelle will be sunken on physical examination.

In a systematic review of the literature, the most useful clinical signs that predicted 5 percent hypovolemia were delayed capillary refill time, reduced skin turgor, and deep respirations with or without an increase in rate [ 4] . A combination of signs and symptoms was better than an individual finding at predicting hypovolemia.

- Severe dehydration ( $\geq 10$  percent volume loss) — Such patients typically have a near-shock presentation as manifested by hypotension, decreased peripheral perfusion with a capillary refill of greater than three seconds, cool and mottled extremities, lethargy, and deep respirations with an increase in rate. Severe hypovolemia requires immediate attention with aggressive isotonic fluid resuscitation to restore the ECV and prevent ischemic tissue damage.

**Type of fluid lost** — The above clinical assessment for volume depletion is derived from children with mainly extracellular fluid losses as is seen with gastroenteritis. In children with diarrheal illness, the fluid loss is isosmotic and is mostly from the extracellular space. The diarrheal fluid has a sodium plus potassium concentration between 40 and 120 meq/L [ 5-7] ; organic solutes such as urea and fermentation products make up the remaining osmoles.

In contrast to diarrheal fluid loss, insensible losses and losses in states of urinary concentrating defects, such as diabetes insipidus, represent water loss alone and, as noted above, result in hypernatremia. The associated increase in serum osmolality pulls water out of the cells, which minimizes initially the degree of extracellular fluid volume loss.

These considerations also apply to children with diabetic ketoacidosis in whom hyperglycemia causes a hyperosmolar state that pulls water out of the cells, minimizing the degree of hypovolemia. ( See "Clinical features and diagnosis of diabetic ketoacidosis in children").

**LABORATORY TESTING** — Laboratory testing can confirm the presence of hypovolemia (low spot urine sodium concentration  $\leq 25$  mEq/L) and can detect associated electrolyte and acid-base abnormalities. Measurement of serum electrolytes is typically limited to children who require intravenous fluid repletion. These children are more severely volume depleted and are therefore at greater risk for electrolyte abnormalities.

Laboratory testing is less useful for assessing the degree of volume depletion. This was illustrated in the systematic review of the literature cited above and a prospective study of children who required intravenous fluid for volume repletion [ 4,8] . The following findings were noted:

- Serum bicarbonate was the most useful laboratory test to assess dehydration. A value below 17 meq/L differentiated children with moderate and severe hypovolemia from those with mild hypovolemia [ 4,8] .
- The blood urea nitrogen (BUN) rose with increasing severity of hypovolemia, reflecting the decline in glomerular filtration rate and increase in sodium and water reabsorption, but the sensitivity was not sufficient to be clinically useful. At least two other factors also contribute to the limited utility of the BUN: it can

be increased by other factors such as bleeding or tissue breakdown; and the rise can be minimized by a concurrent decrease in protein intake.

**Serum sodium** — The serum sodium concentration is determined by the ratio between total body solutes (primarily sodium salts in the extracellular fluid and potassium salts in the intracellular fluid) and the total body water ( show figure 1) [ 5,9] . Thus, the serum sodium concentration in a child with hypovolemia varies with the relative loss of solute to water. Changes in the serum sodium concentration play an important role in deciding the type and speed of fluid repletion therapy, especially in children with severe hyponatremia or hypernatremia. ( See "Treatment of hypovolemia (dehydration) in children").

- **Hyponatremia** — The development of hyponatremia (serum sodium less than 130 meq/L) reflects net solute loss in excess of water loss. This does not occur directly, as fluid losses such as diarrhea are not hypertonic to plasma. Rather, solute and water are lost in proportion, but water is taken in and retained (because hypovolemia-induced secretion of antidiuretic hormone limits water excretion), lowering the serum sodium concentration (see below).
- **Isonatremia** — A serum sodium between 130 and 150 meq/L reflects isonatremia. In this setting, solute is lost in proportion to water loss.
- **Hypernatremia** — The development of hypernatremia (serum sodium greater than 150 meq/L) reflects water loss in excess of solute loss.

**Effect of fluid loss** — The direct effect of fluid loss on the serum sodium varies with the sum of the sodium and potassium concentrations [ 5] . ( See "Chapter 7A: Exchange of water between the cells and ECF", section on Determinants of the plasma sodium concentration). The composition of diarrheal fluid can be used to illustrate this point:

- Patients with secretory diarrheas (eg, as a result of *Vibrio cholerae* or enterotoxigenic *Escherichia coli*) have a sodium plus potassium concentration in the diarrheal fluid that is similar to that in the plasma [ 6,10] . Loss of this fluid will lead to volume and potassium depletion, but will not directly affect the serum sodium concentration.
- In contrast, the sodium plus potassium concentration is typically between 40 and 100 meq/L in viral gastroenteritis, such as rotavirus; organic solutes, which do not affect the serum sodium concentration, make up the remaining osmoles [ 6,10] . Loss of this relatively dilute fluid will tend to induce hypernatremia if there is concomitant inadequate fluid intake [ 5] . This entity has been called hypernatremic (hypertonic) dehydration [ 11,12] .

Fever and/or tachypnea often accompany gastroenteritis and other diseases associated with hypovolemia, resulting in increased insensible water losses, especially in young children. Water is again lost in excess of solute, contributing to an increase in sodium concentration. A similar effect is seen with dilute urinary losses in children with diabetes insipidus.

**Secretion of ADH** — Although the composition of the fluid that is lost is the initial factor that affects the serum sodium, subsequent ADH release also may be important. The secretion of ADH, which promotes the retention of free water in the distal nephron, is stimulated by hyperosmolality and moderate to severe hypovolemia ( show figure 2). In children with hypernatremia, this decrease in urinary water loss, because of ADH secretion and avid water reabsorption by the kidney, tends to prevent a further increase in serum sodium. In children with hypovolemia who are not hypernatremic, ADH-induced decreases in water loss can lead to hyponatremia if water intake is maintained. ( See "Physiologic regulation of effective circulating volume and plasma osmolality").

**Prior fluid replacement** — Prior to seeking medical treatment, replacement therapy with varying concentrations of sodium may have been administered to the patient. Most often, fluid replacement is hypotonic and will lower sodium concentration.

In the United States, rotavirus gastroenteritis is the major cause of hospitalization for treatment of hypovolemia resulting from diarrhea. On admission patients most likely will present with isonatremic (isotonic) hypovolemia, but up to 25 percent of patients with rotavirus will have hypernatremic dehydration [ 13,14] .

**Serum potassium** — Either hypokalemia or hyperkalemia can occur in hypovolemic patients. Hypokalemia is more common as children with gastroenteritis lose potassium in diarrheal stool. However, the serum potassium concentration may be higher than expected or even elevated if a marked acidosis is present. In this setting, excess hydrogen ions enter the cells to be buffered, and electroneutrality is maintained in part by potassium movement from the cells into the extracellular fluid [ 15] . This effect of pH does not appear to be important with lactic acidosis or ketoacidosis [ 16] . Hyperkalemia can occur in these disorders but is because of other factors. ( See "Potassium balance in acid-base disorders").

These effects are reversed with correction of the acidosis, leading to a fall in the serum potassium concentration to a degree consistent with the true potassium deficit. In children with borderline potassium reserves, this fall can result in hypokalemic symptoms such as muscle weakness, intestinal ileus, flattening of the T waves and the development of U waves on electrocardiogram, and potentially lethal arrhythmias [ 17] . Thus, physicians managing children with significant hypovolemia must be prepared to recognize and treat acute hypokalemia, especially if the child's serum potassium is low, borderline low, or depressed in a child with acidosis.

**Serum bicarbonate** — As mentioned above, a low serum bicarbonate concentration (less than 17 meq/L) may be useful in assessing the degree of hypovolemia [ 4,8] . The low serum bicarbonate in hypovolemia almost always represents metabolic acidosis. In children with gastroenteritis, the acidosis is because of the loss of bicarbonate in the stool.

Other causes of acidosis associated with diarrheal losses include:

- Increased acid production from shock (lactic acidosis) or from enhanced fat breakdown (eg, starvation or fasting ketosis). ( See "Alcoholic and fasting ketoacidosis").
- Decreased renal acid excretion caused by the reduction in renal perfusion.

The acid-base status will be different in children in whom vomiting is predominant. In this setting, the loss of hydrochloric acid in gastric secretions will lead to metabolic alkalosis and an elevated serum bicarbonate.

**Urine sodium** — The response of the kidney to volume depletion is to conserve sodium and water to restore the ECV. The urine sodium should be less than 25 meq/L and may actually be non-detectable.

Values higher than 25 meq/L do not necessarily exclude hypovolemia, as there also may be a high rate of water reabsorption. In this setting, the rates of sodium excretion and urine volume are low, but the urine sodium concentration is higher than expected as a result of concentration. The effect of differences in water reabsorption can be eliminated by calculating the fractional excretion of sodium (FENa) ( show calculator 1 or, for standard units, show calculator 2). The FENa is most useful in patients with an increasing serum creatinine and concern regarding an evolving acute renal failure. It is fraught with potential error in other patients because the value for FENa that defines hypovolemia varies inversely with the glomerular filtration rate. This issue is discussed in detail separately. ( See "Fractional excretion of sodium in acute kidney injury (acute renal failure)").

**Urine osmolality and specific gravity** — In hypovolemic states, the urine is concentrated with an osmolality exceeding 450 mosmol/kg. However, this response may not be seen if concentrating ability is impaired by renal disease, an osmotic diuresis, the administration of diuretics, or central or nephrogenic diabetes insipidus. Thus, a high urine osmolality is consistent with hypovolemia, but a relatively isosmotic value does not exclude hypovolemia.

Measuring the specific gravity also can assess urinary concentration. This test, however, is less accurate than the osmolality, as it is dependent upon the size as well as the number of solute particles in the urine. As a result, it should be used only if the osmolality cannot be measured; a value above 1.015 is suggestive of a concentrated urine, as is usually seen with hypovolemia. This does not apply to diabetic ketoacidosis, as glucose raises the specific gravity without affecting the urine osmolality. ( See "Urine osmolality vs specific gravity").

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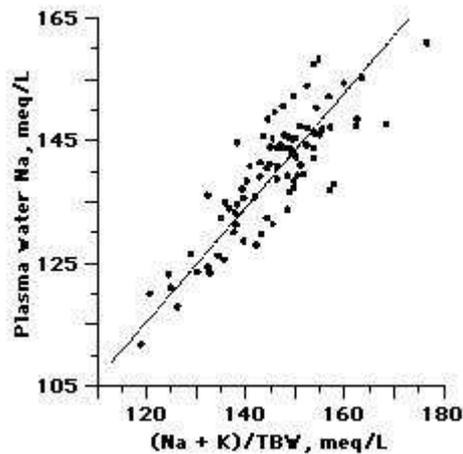
## GRAPHICS

### Physical findings of volume depletion in infants and children

Finding	Mild (3-5 percent)	Moderate (6-9 percent)	Severe ( ≥10 percent)
Pulse	Full, normal rate	Rapid	Rapid and weak
Systolic pressure	Normal	Normal to low	Low
Respirations	Normal	Deep, rate may be increased	Deep, tachypnea
Buccal	Tacky or	Dry	Parched

mucosa	slightly dry		
Anterior fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin turgor	Normal	Reduced	Tenting
Skin	Normal	Cool	Cool, mottled, acrocyanosis
Urine output	Normal or mildly reduced	Markedly reduced	Anuria
Systemic signs	Increased thirst	Listlessness, irritability	Grunting, lethargy, coma

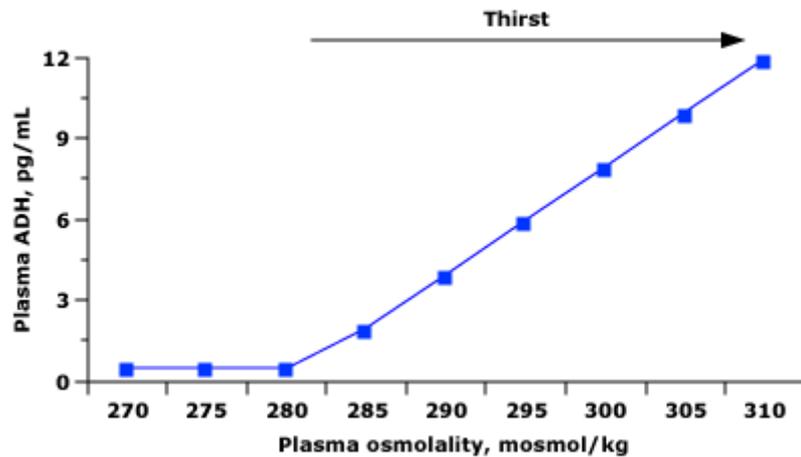
### Determinants of the plasma sodium concentration



Among both normal subjects and patients with a variety of diseases, there is a very close correlation between the plasma water sodium concentration and the ratio of total body exchangeable solutes (primarily Na salts in the extracellular fluid + K salts in the cells) to the total body water (TBW). The exchangeable portion is used since about 30 percent of the body Na and a smaller fraction of the body K are bound in areas such as bone where they are "nonexchangeable" and therefore osmotically inactive. *Adapted from Edelman, I, Leibman, J, O'Meara, MP, Birkenfeld, L, J Clin Invest 1958; 37:1236, by copyright permission of the American Society for Clinical Investigation.*

### Osmotic regulation of ADH release and thirst

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Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH. *Data from Robertson, GL, Aycinena, P, Zerbe, RL, Am J Med 1982; 72:339.*

The fractional excretion of sodium ( **FENa**) can be calculated by entering the values from simultaneously obtained urine and blood samples. (See "Fractional excretion of sodium in acute renal failure").

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## **Evaluation of congenital anomalies of the kidney and urinary tract**

**INTRODUCTION** — Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period [ 1] . Routine antenatal ultrasonography during pregnancy detects the majority of CAKUT.

Antenatal screening for CAKUT and the postnatal evaluation of infants diagnosed prenatally with CAKUT are discussed here.

**ANTENATAL SCREENING** — The majority of renal malformations are detected antenatally because of the widespread use and sensitivity of fetal ultrasonography. In 2002, a prenatal ultrasound was performed in about two-thirds of all live births in the United States. The frequency of CAKUT as detected sonographically in unselected populations has been reported to be between 0.1 to 0.7 percent [ 2-4] .

In general, the optimal timing recommended for a screening antenatal ultrasound is between 16 to 20 weeks of gestation because of the following factors at this gestational age:

- There is good visualization of anatomy with a high sensitivity in detecting anomalies.
- It is early enough in the pregnancy to allow completion of prenatal diagnostic procedures (eg, fetal karyotype, additional imaging studies) while legal termination of pregnancy is possible, if desired.

( See "Routine prenatal ultrasonography as a screening tool").

**Fetal kidney** — Between the 12th and 15th week of gestation, the fetal kidney can be detected by transabdominal ultrasonography [ 1] . On transverse ultrasound images, normal fetal kidneys are hypoechoic ovoid masses located in the renal fossa on either side of the spine corresponding to the level of the second lumbar vertebrae. The renal cortex and medulla are distinctly demonstrated by ultrasound by the 20th to 25th week of gestation. Fetal renal length based upon gestational age is a marker of renal growth and is illustrated in the table ( show table 1) [ 5] .

Normally, the fetal ureters are not seen on ultrasonography. However, if they are visualized, it may be indicative of ureteric or bladder obstruction, or vesicoureteral reflux (VUR).

The urine-filled bladder is normally identified at 13 to 15 weeks gestation [ 6] . Urine in the bladder suggests at least one functioning kidney. The normal bladder wall is normally thin. If the bladder wall is thick, urethral obstruction such as posterior urethral valves in a male fetus may be present.

The sensitivity of detecting renal malformations by antenatal ultrasonography depends upon the gestational age and the skill of the ultrasonographer. In one study, the sensitivity of antenatal screening for renal malformations was reported as 82 percent at a mean gestational age of 23 weeks [ 7] . ( See "Indications for diagnostic obstetrical ultrasound examination", section on Congenital anomalies).

**Amniotic fluid** — Assessment of amniotic fluid volume and analysis of biochemical markers are used to evaluate fetal renal function.

**Volume** — Although, fetal urine production begins at nine weeks of gestation, its contribution to amniotic fluid volume becomes significant at the start of the second trimester. By 20 weeks gestation, fetal urine accounts for more than 90 percent of the amniotic fluid volume [ 7] . Thus, a decrease in amniotic fluid volume (oligohydramnios) at or beyond the 20th week of gestation is an excellent predictor of abnormal fetal renal function.

Severe oligohydramnios due to CAKUT either involves both kidneys or occurs in a solitary kidney in the fetus. Bilateral renal agenesis or severe dysgenesis, bilateral ureteric obstruction, or obstruction of the bladder outlet or urethra, can result in severe oligohydramnios as early as 18 weeks gestation. Because an adequate amniotic fluid volume is critical for lung development, severe oligohydramnios due to abnormal fetal renal function in the second trimester can result in lung hypoplasia, a potentially fatal disorder [ 8] . In its most severe form, this sequence of events results in Potter's syndrome, which consists of a typical facial appearance characterized by pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears and flattened nose, decreased fetal movement, musculoskeletal features including clubfoot and clubhand, hip dislocation and joint contractures, and pulmonary hypoplasia ( show figure 1).

The assessment of amniotic fluid volume is discussed in greater detail separately. ( See "Assessment of amniotic fluid volume").

**Analysis** — Although oligohydramnios is the most reliable predictor of abnormal fetal renal function, its absence does not assure normal fetal renal function. Because amniotic fluid is predominantly composed of fetal urine, measurement of biochemical markers contained in amniotic fluid (fetal urine) can be used to assess fetal renal function.

With increasing gestational age, renal tubular resorptive function increases. As a result, the urinary levels of sodium and beta-2-microglobulin decrease with increasing gestational age, while urine osmolality increases [ 9,10] . Impaired resorption is seen in fetuses with bilateral renal dysplasia or severe bilateral obstructive uropathy resulting in abnormal urinary levels of electrolytes, beta-2-microglobulin, and osmolality [ 11] .

In general, high urinary electrolyte excretion, sodium and chloride concentration greater than 90 meq/L (90 mmol/L), and urinary osmolality less than 210 mosmol/kg H<sub>2</sub>O (210 mmol/kg H<sub>2</sub>O) in the amniotic fluid are indicative of fetal renal tubular impairment and poor renal prognosis [ 12] . In addition, urinary beta-2- microglobulin levels >6 mg/L are predictive of severe renal damage with a sensitivity and specificity of 80 and 71 percent, respectively [ 13] .

Tests to assess fetal glomerular function include fetal serum measurement of cystatin C and beta-2-microglobulin [ 14] . However, these tests are not used in clinical practice because of technical difficulties in obtaining fetal blood.

In addition, amniocentesis can be used to detect chromosomal abnormalities often associated with renal defects such as trisomy 18 [ 15] . ( See "Amniocentesis: Technique and complications").

**Management** — Counseling of families with fetuses with CAKUT should be universally available. If the fetal prognosis is poor, as determined by severe bilateral disease, bilateral renal agenesis, oligohydramnios, or unfavorable amniotic fluid analysis, legal termination, if possible, can be offered.

In all other cases, continued counseling throughout the pregnancy including discussion on postnatal management is required. In particular, discussion with parents regarding their wishes on the level of support given to offspring with severe oligohydramnios, who are at risk for lung hypoplasia that may be incompatible with life, is helpful in establishing guidelines for initial postnatal care.

**In utero intervention** — Intervening in pregnancy to attempt definitive or temporary correction of fetal renal anomalies would be reasonable if one could prevent the development of renal dysplasia, renal scarring, chronic renal failure, or the occurrence of pulmonary hypoplasia [ 16-19] . Although there have been case series of antenatal surgery in fetuses with severe hydronephrosis and oligohydramnios, this intervention has not been shown to improve renal outcome. These procedures may increase the amount of amniotic fluid, thus potentially improving lung development and survival rate. In these rare cases, the procedure should only be performed in select centers with expertise and in infants with severe bilateral hydronephrosis, absent of severe renal parenchymal or cystic disease, favorable urinary electrolyte levels and osmolality, and normal karyotype. ( See "Overview of antenatal hydronephrosis").

## **POSTNATAL EVALUATION**

**History and physical examination** — After delivery, a detailed history and careful physical examination should be performed in all infants with an antenatally detected renal malformation. The examination should include the following:

- Pulmonary evaluation especially in infants with severe oligohydramnios who are at risk for lung hypoplasia. In these severely affected children, decisions on the use of intensive supportive care are often made in the delivery room. If at all possible, prior discussion with the family regarding management decisions is helpful in establishing guidelines for initial postnatal care.
- Examination of the abdomen to detect the presence of a mass that could represent an enlarged kidney due to obstructive uropathy or multicystic dysplastic kidney (MCDK).
- A palpable bladder in a male infant, especially after voiding, may suggest posterior urethral valves.
- A male infant with prune belly syndrome will have deficient abdominal wall musculature and undescended testes. The presence of associated anomalies should be investigated. ( See "Examination of the newborn").
- The presence of outer ear abnormalities are associated with an increased risk of congenital anomalies of the kidney and urinary tract (CAKUT). ( See "Congenital anomalies of the ear", section on Association with renal anomalies").

- A single umbilical artery is associated with an increased risk of CAKUT, particularly vesicoureteral reflux. ( See "Examination of the newborn", section on Single umbilical artery).

**Timing of postnatal renal studies** — Postnatal evaluation by ultrasonography is performed within the first 24 hours of life for infants with bilateral involvement, a solitary affected kidney, and/or a history of oligohydramnios because they are at increased risk for a serious renal anomaly that may be amenable to intervention. As an example, a distended bladder with thickened bladder wall and bilateral hydronephrosis may be caused by posterior urethral valves (PUV) that requires surgical intervention.

In general, conditions that have unilateral involvement do not need immediate attention. Renal ultrasonography is recommended after the infant returns to birth weight (after 48 hours of age and within the first week of life) to ensure volume repletion and increased urine output as renal plasma flow and glomerular filtration rate rise in the first 48 hours of life [ 20] . Thus, in an infant with hydronephrosis, the level of severity might be underestimated if ultrasonography is performed before 48 hours of life.

**Other diagnostic tests** — Diagnostic testing includes measurement of serum creatinine to assess renal function and other radiologic tests that can be useful in determining underlying renal pathology, renal function, and the presence of other urological anomalies.

**Serum creatinine** — Estimation of the renal function by measurement of the serum creatinine concentration is used clinically to assess the presence and extent of renal impairment and to follow the infant's renal function. Measurement of creatinine should be considered when there is bilateral renal disease or an affected solitary kidney.

The serum creatinine concentration at birth is similar to that in the mother (usually  $\leq$  1.0 mg/dL [88 micromol/L]). It declines to normal values (serum creatinine 0.3 to 0.5 mg/dL [27 to 44 micromol/L]) in approximately one week in term infants and two to three weeks in preterm infants. Serum creatinine should be measured after the first 24 hours to avoid overestimation of creatinine that may be high and reflective of maternal creatinine values. ( See "Acute renal failure in the newborn", section on serum creatinine).

**Voiding cystourethrography** — Voiding cystourethrography (VCUG) is the definitive method for assessment of the lower urinary tract. It requires urethral catheterization and injection of a contrast agent. Indications include any suspicion of a thick-walled bladder, ureteric dilatation, hydronephrosis, and in male infants, any urethral pathology (eg, posterior urethral valves).

VCUG is the definitive study to demonstrate vesicoureteral reflux (VUR), which often accompanies other CAKUT (eg, multicystic dysplastic, hypoplastic, or ectopic kidney). VUR is one of the most common causes of antenatal hydronephrosis and infants with hydronephrosis (without any other apparent cause) should undergo VCUG. Infants who are at risk for VUR should be given prophylactic antibiotics. Infants with VUR demonstrated by VCUG are continued on prophylactic antibiotics. ( See "Postnatal management of antenatal hydronephrosis" and see "Management of vesicoureteral reflux").

**Dynamic renal scan** — Dynamic radionuclide scans assess renal excretory function and utilize either technetium 99mTc-diethylenetriamine pentaacetic acid (DTPA) or 99mTc-mercaptotriglycylglycine (MAG-3) as radiotracers. MAG-3 is recommended over DTPA [ 21] . MAG-3 has a lower volume of distribution than DTPA because unlike DTPA it is not distributed outside the intravascular space and it has a higher renal extraction rate with a higher signal to noise ratio [ 21] .

In the authors' center, MAG-3 is used for investigation of urinary tract obstruction, particularly in neonates because DTPA scans are characterized by poor visualization of the kidneys and a relatively flat renal curve. Better-quality images are only achieved at the end of the neonatal period as glomerular filtration increases.

The radiotracer is injected intravenously, taken up by the nephrons, and is excreted primarily by glomerular filtration and proximal tubule secretion into the tubular lumen and subsequently into the bladder.

Dynamic renal scans are used to differentiate between obstructive versus nonobstructive causes of hydronephrosis. ( See "Postnatal management of antenatal hydronephrosis", section on Diuretic renography).

**Static renal scan** — Static radionuclide scan is most useful for detection of focal renal parenchymal abnormalities and the differential assessment of renal function between the two kidneys. 99mTc– dimercaptosuccinic acid (DMSA) is used as the radiotracer. Following intravenous injection, DMSA is taken up by proximal tubular cells with only a minimal amount excreted in the urine, so the tracer accumulates over several hours within the tubule, providing a static image of functioning nephrons. There is no minimum age at which a DMSA scan can be performed. However, the quality of both dynamic and static radionuclide scans improve with renal maturity.

DMSA renal scan is used to assess whether a suspected renal lesion contains normal-functioning nephrons and/or the differential function of the two kidneys and also to detect renal scarring.

**Serial ultrasound** — Serial ultrasounds are used to assess compensatory renal growth of unaffected kidneys in patients with unilateral CAKUT. In addition, serial ultrasounds are used to monitor for progressive hydronephrosis in patients with mild/moderate obstructive uropathy or changes in the affected kidneys (eg, size of multicystic dysplastic kidney).

**SUMMARY** — Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period.

- Routine antenatal ultrasonography during pregnancy detects CAKUT in most affected patients.
- The fetal kidney can be detected by the 12th and 15th week of gestation, however, the renal cortex and medulla are not distinctly differentiated from one another until the 20th to 25th week of gestation. Fetal renal length based upon gestational age is a marker of renal growth ( show table 1). ( See "Fetal kidney" above).

- By 20 weeks gestation, fetal urine accounts for more than 90 percent of the amniotic volume. A decrease in amniotic volume (oligohydramnios) at or beyond 20 weeks gestation is an excellent predictor of abnormal fetal renal function and indicates bilateral fetal renal dysfunction or, rarely a poorly functioning solitary kidney. ( See "Volume" above).
- Biochemical analysis of amniotic fluid is useful in assessing fetal renal function. Sodium and chloride concentration  $>90$  meq/L (90 mmol/L), and urinary osmolality less than 210 mosmol/kg H<sub>2</sub>O (210 mmol/kg H<sub>2</sub>O) in the amniotic fluid are indicative of poor fetal renal prognosis. Amniotic beta-2-microglobulin concentration  $\geq 6$  mg/L is also associated with severe renal damage. ( See "Analysis" above).
- Counseling should be available to all families with fetuses who have a CAKUT. If the fetal prognosis is poor, legal termination, if available, can be offered. In all other cases, continued counseling including discussion on postnatal management is required. ( See "Management" above).
- Initial postnatal evaluation by ultrasonography is performed within the first 24 hours of life for infants with bilateral involvement, a solitary affected kidney, and/or a history of oligohydramnios. Infants with unilateral involvement should be evaluated after 48 hours of life. ( See "Timing of postnatal renal studies" above).
- Further postnatal diagnostic testing includes measurement of serum creatinine to assess renal function in cases of bilateral kidney disease or in an affected solitary kidney, and the following radiological studies:
  - Voiding cystourethrography (VCUG) is indicated in patients with hydronephrosis and in male infants suspected to have urethral pathology (eg, posterior urethral valves). It detects vesicoureteral reflux and abnormalities of the male urethra. ( See "Postnatal management of antenatal hydronephrosis").
  - <sup>99m</sup>Tc-mercaptotriglycylglycine (MAG-3) and technetium <sup>99m</sup>Tc-diethylenetriamine pentaacetic acid (DTPA) renal scan are used to differentiate between obstructive versus nonobstructive causes of hydronephrosis.
  - <sup>99m</sup>Tc- dimercaptosuccinic acid (DMSA) is used to assess whether a suspected renal lesion contains normally functioning nephrons and/or the differential function between the two kidneys, or detect renal scarring.
  - Serial ultrasounds are used to monitor compensatory renal growth of unaffected kidneys in patients with unilateral CAKUT, progressive hydronephrosis in patients with mild/moderate obstructive uropathy, or changes in the affected kidneys( See "Other diagnostic tests" above).

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### GRAPHICS

#### Normal fetal renal lengths

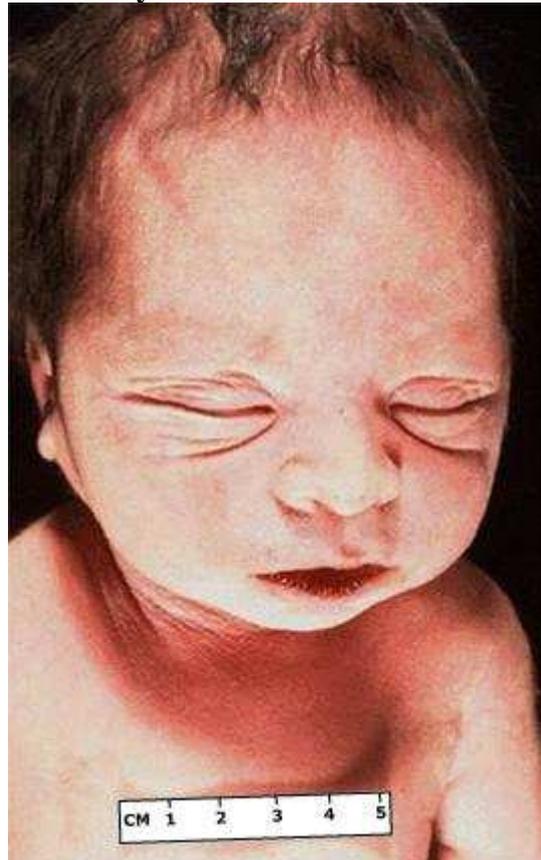
<b>Gestational age, weeks</b>	<b>Mean kidney length, cm</b>	<b>95% CI, cm</b>
18	2.2	1.6 - 2.8
19	2.3	1.5 - 3.1
20	2.6	1.8 - 3.4
21	2.7	2.1 - 3.2
22	2.7	2.0 - 3.4
23	3.0	2.2 - 3.7
24	3.1	1.9 - 4.4
25	3.3	2.5 - 4.2

26	3.4	2.4 - 4.4
27	3.5	2.7 - 4.4
28	3.4	2.6 - 4.2
29	3.6	2.3 - 4.8
30	3.8	2.9 - 4.6
31	3.7	2.8 - 4.6
32	4.1	3.1 - 5.1
33	4.0	3.3 - 4.7
34	4.2	3.3 - 5.0
35	4.2	3.2 - 5.2
36	4.2	3.3 - 5.0
37	4.2	3.3 - 5.1
38	4.4	3.2 - 5.6
39	4.2	3.5 - 4.8
40	4.3	3.2 - 5.3
41	4.5	3.9 - 5.1

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*HL, Cooper, J, Eisenberg, P, et al. Normal length of fetal kidneys: sonographic study in 397 obstetric patients. AJR Am J Roentgenol 1991; 157:545. Copyright © 1991 The American Journal of Roentgenology.*

**Facial appearance of a patient with Potter's syndrome**



Typical facial appearance observed in Potter's syndrome. Characteristic abnormalities include pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears, and flattened nose.

## **LES NEPHROPATHIES HEREDITAIRES**

### **Syndrome d'Alport**

La plus commune des néphrites héréditaires

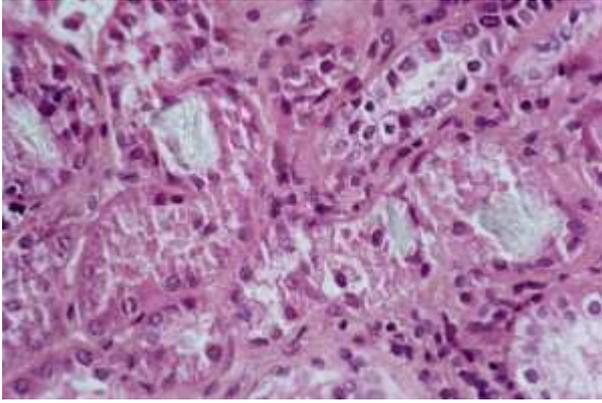
- Mutation portant sur la synthèse de la chaîne alpha du collagène de type IV, composant de la membrane basale glomérulaire, mais également au niveau de l'oreille;interne et de l'oeil (cristallin).
- Lié à l'X ==> hommes malades, femmes peu atteintes.
- Si pas d'antécédents familiaux, sans doute néo-mutation spontanée.
- Sclérose glomérulaire progressive
- Hématurie asymptomatique ou épisodes d'hématurie macroscopique dès les premières années de vie
- Protéinurie plus tardive.
- Surdit  progressive (10-25 ans)
- Déformation du cristallin
- Insuffisance rénale à l'âge adulte chez l'homme (20-40 ans)

### **Hyperoxalurie Primaire**

- Déficit enzymatique hépatique (glyoxylate alanine transférase) responsable de la formation excessive d'oxalate (voie métabolique alterne), excrété par les urines. Les cristaux d'oxalate s'accumulent dans le parenchyme rénal et provoquent uen néphrite tubulo interstitielle chronique. Au stade d'insuffisance rénale, les cristaux se déposent dans tout de l'organisme.
- Autosomial récessif (<==> consanguinité parentale)
- Symptômes apparaissent dans les premières années
- Polyurie, polydipsie, retard de croissance
- Lithiases urinaires ou néphrocalcinose diffuse
- Crises de coliques néphrétiques.
- Insuffisance rénale terminale avant 15 ans
- Accumulation ensuite généralisée d'oxalate: coeur, rétine, os, artères...
- Diagnostic par dosage de l'enzyme sur le foie et recherche mutations
- Diagnostice anténatal possible si 2 allèles mutants identifiés

### **Traitement :**

- Hyperhydratation, alcalinisation des urines (citrate de Na, 150 mg/kg). Réduction calciurie
- Certaines formes (~ 50%) répondent au moins partiellement à la pyridoxine, co-facteur de la GAT (activité résiduelle)
- Transplantation hépatique préemptive ou hépatique et rénale si IR terminale



Cristaux d'oxalate dans le parenchyme



rénal



Ultrasons et AAB: précipitations oxalates dans le rein



### **Acidose Tubulaire de de Toni Debré Fanconi.**

- Dès les premiers mois de vie
- Tubulopathie complexe. Néphrite interstitielle.
- Fuite urinaire de glucose, acides aminés, phosphore, potassium, calcium, ac urique...
- Polyurie, Polydipsie
- Retard de croissance
- Déshydratation hyponatrémiques
- Acidose chronique tubulaire
- Rachitisme vitamino résistant
- Insuffisance rénale progressive dans l'enfance avant la puberté

Le syndrome de Toni Debré Fanconi a plusieurs étiologies dont::

#### **- Néphronophtise**

- Autosomique récessif
- Acidose tubulaire
- Dysplasie multikystique
- Début insidieux
- Polyurie, polydipsie, retard de croissance
- Insuffisance rénale progressive

#### **- Cystinose**

- Autosomique récessif
- Cheveux blonds très clairs et pâleur des téguments (cfr photo)
- Polyurie, Polydipsie, Retard de croissance
- Acidose tubulaire majeure, polyurie, polydipsie, rachitisme vitamino résistant, protéinurie tubulaire, insuffisance rénale
- Hépatomégalie liée à l'accumulation de cystine dans les cellules de Küpfer (maladie de surcharge). Déficit en cystinosine, responsable du transport de cystine en dehors du lysosome
- *Traitement* par Cystéamine, qui favorise la sortie de cystine du lysosome
- Cheveux blonds très clairs et pâleur des téguments Cristaux cornée

#### **- Cystinurie:**

Déficit différent de la cystinose: La cystinurie est liée à un déficit héréditaire (autosomal récessif) du transport des acides aminés dibasiques : cystine, ornithine, lysine et arginine. Ce déficit entraîne une élimination urinaire majorée et un trouble de l'absorption intestinale de cystine. La lithiase cystinique est la seule manifestation clinique de la cystinurie, cause

principale de lithiase urinaire chez l'enfant. La formation de calculs est liée à la faible solubilité de la cystine dans l'urine. Le défaut d'absorption digestive des acides aminés n'a pas de conséquence clinique, car ces acides aminés sont absorbés dans les oligopeptides qui les contiennent et qui sont normalement absorbés par le tube digestif.

Traitement: Régime pauvre en méthionine (précurseur de la cystine). Augmenter diurèse par hyperhydratation, alcalinisation des urines (citrate de K/Na, 150 mg/kg/jr)



Lithiase rénale- Cystinurie

**Polykystose infantile (ARPKD= autosomal recessive polykystic kidney disease)**

- Affection autosomiale récessive
- Bilatéral
- Formes néonatales, néphromégalie
- Apparition dans l'enfance ou l'adolescence
- Déficit pouvoir de concentration, polyurie. HTA
- Insuffisance rénale terminale parfois durant l'adolescence, parfois tardive.
- Dilatation kystiques des tubes collecteurs
- Dédifférenciation cortico-médullaire
- Associée à la fibrose hépatique congénitale: élargissement fibreux des espaces portes, parfois hépatomégalie majeure, hypertension portale pré-sinusoidale  
Mode de présentation possible par rupture de varices oesophagiennes.

*Traitement*

- Symptomatique de l'insuffisance rénale, HTA
- Ligature de varices, TIPS, shunt en général bien tolérés au vu de la fonction hépatique normale
- Transplantation hépatique et rénale combinée parfois nécessaire dès l'enfance

## **Evaluation of microscopic hematuria in children**

**INTRODUCTION** — Microscopic hematuria is a common finding in children. As illustrated in two large population-based studies, 3 to 4 percent of unselected school-age children between 6 to 15 years of age had a positive dipstick for blood in a single urine sample [1,2] .

There is a long list of causes of microscopic hematuria, most of which are benign, especially in children with isolated asymptomatic microscopic hematuria. The dilemma that faces the clinician is to identify the child in whom hematuria caused by significant underlying disease.

The etiology and evaluation of microscopic hematuria in children will be reviewed here. The evaluation of children with gross hematuria is discussed separately.

**DETECTION** — Hematuria is defined by the presence of an increased number of red blood cells (RBCs) in the urine. Hematuria can either be visible to the naked eye (gross) or apparent only upon urinalysis (microscopic). Microscopic hematuria may be discovered as an incidental finding on an urinalysis prompted by urinary or other symptoms.

**Urinary dipstick** — The most common screening test for hematuria is the urinary dipstick test for blood. The reagent strip that detects blood utilizes hydrogen peroxide, which catalyzes a chemical reaction between hemoglobin (or myoglobin) and the chromogen tetramethylbenzidine. Different shades of blue-green are produced according to the concentration of hemoglobin in the urine sample. These strips can detect 5 to 10 intact RBCs/ $\mu$ L, which roughly corresponds to a finding on microscopic examination of two to five RBCs per high-power field from the sediment of a centrifuged 10 to 15 mL urine sample.

False-negative results can occur in the presence of formalin or high urinary concentration of ascorbic acid. False-positive results may occur with alkaline urine (ie, pH greater than 9) or contamination with oxidizing agents used to clean the perineum.

**Microscopic examination** — A positive dipstick for hematuria is confirmed by a microscopic examination of the sediment of 10 to 15 mL of centrifuged fresh urine. Microscopic hematuria is defined as the presence of more than five RBCs per high-power field (40x magnification) [3,4] .

The microscopic examination is the gold standard for the detection of microscopic hematuria. Dipsticks for hemoglobin are as sensitive as the urine sediment examination, but result in more false-positive tests. In comparison, false-negative dipstick tests are unusual; as a result, a negative dipstick reliably excludes abnormal hematuria.

The procedures for obtaining and processing urine samples in children are reviewed separately.

**Glomerular versus nonglomerular bleeding** — Urinalysis including microscopic examination may identify a potential site of bleeding (glomerular versus nonglomerular) and aid in determining the underlying cause. The identification of the glomeruli as the source of blood is important both prognostically and to optimize the subsequent diagnostic evaluation.

Signs of glomerular bleeding in children with microscopic hematuria include the following ([show table 1](#)):

- Red cell casts (pathognomonic for glomerular disease) ([show sediment 1](#)).
- Protein excretion greater than 100 mg/m<sup>2</sup> at a time when there is no gross bleeding. The optimal method is obtaining a first morning sample to determine the protein to creatinine ratio because it excludes orthostatic proteinuria, a normal variant.
- Red blood cells (RBCs) having a dysmorphic appearance.

Although helpful if present, the absence of these findings does not exclude glomerular disease.

Morphologic study of urinary RBCs, particularly with a phase-contrast microscope, may be helpful in distinguishing glomerular from nonglomerular bleeding. The presence of more than 30 percent dysmorphic RBCs or of more than 5 percent of a specific form named an "acanthocyte" is highly suggestive of glomerular hematuria ([show sediment 2A-2B](#)). However, confident identification of such cells requires expertise in urinalysis.

In nonglomerular hematuria, microscopic examination demonstrates urinary RBCs with a uniform normal size and shape ([show sediment 3](#)). However, hypercalciuria, a nonglomerular cause of hematuria, can be associated with dysmorphic red blood cells but not red cell casts.

**EPIDEMIOLOGY** — Several population-based studies of unselected school-age children have shown that the prevalence rate for microscopic hematuria detected in a single urine sample is 3 to 4 percent, which falls to 1 percent or less for two or more positive samples [[1,2,5](#)]. Among the 1 percent of children with two or more positive urines for hematuria, only one-third have persistent hematuria, defined as a positive repeat test after six months [[1,2](#)].

The combination of hematuria and proteinuria is less common with a prevalence rate of less than 0.7 percent in unselected school-age children in a single urine sample [[1,2](#)].

**ETIOLOGY** — Both benign and serious conditions can cause microscopic hematuria in children. The most common causes of persistent microscopic hematuria include glomerulopathies, hypercalciuria, and nutcracker syndrome [[3](#)].

- IgA nephropathy — IgA nephropathy is diagnosed by renal biopsy with mesangial IgA deposits on immunofluorescence study ([show pathology 1A-1B](#)). There is often a history of gross hematuria preceded by an upper respiratory tract or gastrointestinal illness and usually a negative family history of renal disease.
- Alport syndrome — Classic Alport syndrome (hereditary nephritis) is a recessive X-linked disorder that is typically seen in males and is often accompanied by high-frequency sensorineural hearing loss, ocular abnormalities including anterior lenticonus, and, over time, progressive renal failure ([show pathology 2A-2B](#)). Heterozygous carrier-females also can have hematuria, but do not

have progressive renal disease. (See "Clinical manifestations, diagnosis and treatment of hereditary nephritis (Alport syndrome)").

The genetic abnormality in these patients involves the gene for the alpha-5 chain of type IV collagen (COL4A5). In addition, there are autosomal recessive and dominant forms of Alport syndrome with mutations in the COL4A3 and COL4A4 genes.

- Thin basement membrane disease (TBM) — TBM, also called benign familial hematuria, is an autosomal dominant condition. Kidney biopsy reveals an isolated thinning of the glomerular basement membrane on electron microscopy (show pathology 3). In many cases, TBM disease is the heterozygous form of autosomal recessive Alport syndrome involving the COL4A3 or COL4A4 genes; two abnormal genes are required for the Alport phenotype.
- Postinfectious glomerulonephritis — In children with poststreptococcal glomerulonephritis, hematuria generally resolves within three to six months after the presentation.
- Hypercalciuria — Hypercalciuria, defined in children as a urine calcium/creatinine ratio >0.2 (mg/mg) in children older than six years of age, has been associated with asymptomatic microscopic hematuria. In studies performed in the United States, the prevalence has ranged from as low as 11 percent in the Northeast [6] to as high as 35 percent in the South [7,8]. Thus, the association between hypercalciuria and hematuria may be more common in areas where there is a higher prevalence of nephrolithiasis.
- Nutcracker syndrome — Left renal vein compression between the aorta and proximal superior mesenteric artery, referred to as "nutcracker syndrome," has been suggested as a cause of hematuria in children that is usually asymptomatic but may be associated with left flank pain [9-11]. Nutcracker syndrome is detected by Doppler ultrasonographic assessment of left renal vein diameter and peak velocity [9,10].

The frequency of nutcracker syndrome as a cause of hematuria in children appears to be highest in Asia as illustrated by the following case series:

- In a Japanese case series of 85 children with hematuria without nephritis, nephrolithiasis, or a tumor, Doppler ultrasonographic findings were consistent with nutcracker syndrome in 21 of 23 with gross hematuria and 17 of 52 with microscopic hematuria [9].

- Similar results were seen in a Korean case series of 216 children with isolated hematuria; 176 microscopic and 40 gross hematuria cases [11]. Doppler ultrasonographic results were consistent with nutcracker syndrome in 33 percent of patients with hematuria. There was no evidence of nutcracker syndrome in 32 healthy normal children.

Nutcracker syndrome can also cause orthstatic proteinuria in children.

The distribution of causes of transient hematuria is much larger and includes urinary tract infection (which is typically accompanied by dysuria and pyuria), trauma, fever, and exercise. The supporting data are presented separately in the adult section.

**EVALUATION** — The diagnostic evaluation depends upon the clinical presentation, which falls into the following three categories:

- Asymptomatic isolated microscopic hematuria
- Asymptomatic microscopic hematuria with proteinuria
- Symptomatic microscopic hematuria

**Asymptomatic isolated microscopic hematuria** — As noted above, asymptomatic isolated microscopic hematuria (ie, no proteinuria) is present in 3 to 4 percent of unselected school-age children [1,2,5] . However, significant clinical disease is rarely detected. (See "Epidemiology" above).

This was illustrated in a 1979 study of an unselected population of 8954 children who were screened for hematuria. Among the 28 patients (0.3 percent) with two or more urine samples that tested positive for blood, extensive evaluation was performed including renal biopsy and intravenous pyelogram [2] . A cause was found in only five: two with IgA nephropathy, one with thin basement membrane disease, and two with uretero-pelvic stenosis.

In retrospective reviews of patients who were referred to a single center for evaluation of asymptomatic isolated microscopic hematuria, standard laboratory and imaging evaluations were unnecessary, as they typically failed to detect any abnormality. This was illustrated by the following two observations:

- In a study of 325 children with asymptomatic isolated microscopic hematuria, serum creatinine and electrolyte concentrations were normal in all 254 patients who were tested [6] . No clinically significant findings were detected in the 283 patients who underwent ultrasonography. Hypercalciuria was present in 11 percent of the 263 patients whose urine was tested for urinary calcium/creatinine ratio. (See "Etiology" above).
- In another series of 342 children with asymptomatic microscopic hematuria, evaluation included complete blood count, urinalysis, serum creatinine, C3, and ultrasonography or intravenous pyelography [12] . No diagnosis was made in 80 percent of patients. Among those with positive findings, the most common was hypercalciuria in the absence of stone disease in 16 percent of the total group.

These findings have led to recommendations for observation of children with asymptomatic microscopic hematuria with normal physical examinations. Extensive diagnostic evaluation including laboratory testing is reserved only in children with proteinuria, hypertension, or gross hematuria [6,12,13] .

The following is our recommended approach to children with asymptomatic isolated microscopic hematuria based upon the available literature [1-4,6,14] .

- Evaluation including blood pressure measurement and a urinalysis should be performed weekly for two weeks. One should ensure that there is no exercise prior to obtaining the urine sample, since vigorous exercise can induce hematuria. A thorough evaluation should be undertaken only if the patient becomes symptomatic or develops hypertension, gross hematuria, or proteinuria.
- If isolated hematuria persists, obtain a urine culture. If the culture is positive, treat with appropriate antibiotics.
- If the patient remains asymptomatic and the urine culture is negative, continue to observe the patient every three to six months including physical examination with blood pressure measurement and urinalysis.
- If the asymptomatic isolated hematuria persists for one year, the following subsequent evaluation should be performed:

- Measure urine calcium/creatinine ratio for hypercalciuria. Hypercalciuria, defined as a urine calcium/creatinine ratio  $>0.2$  (mg/mg), has been associated with asymptomatic microscopic hematuria.

There is disagreement as to whether children with hypercalciuria have an increased likelihood of a family history of nephrolithiasis and whether hypercalciuria leads to renal stones [6-8]. Although lowering urinary calcium excretion with a thiazide diuretic can lead to resolution of the hematuria [8], there is at present no consensus on the further evaluation or treatment of children with isolated microscopic hematuria who have hypercalciuria.

- Test parents and siblings for hematuria to detect possible thin basement membrane disease (autosomal dominant) or hereditary nephritis (mostly X-linked recessive).
- Consider hemoglobin electrophoresis if there is a clinical suspicion for sickle cell trait.
- Perform Doppler ultrasonography for the "nutcracker syndrome". This study should only be performed by clinicians with expertise in detecting this abnormality.

**Asymptomatic microscopic hematuria and proteinuria** — The combination of hematuria and proteinuria is significantly less common than either isolated proteinuria or hematuria. Although asymptomatic hematuria with proteinuria has a prevalence rate of less than 0.7 percent in unselected school-age children, it is associated with a higher risk for significant renal disease [1,2,4,15].

Evaluation of these patients starts with measurement of serum creatinine and quantification of proteinuria either by a 24-hour urine collection or determination of the urine protein-to-creatinine ratio on a first morning urine sample.

- If protein excretion is  $>4$  mg/m<sup>2</sup> per hour or if in a first morning urine specimen, the urine protein-to-creatinine ratio is  $>0.2$  mg protein/mg creatinine in children older than 2 years of age and  $>0.5$  mg protein/mg creatinine in younger children, the patient should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) since it is likely that there is significant renal disease.

- If protein excretion is less than the above values, the patient should be reevaluated in two to three weeks.
- If the hematuria and proteinuria have resolved, no further evaluation is needed.
- If there is only asymptomatic microscopic hematuria, the patient is monitored in the same fashion as those described above with asymptomatic isolated microscopic hematuria.
- If proteinuria is persistent the patient should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) for further evaluation.

Patients with significant proteinuria or an elevated serum creatinine at baseline, or persistent proteinuria at follow-up should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) because they are likely to have renal disease. Further assessment should include microscopic examination of the urine by an experienced clinician, serum creatinine, C3, C4, albumin, and complete blood count. Depending upon the findings, other tests that may be considered include ASO titer, streptozyme testing, antinuclear antibody testing, imaging, and renal biopsy.

**Symptomatic microscopic hematuria** — The evaluation of symptomatic microscopic hematuria is directed by the patient's symptoms and clinical findings ([show algorithm 3](#)). This category is the most challenging because it encompasses a wide range of diseases with varying clinical presentations [3,14]. The clinical manifestations may be nonspecific (eg, fever, malaise, weight loss), extrarenal (eg, rash, purpura, arthritis), or related to kidney disease (eg, edema, hypertension, dysuria, oliguria).

The presence of nonspecific or extrarenal manifestations suggests a systemic process such as lupus nephritis or Henoch-Schönlein purpura. Renal causes of symptomatic microscopic hematuria include glomerular or interstitial diseases of the kidney, lower urinary tract disease, nephrolithiasis, tumors, and vascular disease.

The diagnosis may be evident and straightforward from the history and physical examination. The urinalysis can be helpful in differentiating between glomerular and nonglomerular causes of bleeding. ([See "Glomerular versus nonglomerular bleeding" above](#)).

**Historical clues** — There are often clues from the history that point towards a specific diagnosis. ([See "Etiology" above](#)).

- Recent trauma.
- A history of new onset of incontinence, dysuria, frequency, or urgency, suggests urinary tract infection.
- A history of unilateral flank pain that radiates to the groin suggests obstruction caused by a calculus or blood clot. In comparison, flank pain without radiation but with fever, dysuria, and frequency and/or urgency is suggestive of acute pyelonephritis.
- A history of pharyngitis or impetigo (two or three weeks prior to onset of hematuria) suggests poststreptococcal glomerulonephritis, although a recent upper respiratory (one or two days prior to onset of hematuria) infection can be associated with IgA nephropathy.

- A history of predisposing or preexisting clinical conditions such as sickle cell disease or trait, a coagulopathy such as severe hemophilia, or deafness (Alport syndrome).
- A family history of hematuria, kidney disease (eg, Alport syndrome or thin basement membrane nephropathy), or kidney stones.
- Exposure to medications that can cause interstitial nephritis, although hematuria is not typically the central manifestation in such patients.

**Physical examination** — The physical examination should include measurement of blood pressure, assessment for edema and recent weight gain, close skin examination (eg, purpura), direct visualization of the genitals (looking for penile urethral meatal erosion or female introitus pathology), and evaluation for abdominal discomfort or masses (eg, Wilms' tumor).

**Urinalysis** — Examination of the urine may suggest an underlying etiology and potential site of bleeding (glomerular versus extraglomerular). Glomerular causes of symptomatic hematuria include IgA nephropathy, Alport syndrome, and postinfectious glomerulonephritis. (See "Glomerular versus nonglomerular bleeding" above and see "Hematuria: Glomerular versus extraglomerular bleeding" and see "Etiology" above).

**Further evaluation** — Based upon the history, physical examination, and urinalysis, a preliminary diagnosis will be made in the majority of cases and will guide further evaluation and/or intervention (show algorithm 3).

- Trauma history — Obtain a CT scan of the abdomen and pelvis to determine the source of blood.
- Signs or symptoms of UTI — Additional findings on urinalysis suggestive of a UTI include positive dipstick tests for leukocyte esterase and/or nitrite, more than five white blood cells per high-power field (spun urine), and the presence of bacteria on a Gram stain of unspun urine.

An appropriately collected urine culture is obtained. If the culture is positive, treat appropriately and repeat urinalysis after the infection has cleared.

Adenovirus should be considered as a potential etiology if urinary symptoms and urinalysis are suggestive of infection but the culture is negative [14,15]

Signs or symptoms of perineal/meatal irritation — Supportive care and reassurance.

- Signs or symptoms of nephrolithiasis — The evaluation begins with imaging. Renal ultrasonography is the preferred modality in children. Abdominal plain films may be useful in identification of radiopaque stones but will miss radiolucent uric acid stones, small stones or stones overlying bony structures, and will not detect obstruction.

Spiral CT scan is the most sensitive imaging modality. However, because of concerns related to radiation exposure, it is not typically the initial test in young children as it is in adolescents and adults. Consultation with radiology may be warranted in younger children to determine the risk-to-benefit ratio of the test.

- Signs or symptoms suggestive of glomerular disease — Manifestations such as proteinuria, red blood cell casts, edema, and hypertension suggest a glomerular source for the hematuria. The evaluation includes serum creatinine, complete blood count, C3, C4, and serum albumin. Other tests to consider based upon the history and the physical examination include ASO titer, streptozyme testing, and antinuclear antibody testing. Such patients should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease).

**Indications for renal biopsy** — A renal biopsy is not usually performed for isolated microscopic hematuria. However, biopsy should be considered if there is evidence of substantial or progressive disease as manifested by an elevation in the creatinine concentration, significant proteinuria, or an otherwise unexplained rise in blood pressure even when the values remain within the normal range. Biopsy also may be considered in the child with persistent glomerular hematuria, in whom the parents are worried about the diagnosis and prognosis. In addition, a kidney biopsy may be considered in a child with microscopic hematuria and a family history of kidney failure in early adulthood in a first order relative.

Patients with clear evidence of poststreptococcal glomerulonephritis represent an exception to these general recommendations, since gradual spontaneous recovery is the rule, although proteinuria may gradually return to normal over many years.

The value of renal biopsy with different hematuria presentations was evaluated in a report of Korean children with an abnormal urinalysis detected by school screening: 289 patients with persistent isolated microscopic hematuria ( $\geq 6$  RBCs per high-power field in a centrifuged sample for more than six months) and 163 patients with microscopic hematuria and proteinuria underwent renal biopsy [15].

- In children with isolated microscopic hematuria, biopsy results demonstrated normal biopsy, thin basement membrane disease, and IgA nephropathy in 47, 34, and 16 percent of cases, respectively.
- In children with microscopic hematuria and proteinuria, biopsy results demonstrated normal findings, thin basement membrane disease, and IgA nephropathy in 25, 18, and 46 percent of the cases, respectively. Other findings included mesangial proliferative glomerulonephritis (3 percent), poststreptococcal glomerulonephritis (3 percent), Alport syndrome (2 percent), and focal glomerulosclerosis (2 percent).

These results demonstrate that renal biopsy findings in most cases of isolated microscopic hematuria are normal or are consistent with thin basement membrane disease, a benign condition. Although a significant number of patients with isolated microscopic hematuria had IgA nephropathy, these patients have a minimal risk of disease progression as long as they do not develop proteinuria. In contrast, patients with persistent hematuria and proteinuria are more likely to have significant renal disease.

**Cystoscopy** — Cystoscopy is rarely indicated for hematuria in children. It should be reserved for the rare child with a bladder mass noted on ultrasound and those with urethral abnormalities due to trauma.

**SUMMARY AND RECOMMENDATIONS** — Microscopic hematuria is a common finding in children with 3 to 4 percent of normal school-age children having a positive dipstick for blood. (See "Epidemiology" above).

- The most common screening test for hematuria is urinary dipstick test for blood. Hematuria is confirmed by microscopic examination. Hematuria is defined as 5 to 10 intact RBCs/ $\mu$ L, which corresponds to a finding on microscopic examination of two to five RBCs per high-power field of the sediment of a 10 to 15 mL centrifuged urine sample. (See "Detection" above).
- The presence of red cell casts, proteinuria, and/or dysmorphic red blood cells (by an experienced observer) indicates a glomerular source of bleeding. (See "Glomerular versus nonglomerular bleeding" above).
- Both benign and serious conditions can cause microscopic hematuria in children. The most common causes of persistent microscopic hematuria beyond six months are IgA nephropathy and thin basement membrane disease. Less frequent causes of microscopic hematuria include hereditary nephritis (Alport syndrome), hypercalciuria, urinary tract infection, and nutcracker syndrome. (See "Etiology" above).
- The evaluation depends upon the clinical presentation, which falls into three categories:
  - Asymptomatic isolated microscopic hematuria
  - Asymptomatic microscopic hematuria with proteinuria
  - Symptomatic microscopic hematuria
- Asymptomatic isolated microscopic hematuria is the most common presentation of microscopic hematuria. It is usually transient and is generally not associated with significant clinical disease. As a result, our approach starts with initial observation with repeated examination and urinalyses . If hematuria persists, subsequent evaluation includes a urine culture, measurement of urine calcium/creatinine ratio, and testing of parents and siblings for hematuria. More extensive evaluation is warranted if, during the period of observation, symptoms, hypertension, proteinuria, or gross hematuria develops. (See "Asymptomatic isolated microscopic hematuria" above).
- Patients with asymptomatic microscopic hematuria and urinary protein excretion greater than 4 mg/m<sup>2</sup> per hour or a urine protein-to-creatinine ratio  $>0.2$  mg protein/mg creatinine in children older than 2 years of age and  $>0.5$  mg protein/mg creatinine in younger children should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) since it is likely that there is significant renal disease. If protein excretion is less than the above values, the patient should be reevaluated in two to three weeks (show algorithm 2). (See "Asymptomatic microscopic hematuria and proteinuria" above).
- The evaluation of patients with symptomatic microscopic hematuria encompasses a wide range of diseases with varying clinical presentations. Assessment is directed by patient's symptoms, clinical findings, and urinalysis.

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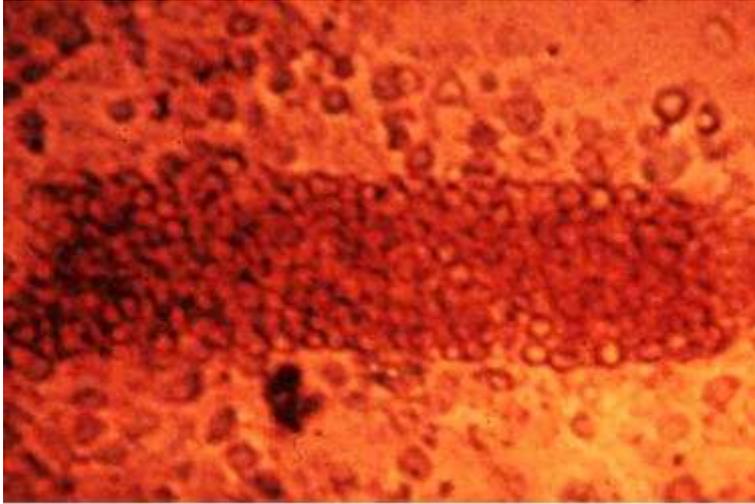
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## GRAPHICS

### Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	Usually absent	May be present
RBC morphology	Normal	Dysmorphic
RBC casts	Absent	May be present

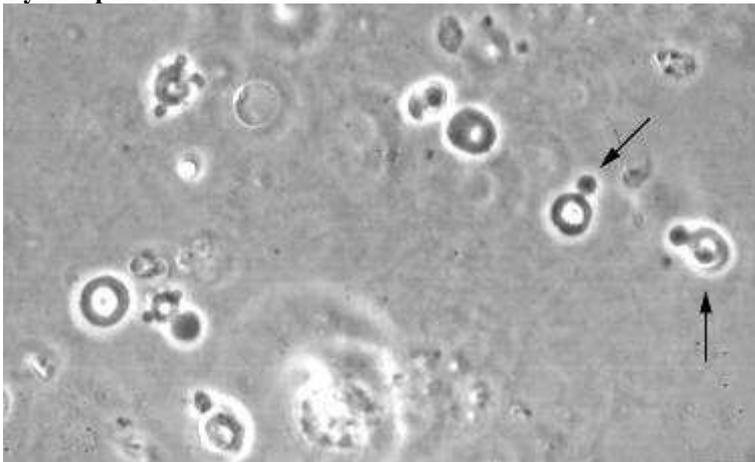
### Red cell cast



Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis. *Courtesy of Harvard Medical School.*

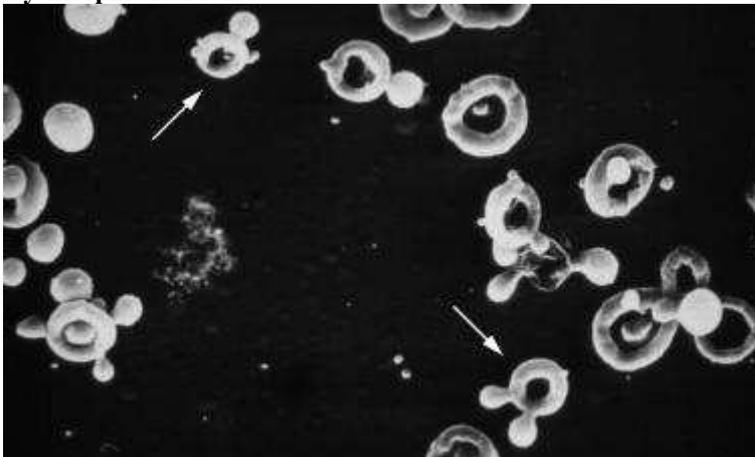
### Dysmorphic rbc I

#### Dysmorphic red cells



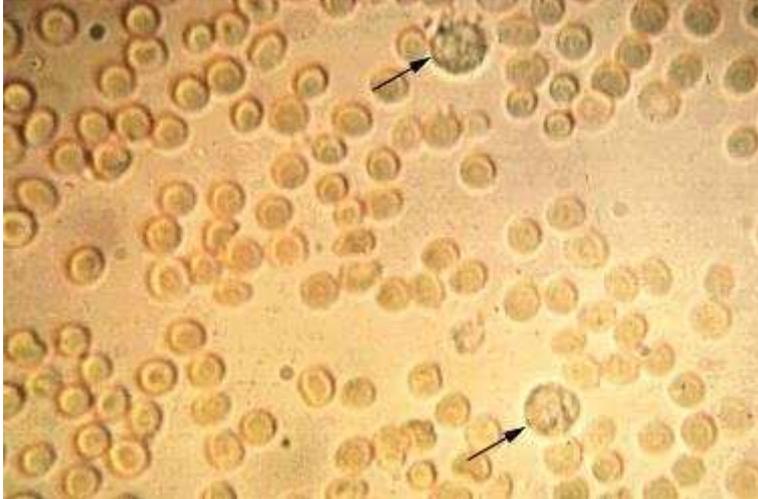
Phase contrast microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows). *Courtesy of Hans Köhler, MD.*

#### Dysmorphic red cells



Scanning microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows). *Courtesy of Hans Köhler, MD.*

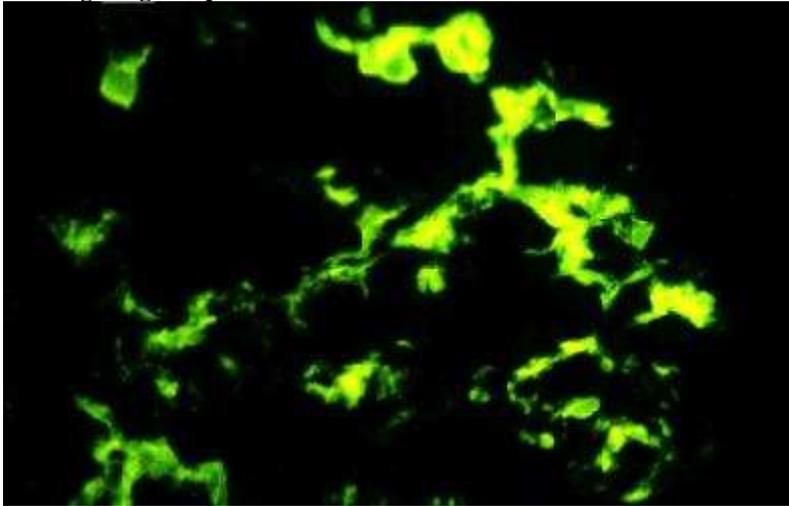
**Monomorphic red cells**



Urine sediment showing many red cells and an occasional larger white cell with a granular cytoplasm (arrows). The red cells have a uniform size and shape, suggesting that they are of nonglomerular origin. *Courtesy of Harvard Medical School.*

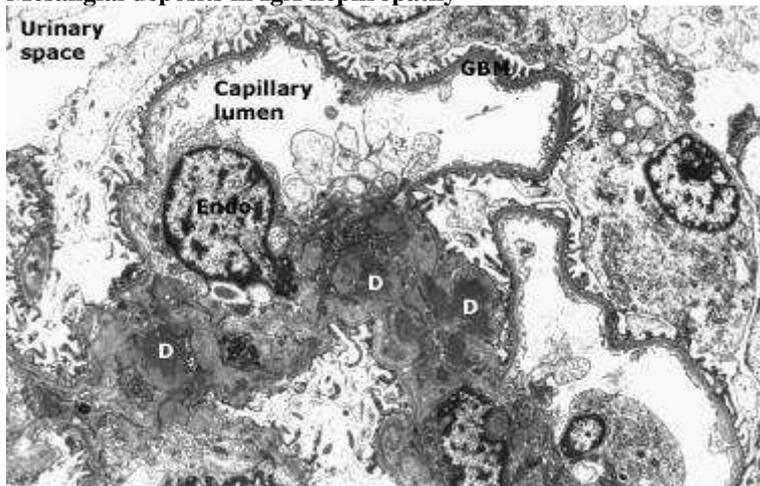
## IgA nephropathy IF

### Mesangial IgA deposits



Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura. Note that the capillary walls are not outlined, since the deposits are primarily limited to the mesangium. *Courtesy of Helmut Rennke, MD.*

### Mesangial deposits in IgA nephropathy



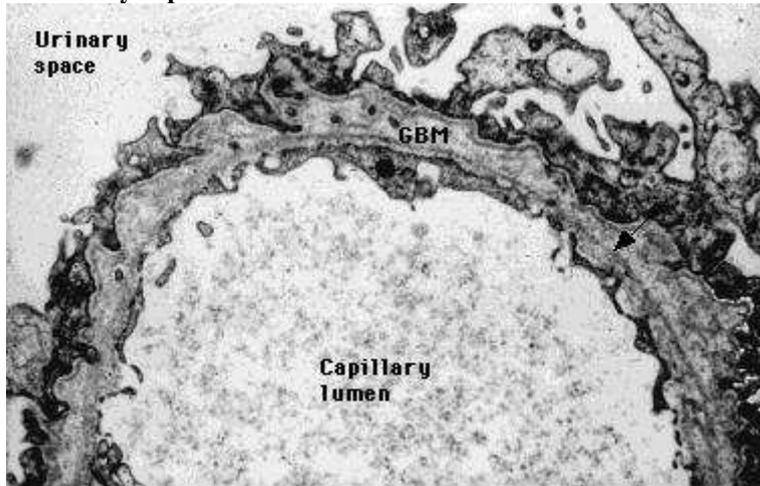
Low power electron micrograph in IgA nephropathy. The primary finding is electron dense deposits that are limited to the mesangial regions (D). The glomerular basement membrane (GBM) is normal and there are no glomerular capillary wall deposits.

Endo: endothelial cell nucleus.

*Courtesy of Helmut Rennke, MD.*

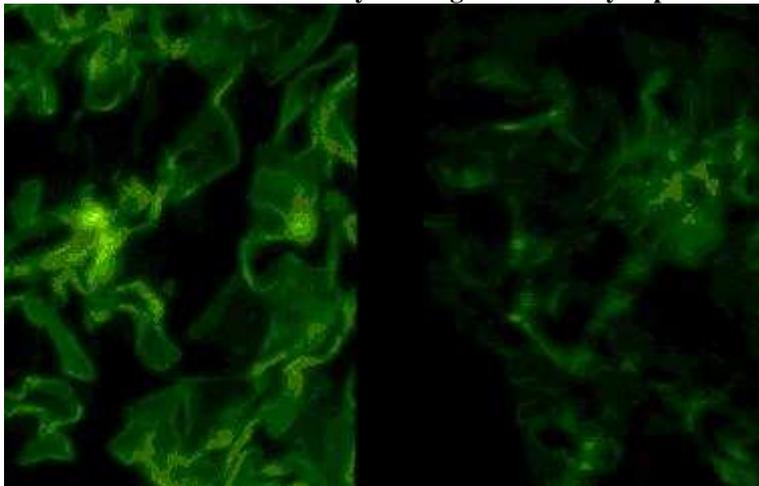
## Hereditary nephritis EM

### Hereditary nephritis



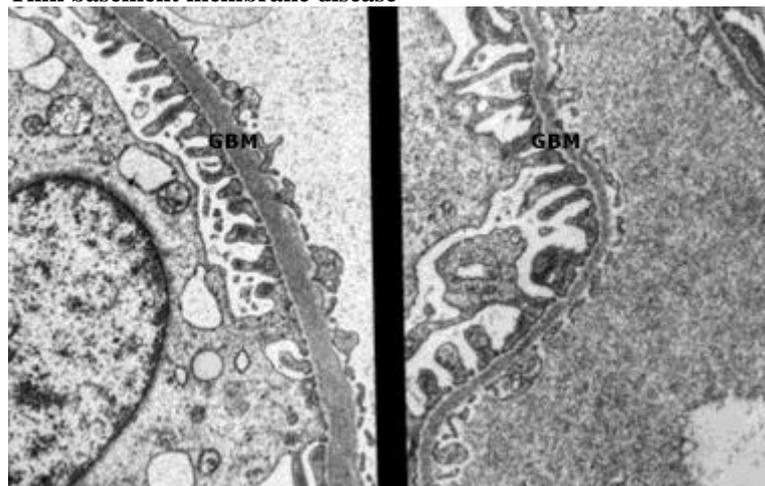
Electron micrograph from a patient with hereditary nephritis (Alport's syndrome) shows the characteristic thickening, fraying, and laminations (arrow) of the glomerular basement membrane (GBM). *Courtesy of Helmut Rennke, MD.*

### Diminished anti-GBM antibody binding in hereditary nephritis



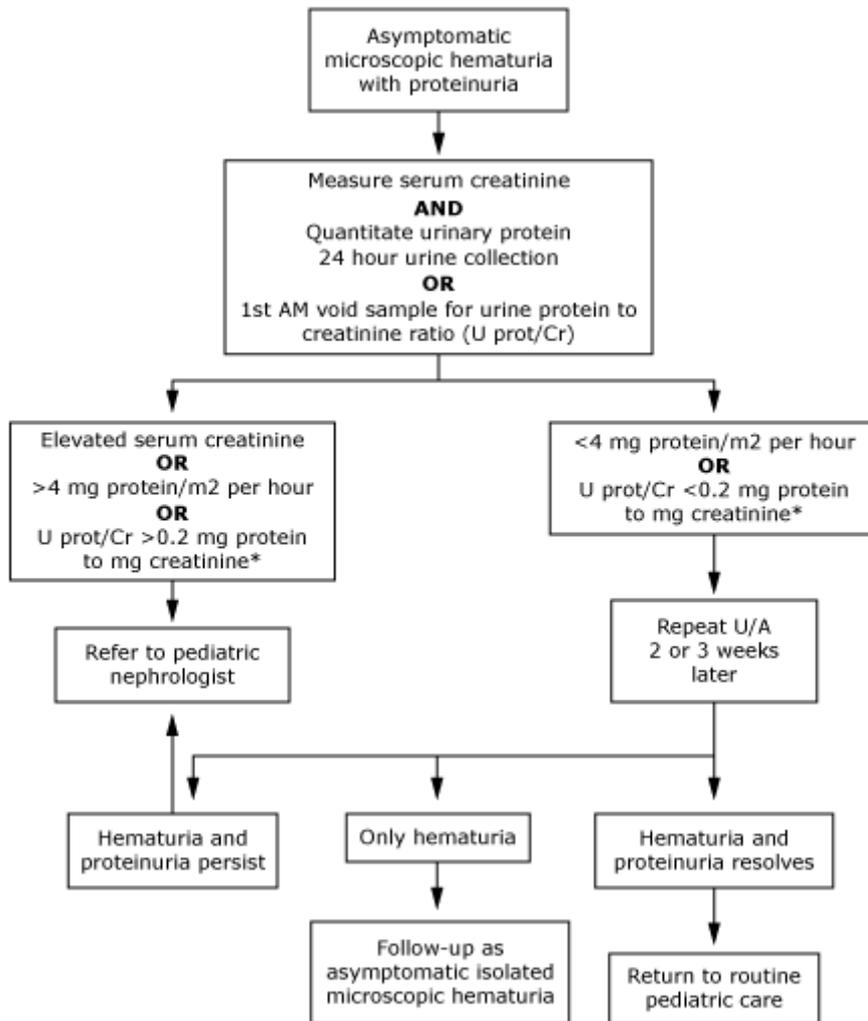
Indirect immunofluorescence microscopy with anti-glomerular basement membrane antibodies shows extensive binding to a normal glomerulus (left panel) but minimal binding to a glomerulus from a patient with hereditary nephritis (right panel). *Courtesy of Helmut Rennke, MD.*

**Thin basement membrane disease**



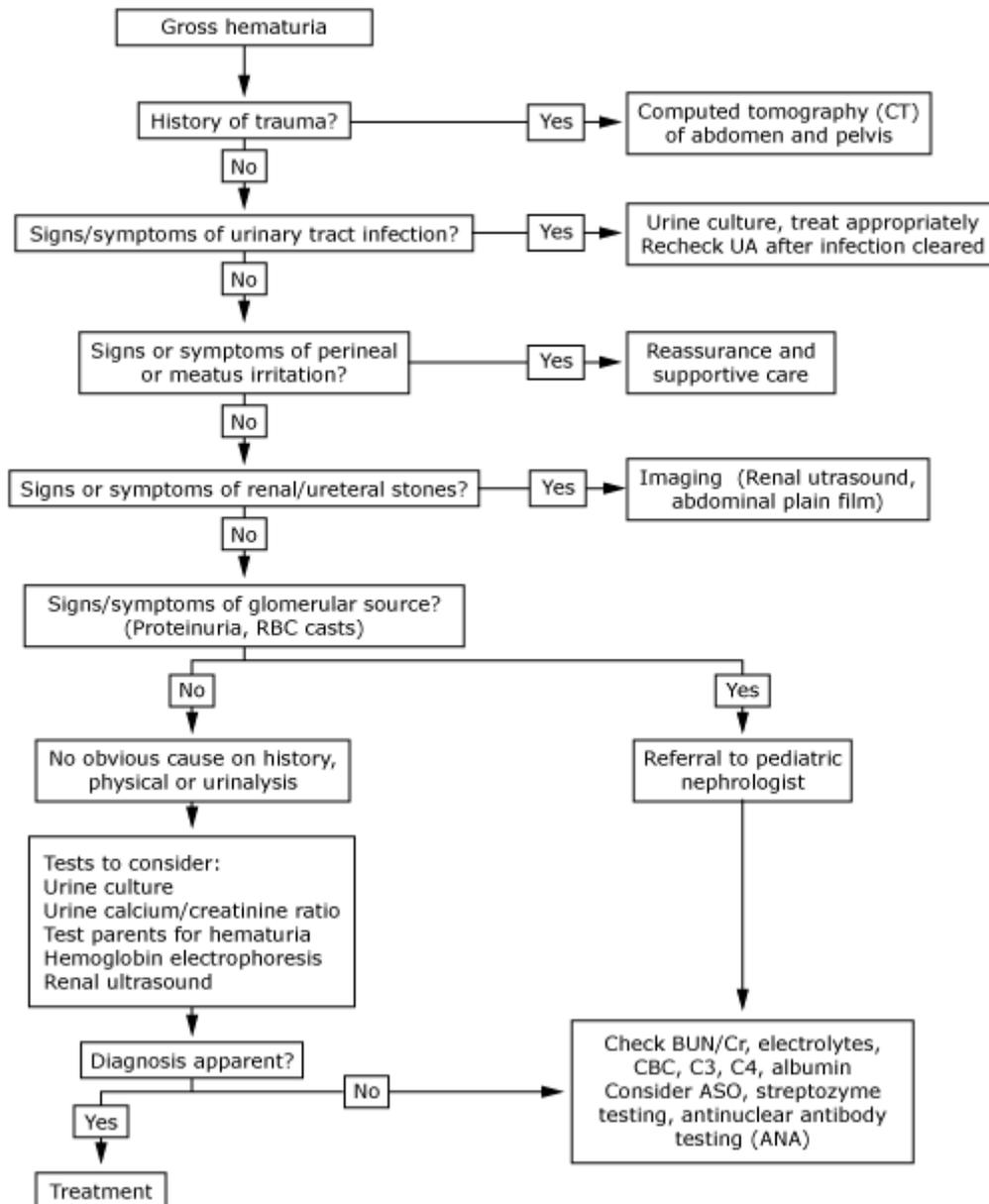
Electron micrograph comparing the thickness of the normal glomerular basement membrane (GBM) (left panel) to the much thinner GBM in thin basement membrane disease (right panel). *Courtesy of Helmut Rennke, MD.*

**Diagnostic algorithm for asymptomatic microscopic hematuria with proteinuria**



\* For children between 6 and 24 months, the threshold value is 0.5 mg protein to mg creatinine. Modified from: Diven, SC, Travis, LB. A practical primary care approach to hematuria in children. *Pediatr Nephrol* 2000; 14:65.

**Algorithm for gross microscopic hematuria**



*Modified with permission from: Patel, HP, Bissler, JJ. Hematuria in children. Pediatr Clin North Am 2001; 48:1519. Copyright ©2001 Elsevier.*

## **Clinical features and diagnosis of nephrolithiasis in children**

**INTRODUCTION** — Nephrolithiasis is increasingly recognized in children. Its presentation varies and often patients, especially young children, do not present with the classic acute onset of flank pain commonly seen in adults. As a result, children are frequently evaluated for other conditions before the diagnosis of nephrolithiasis is made. The clinical features and diagnosis of childhood nephrolithiasis will be reviewed here. The epidemiology, risk factors, acute management, and prevention of recurrent nephrolithiasis in children are discussed separately.

**CLINICAL PRESENTATION** — Most children with nephrolithiasis present symptomatically, usually with flank or abdominal pain. Approximately 15 to 20 percent are asymptomatic, primarily young children who are diagnosed because of stone detection when abdominal imaging is performed for other purposes [1-3] .

In those with symptomatic presentation, the most common symptom is pain [1-4] . Other potential manifestations include gross hematuria, dysuria and urgency, and nausea/vomiting.

- Pain — Pain can be located either as abdominal or flank pain (referred to as renal colic). In several case series, pain was the presenting complaint in 50 to 75 percent of patients [1-5] .

Pain frequency varies with age. In one report, for example, pain was present in 60, 40, and 20 percent of adolescents, school-aged children, and children below five years of age, respectively [2] . The age-related difference in pain may be related to stone location at presentation. Younger children are much less likely to have ureteral stones (32 versus 64 and 82 percent in school-aged children and adolescents, respectively, in a review of 129 children) [6] . Ureteral stones are generally painful, since they cause ureteral obstruction, whereas kidney stones are often asymptomatic and may be diagnosed as an incidental finding on abdominal imaging.

Similar to adults with nephrolithiasis, the intensity of pain can vary from a mild ache to severe debilitating pain. In children below five years of age, the pain, if present, appears to be milder and is nonspecific. In addition, young children often are unable to articulate the location and severity of the pain. As a result, young children are frequently evaluated for other causes of abdominal pain before the diagnosis of nephrolithiasis is made.

- Gross hematuria — In pediatric case series, gross hematuria as a presenting symptom for nephrolithiasis varied from 30 to 55 percent [1-4] . Hematuria can present as the sole symptom or concomitantly with abdominal pain.
- Dysuria and urgency — Approximately 10 percent of children with nephrolithiasis present with symptoms of dysuria and urgency suggestive of a urinary tract infection (UTI) [1,4,5] . In some cases, urinary tract infection is present and is a contributing factor to stone formation, especially in young children [1,2,5] . In other cases, dysuria and urgency can be seen when the stone is present in the bladder or urethra without an associated UTI.

- In addition to these symptoms, nausea and vomiting has been described as a presenting symptom in 10 percent of patients [1] .

**Young children** — As noted above, young children with nephrolithiasis are less likely to display the classical presentation of abdominal/flank pain commonly seen in older children and adults. In one of the largest case series, abdominal pain and gross hematuria were the presenting symptoms in about one-half of the children below six years of age [2] . The other half of patients presented with a urinary tract infection and/or incidental finding of stones on abdominal imaging.

**INITIAL EVALUATION** — Because renal stones can cause urinary obstruction, and are often associated with urinary tract infection, children who present with symptoms suggestive of nephrolithiasis should be evaluated promptly.

**History** — The evaluation begins with a history that identifies any of the following factors that are associated with an increased likelihood for nephrolithiasis.

- History of previous renal stone.
- Family history of nephrolithiasis. In one case series, 16 percent of children had a first-degree relative and 17 percent had a second-degree relative with renal stones [3] .
- History of underlying renal and urinary tract structural abnormalities.
- History of underlying metabolic conditions associated with nephrolithiasis, such as malabsorption leading to enhanced enteric absorption of oxalate and hyperoxaluria..
- History of medications associated with stone formation, such as

indinavir or sulfadiazine [7] .

- History of recurrent urinary tract infection, especially with a urease-producing organism, such as *Proteus* or *Klebsiella*.
- **Physical examination** — The physical examination in the child with suspected nephrolithiasis should include:
  - An abdominal examination for tenderness or mass (eg, evidence of urinary obstruction or another cause of abdominal pain, such as

appendicitis).

- Growth measurements, as poor weight gain and/or failure to thrive may be an indication of a congenital or chronic condition that may be associated with nephrolithiasis, such as renal tubular acidosis or Dent's syndrome.
- Blood pressure measurement and assessment for edema. The

presence of hypertension and/or edema in a child with hematuria suggests an alternative diagnosis to nephrolithiasis, such as glomerular disease. (See "Differential diagnosis" below).

- Documentation of temperature. The presence of fever may represent a urinary tract infection.

**Laboratory evaluation** — The initial laboratory evaluation for the child with suspected nephrolithiasis includes a urine sample for urinalysis and urine culture.

- Urinalysis — Examination of the urine sediment may be useful if

crystals are present. As an example, cystine crystals, which are colorless, flat, and hexagonal, are diagnostic of cystinuria (show sediment 1). Other crystals that can be seen in the sediment include calcium oxalate (show sediment 2A-2B), calcium phosphate, uric acid (show sediment 3A-3B), and phosphate (show sediment 4). Drugs, such as sulfadiazine and indinavir, can also crystallize in the urine (show sediment 5 and show sediment 6).

- Urine culture — A urine culture should be obtained because urinary tract infection (UTI) can be present in a child with nephrolithiasis. A UTI is also the most common condition in the differential diagnosis of pediatric nephrolithiasis. (See "Differential diagnosis" below).

Once the acute episode is over, further evaluation is focused on identifying potential risk factors for stone disease, such as hypercalciuria or hyperuricosuria. **DIAGNOSIS** — The diagnosis of nephrolithiasis is initially suspected by the presentation and initial clinical evaluation. It is confirmed by the detection of a stone on imaging studies or retrieval of a passed stone. As previously mentioned, the diagnosis is made as an incidental finding in about 15 to 20 percent of pediatric cases when abdominal imaging is performed for other purposes [1-3].

**Imaging** — The three imaging modalities currently used to diagnosis nephrolithiasis in children are non-contrast helical computed tomography (CT), ultrasonography, and plain abdominal radiography. CT is the most sensitive for the detection of renal stones, followed by ultrasonography and plain radiography [8]. In small children, there are concerns about radiation exposure from CT [9].

**Non-contrast helical CT** — Similar to adults, non-contrast helical CT is the most sensitive modality to detect renal or ureteral stones in children (show radiograph 1A-1C) [8,10]. CT can detect stones in the following conditions, which may not be detected by the other modalities:

- Ureteral stones, which may not be detected by ultrasonography
- Radiolucent stones (eg, pure uric acid stones), which are not detected by plain radiography
- Small (ie, 1 mm in diameter) stones, which are not detected by ultrasonography or plain radiography

CT also provides more detailed anatomic information including detection of obstruction or a structural abnormality [11].

CT is a rapid procedure requiring less than two minutes to be performed. Patients who undergo CT generally do not require anesthesia. If necessary, contrast can be given after non-contrast images have been obtained to provide additional anatomic detail, such as subtle signs of urinary obstruction or increased detail of an anatomic abnormality.

The radiation exposure during CT varies with different equipment and institutional protocols. Concerns have been raised that small children can be exposed to excessive radiation, if conventional adult radiation doses are used during the procedure [9,12] . However, radiation doses can be significantly reduced through adjusting scanning parameters to the size and weight of the child while still maintaining adequate imaging quality [13] . In institutions that provide care for children, protocols to ensure effective and safe radiation doses for CT should be implemented as outlined by guidelines from the National Cancer Institute [12,14] . If this is not feasible, another imaging modality, such as ultrasonography, should be used.

**Ultrasonography** — Ultrasonography is the modality of choice when radiation should be avoided, as in pregnant girls, or when the radiation dose from CT cannot be reduced to safe levels. Ultrasonography can detect radiolucent stones, such as uric acid stones, and urinary obstruction [15] . However, it is limited in its ability to uncover small stones (eg, less than 5 mm), papillary or calyceal stones, or ureteral stones [16] .

The experience and expertise of the ultrasonographer is an important factor in the sensitivity of the study, especially in the accurate detection of small stones or ureteral stones.

**Abdominal plain radiography** — A plain abdominal radiograph will detect radiopaque stones (eg, calcium, struvite, and cystine stones) ([show radiograph 2](#)), but will miss radiolucent stones (eg, uric acid stones), may miss small stones or those that overlay bony structures, and will not detect urinary obstruction. In settings, where renal ultrasonography and CT are not available in children, plain abdominal radiography remains a reasonable alternative, recognizing that the reported sensitivity of this study is about 60 percent [8] .

**Our approach** — We recommend non-contrast helical CT in the diagnostic evaluation of pediatric nephrolithiasis. Radiation doses are adjusted to the size and weight of the child to reduce the radiation exposure. Abdominal ultrasonography or plain film can be used if appropriate CT imaging for children is not available. Ultrasonography is preferred to plain film since it is a more sensitive test and can also detect radiolucent stones and urinary tract obstruction.

**DIFFERENTIAL DIAGNOSIS** — The differential diagnosis in a child with suspected nephrolithiasis depends upon the presenting symptoms. Nephrolithiasis is differentiated from the other conditions by demonstration of a stone within the kidney or urinary tract by imaging.

- Abdominal or flank pain — Abdominal pain is one of the most

common complaints in children and the differential is extensive.

Infections, such as gastroenteritis, urinary tract infections (UTI), appendicitis, and pneumonia, are the most common cause of abdominal or flank pain. Other signs and symptoms, most commonly fever, usually distinguish them from nephrolithiasis.

- Gross hematuria — In children, the most commonly identified

causes for gross hematuria include UTI, irritation of the meatus or perineum, and trauma. These are differentiated from nephrolithiasis by the history and physical examination. Glomerular disease, such as postinfectious glomerulonephritis, is a less common cause of gross hematuria that is distinguished from nephrolithiasis by cola-colored urine instead of red urine, examination of the urinary sediment, and the possible presence of hypertension and/or edema.

- Urinary tract infection — Many of the symptoms

associated with nephrolithiasis (eg, abdominal/flank pain, gross hematuria, dysuria, and urgency) can also be seen in children with UTI. In addition, the two conditions can present concomitantly with the UTI contributing to the process of stone formation.

Children with UTI diagnosed by urine culture usually begin to show clinical improvement within 24 to 48 hours of initiation of appropriate antibiotic therapy. If the clinical condition worsens or fails to improve as expected within 24 to 48 hours of the start of antimicrobial therapy, imaging should be performed to determine if the failed or slow response to therapy is due to the presence of renal stone, renal abscess, or underlying anatomic abnormalities or obstruction.

## SUMMARY AND RECOMMENDATIONS

- Childhood nephrolithiasis usually presents with symptoms that most commonly include abdominal or flank pain, and/or gross hematuria. However, 15 to 20 percent of children are asymptomatic and are diagnosed because of stone detection when abdominal imaging is performed for other purposes. (See "Clinical presentation" above).
- Abdominal or flank pain as a presenting symptom varies in intensity from a mild ache to severe debilitating pain. Pain is a common feature in adolescents and school-aged children with nephrolithiasis, but is only present in about half of the children below six years of age. Urinary tract infection and/or an incidental finding of a stone on imaging are the presenting findings in almost half of the children below six years of age. (See "Clinical presentation" above).
- The initial evaluation of a child with suspected nephrolithiasis includes the following:
  - History focusing on underlying risk factors for stone formation (eg, family history, renal and urinary tract structural abnormalities, metabolic disorders, or recurrent urinary tract infection).
  - Physical examination that includes measurement of blood pressure and growth parameters, and abdominal examination for signs of urinary obstruction or another cause for abdominal pain.
  - Urinalysis and urine culture.

(See "Initial evaluation" above).

- The diagnosis of nephrolithiasis is made by the detection of a renal stone by imaging studies or retrieval of a passed stone.
- We recommend abdominal imaging for any child suspected to have nephrolithiasis. In most patients, we recommend non-contrast helical computed tomography (CT), which provides the greatest sensitivity of the available imaging modalities. Radiation doses are adjusted to the size and weight of the child to reduce radiation exposure.

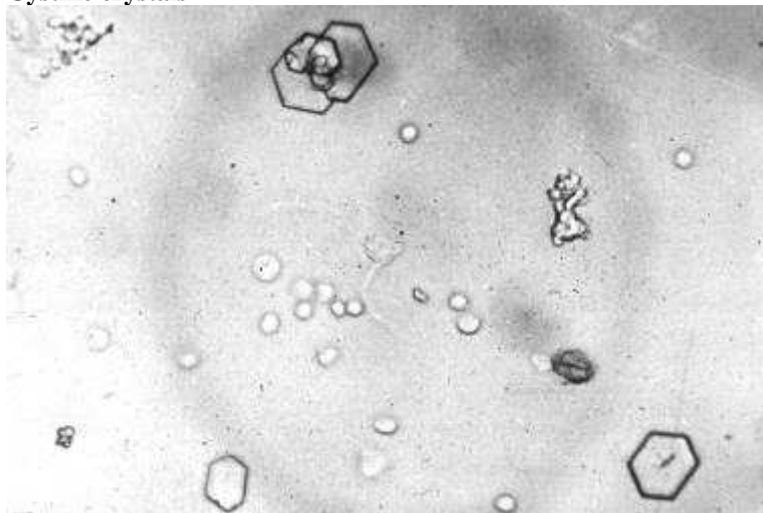
In institutions where appropriately dosed CT imaging for children is not available or when radiation should be avoided, as in pregnant women, imaging alternatives include ultrasonography and plain abdominal radiography. Ultrasonography is preferred as it can detect radiolucent stones and urinary obstruction. Ultrasonography is the overall imaging choice when radiation should be avoided, such as in pregnant patients. (See "Imaging" above).

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## GRAPHICS

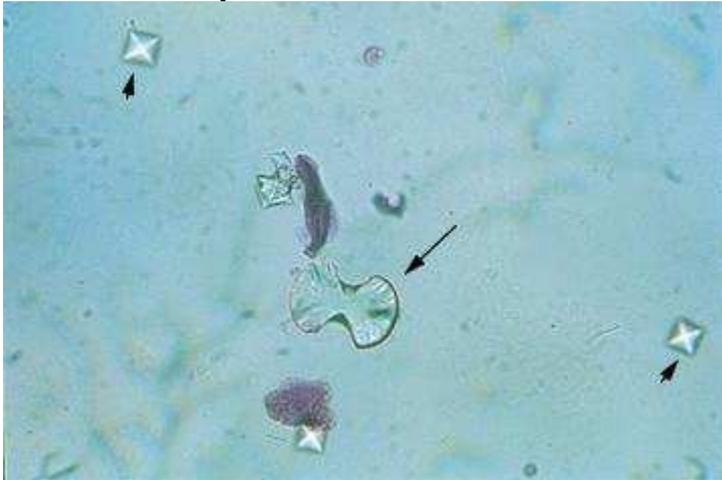
### Cystine crystals



Urine sediment showing hexagonal cystine crystals that are essentially pathognomonic of cystinuria. *Courtesy of Harvard Medical School.*

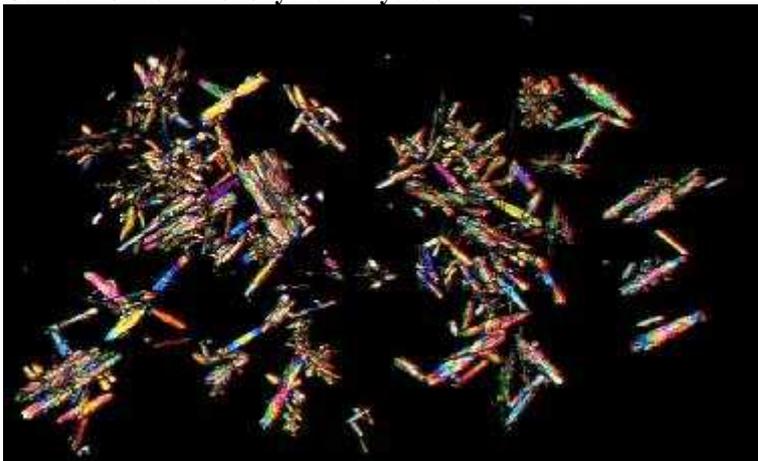
## Calcium oxalate crystals

### Calcium oxalate crystals



Urine sediment showing both dumbbell-shaped calcium oxalate monohydrate (long arrow) and envelope-shaped calcium oxalate dihydrate (short arrows) crystals. Although not shown, the monohydrate crystals may also have a needle-shaped appearance. The formation of calcium oxalate crystals is independent of the urine pH. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Calcium oxalate monohydrate crystals



Urine sediment viewed under polarized light showing coarse, needle-shaped calcium oxalate monohydrate crystals. These crystals have a similar appearance to hippurate crystals. *Courtesy of W Merrill Hicks, MD.*

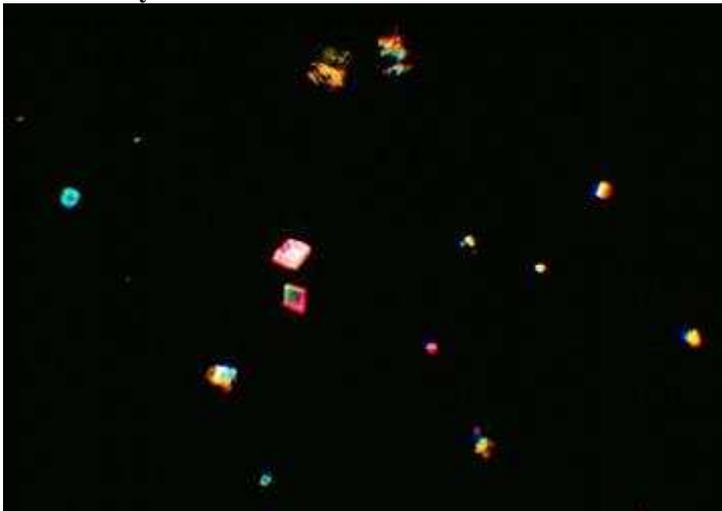
## Uric acid crystals

### Uric acid crystals



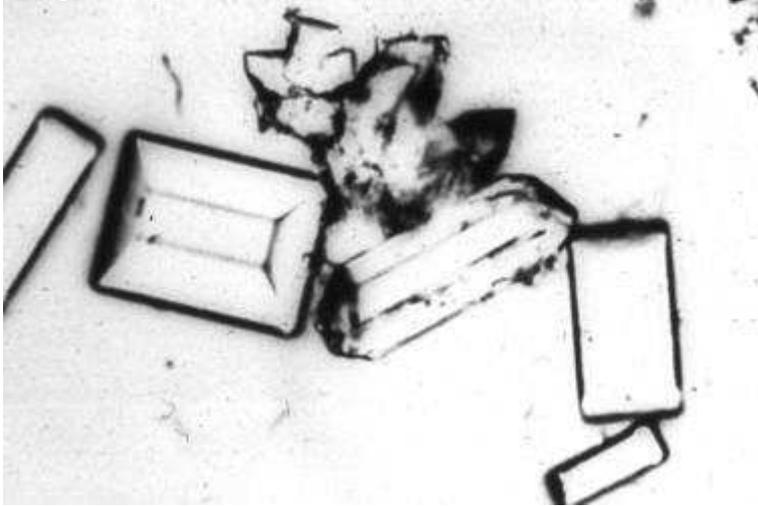
Urine sediment loaded with uric acid crystals. These crystals are pleomorphic, most often appearing as rhombic plates or rosettes. They are yellow or reddish-brown and form only in an acid urine. *Courtesy of Harvard Medical School.*

### Uric acid crystals



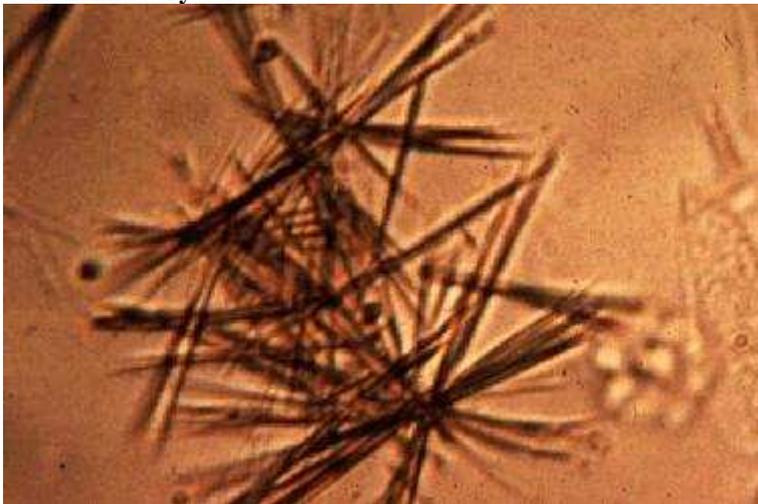
Urine sediment showing uric acid crystals viewed under polarized light. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Phosphate crystals



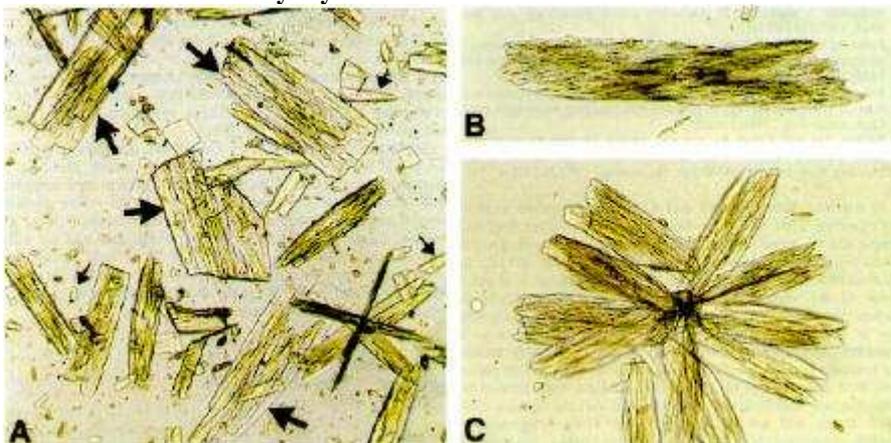
Urine sediment showing multiple "coffin lid" magnesium ammonium phosphate crystals which form only in an alkaline urine (pH usually above 7.0). *Courtesy of Harvard Medical School.*

### Sulfonamide crystals



Urine sediment showing sulfonamide crystals with a needle-shaped appearance. Other forms that may be seen include rosettes and a shock of wheat appearance. *Courtesy of Harvard Medical School.*

### Indinavir sulfate urinary crystals

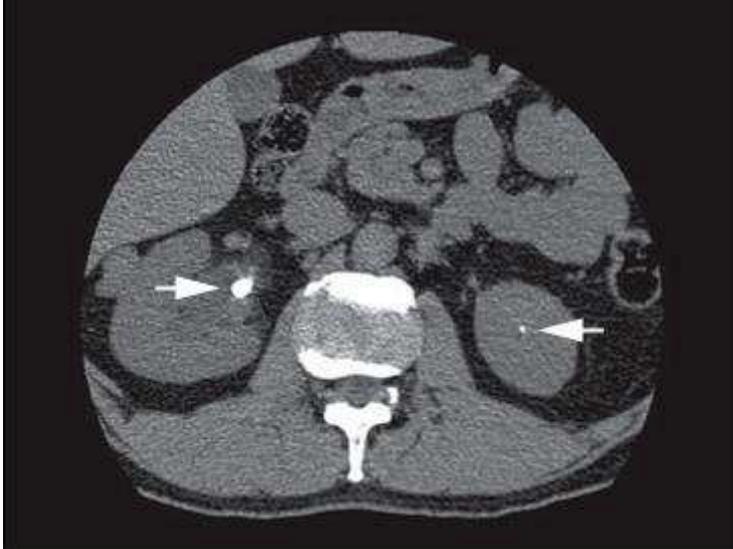


Light microscopic photographs of a fresh unstained preparation of urinary sediment showing three different forms of indinavir sulfate crystals. Panel A: Rectangular plates of various sizes containing needle-shaped crystals. The plates have irregular borders with occasional tapering, and internal layering evident in the largest forms (large arrows). Small, triangular pieces (small arrows) represent broken ends of needles. Panel B: A sheaf of densely packed indinavir sulfate needles. Panel C: A rosette-like structure composed of multiple needles radiating from a central point.

C: Several indinavir crystal groupings are arranged in a rosette. *Reprinted with permission, Gagnon, RF, Tsoukas, CM, Watters, AK, Ann Intern Med 1998; 128:321.*

## Kidney stone helical CT Scan

### Helical computer tomographic scan of the upper abdomen



High-resolution helical computer tomographic image demonstrating a stone in the right renal pelvis and a smaller stone in the left kidney (arrowheads). There is no hydronephrosis. *Reproduced with permission from Curhan, G. A 44-year-old woman with kidney stones. JAMA 2005; 293:1107. Copyright © 2005 American Medical Association.*

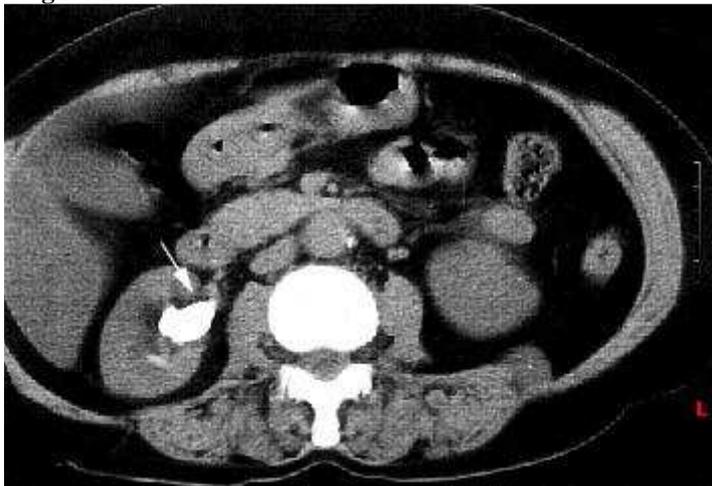
## Ureteral stone CT

### Calculus obstructing left ureter



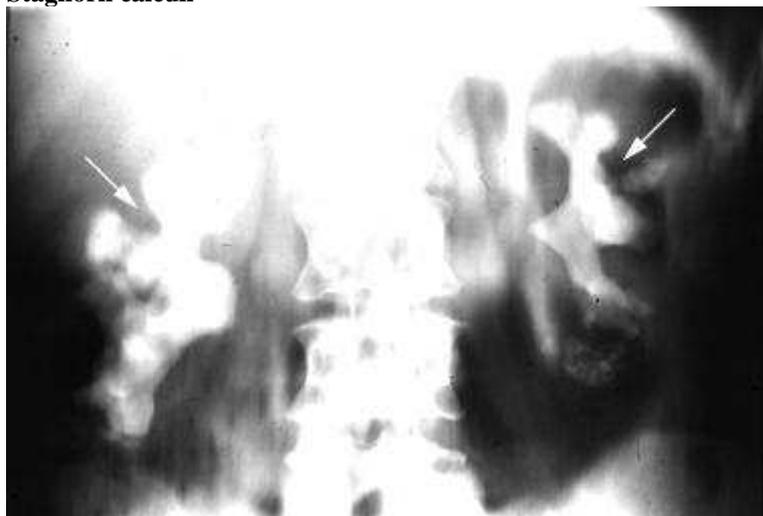
CT scan shows a calculus in the proximal left ureter causing delayed excretion of contrast material from the left kidney (long arrow). All the contrast has been excreted from the normal functioning right kidney and is in the nondilated right ureter (small arrow). *Courtesy of Jonathan Kruskal, MD.*

### Staghorn calculus



CT scan without contrast shows large staghorn calculus in the right kidney (arrow). *Courtesy of Mark D Aronson, MD.*

**Staghorn calculi**



Plain film of the abdomen (no contrast) showing bilateral radiopaque branched, staghorn calculi filling the collecting systems (arrows). *From Rose, BD, Pathophysiology of Renal Disease, 1st ed, McGraw-Hill, New York, 1981.*

## **Diagnostic des malformations et des obstructions des voies urinaires chez l'enfant, ainsi que le suivi des diagnostics anténataux**

Les anomalies, malformatives et obstructives des voies excrétrices sont fréquentes et extrêmement variées. Les circonstances de découverte, chez l'enfant, sont diverses : la malformation peut être mise en évidence à l'occasion du bilan pratiqué en présence d'une infection urinaire. La découverte peut être fortuite : exploration d'un autre appareil, traumatisme révélateur, ou de plus en plus à l'occasion d'une échographie anténatale.

### **1. TECHNIQUES D'IMAGERIE**

#### **1.1 Moyens d'exploration**

L'imagerie est essentielle pour réaliser un bilan morphologique, préciser le niveau et la nature des obstacles, apprécier le retentissement fonctionnel.

*L'échographie* constitue le premier examen à réaliser dans la majorité des cas. Cette échographie doit analyser l'ensemble de l'arbre urinaire, haut et bas appareil. Elle permet une étude satisfaisante du parenchyme rénal et apprécie l'importance d'une stase urinaire supérieure. Au niveau du pelvis, l'échographie doit étudier la vessie et l'existence éventuelle d'une dilatation des bas uretères.

La *cystographie* permet l'étude morphologique du bas-appareil, en particulier chez le garçon; chez celui-ci, toute suspicion d'obstacle sous-vésical impose la ponction sus-pubienne. L'existence d'un reflux vésico-urétéral est fréquente dans le cadre des uropathies malformatives.

*L'urographie intraveineuse* est actuellement un examen de seconde intention. Elle permet une bonne analyse morphologique du parenchyme rénal, des voies excrétrices supérieures. Elle donne une appréciation relative des capacités d'excrétion de chaque rein.

Ces trois examens sont le plus souvent suffisants pour préciser le diagnostic d'une uropathie malformative. Dans le cas contraire, il est nécessaire de faire appel à d'autres techniques :

- *Ponction directe et opacification* d'une cavité dilatée en amont d'un obstacle ;
- *Scintigraphie rénale, en particulier au DTPA*, pour mesurer l'importance et le retentissement d'un obstacle, en particulier lors d'épreuves d'hyperdiurèse.

#### **1.2 Conduite à tenir à la naissance lors du dépistage anté-natal d'une uropathie malformative**

La réalisation systématique, durant la grossesse, d'une échographie de dépistage modifie le mode de présentation et les enfants sont souvent explorés avant que l'uropathie ne se manifeste cliniquement

Tout diagnostic anté-natal d'une malformation urinaire impose une exploration postnatale. Cette exploration doit être réalisée assez rapidement, de façon à confirmer le diagnostic, préciser le bilan lésionnel et rechercher des lésions associées. Il faut distinguer les nouveau-nés supposés porteurs d'une uropathie unilatérale, peu sévère, et ceux atteints d'une malformation grave avec retentissement néphrologique et/ou vital :

- Les nouveau-nés suspects d'une uropathie non sévère ne doivent pas être explorés trop tôt, car la diurèse physiologique est basse pendant les premiers jours de vie, ce qui peut masquer une dilatation en amont d'un obstacle: la fin de la première de semaine constitue la bonne période.
- Les nouveau-nés atteints d'une malformation grave avec retentissement néphrologique et/ou vital sont explorés plus précocement, de façon à prendre, le cas échéant, une décision thérapeutique urgente.

Le bilan est réalisé avec une échographie première, qui permet d'orienter la chronologie des explorations ultérieures : cystographie, urographie intra-veineuse. Chaque cas particulier sera discuté au chapitre pathologique correspondant.

## **2. Anomalies de nombre et de taille des reins**

### **2.1 Agénésie rénale**

L'agénésie rénale est définie par l'absence de toute ébauche parenchymateuse. Il n'existe pas d'artère rénale, ni de voie excrétrice, ni d'orifice urétéral vésical. L'agénésie rénale peut être:

- bilatérale: rare, elle est incompatible avec la vie. L'échographie anténatale montre l'absence de structures rénales au niveau des fosses lombaires, associée à un oligo-amnios responsable d'un faciès de Potter à la naissance. La survenue d'un pneumothorax lié à l'hypoplasie pulmonaire est classique;
- unilatérale: cette anomalie est considérée comme fréquente, environ 1/1000. Elle est sûrement plus rare, car beaucoup de C fosses lombaires vides È assimilées à des agénésies correspondent en fait à la présence d'un petit rein hypoplasique et/ou dysplasique. L'association à des anomalies génitales homo latérales est classique, en particulier chez la fille: duplication de l'appareil génital, hypoplasie utérine ou ovarienne. Devant ces malformations, il faut rechercher un petit rein dysplasique avec abouchement urétéral ectopique avant d'affirmer l'agénésie.

Le diagnostic de cette agénésie repose sur:

- L'abdomen sans préparation, qui confirme la vacuité de la fosse lombaire avec une absence d'ombre rénale, une médialisation de l'angle colique qui vient combler l'espace laissé libre;
- L'échographie, qui montre l'absence de structure rénale individualisable dans une fosse lombaire et le reste de la cavité abdominale associée à l'hypertrophie compensatrice du rein controlatéral.

## **2.2 Aplasie rénale**

Elle correspond à la forme majeure de la dysplasie rénale (cf. infra). Il existe une ébauche rénale fibreuse ou fibrokystique avec quelques dérivés wolffiens, des lésions d'endartérite et des îlots cartilagineux. L'artère rénale est de petite taille. La voie excrétrice est présente avec un orifice urétéral vésical. L'uretère peut être borgne et relié au rénicule par un cordon fibreux (aplasie majeure) ou perméable sur toute sa longueur (aplasie mineure).

## **2.3 Hypoplasie rénale**

Elle est définie par un rein de petite taille en rapport avec une anomalie de son développement. L'hypoplasie doit être distinguée de la dysplasie d'une part, d'un petit rein atrophique secondaire à une affection acquise d'autre part. Trois formes sont individualisées :

### **2.3.1. Hypoplasie simple**

C'est une réduction de taille sans lésion parenchymateuse. C'est le "rein de poupée", ou hypoplasie harmonieuse organoïde. Elle peut être unilatérale ou bilatérale. La fonction rénale est normale. En échographie, la différenciation cortico-médullaire est respectée. L'urographie montre des cavités non dilatées, avec une conservation de l'index parenchymateux.

### **2.3.2. Hypoplasie oligoméganéphronique**

Il existe deux petits reins harmonieux, sans anomalie des cavités. Histologiquement, les néphrons sont en nombre réduit, avec une augmentation de taille des glomérules et un allongement des tubules. Cette affection prédomine chez le garçon, et évolue constamment vers l'insuffisance rénale à l'adolescence.

### **2.3.3. Hypoplasie rénale segmentaire: rein de Ask-Upmark:**

Elle correspond à une réduction de taille du rein, avec des encoches corticales s'accompagnant d'une dilatation calicielle en regard. Anatomiquement, les tubes sont dilatés ou atrophiques. Les glomérules sont absents (hypoplasie segmentaire "agglomérulaire") ou comprimés. Il existe une endartérite oblitérante des artères arquées et inter lobulaires.

Sur le plan clinique, il existe une prédominance féminine. L'hypertension artérielle est fréquente. L'échographie et l'urographie intraveineuse confirment l'atteinte segmentaire. L'atteinte peut être uni- ou bilatérale. Le diagnostic différentiel avec la néphropathie de reflux, où il existe des cicatrices rétractiles, est impossible. La recherche d'un reflux vésico-urétéral est capitale, mais il peut y avoir un reflux associé à une hypoplasie et le diagnostic exact ne peut être qu'histologique.

## **2.4 Dysplasie rénale**

Elle est définie par un arrêt du développement embryonnaire normal du rein avec une différenciation anormale du tissu méta-néphrogène. Elle doit être distinguée de l'hypoplasie simple, les structures histologiques sont normales, et de l'atrophie, il existe une destruction secondaire du rein. Lorsque le rein est petit, il s'agit d'une hypodysplasie. S'il existe des

formations kystiques, avec un rein de taille variable, le terme de "dysplasie multikystique" est utilisé.

#### **2.4.1. Anatomopathologie**

Les critères diagnostiques de la dysplasie sont histologiques : présence de tubes primitifs médullaires, parfois bordés de cellules fibro-musculaires; mise en évidence d'îlots de cartilage métaplasique. L'atteinte peut être corticale et/ou médullaire, totale ou segmentaire, avec alternance de zones saines et de zones pathologiques. Elle est le plus souvent unilatérale.

#### **2.4.2. Pathogénie**

La pénétration du bourgeon urétéral au centre du blastème métanéphrogène induit le développement normal du parenchyme rénal. La naissance du bourgeon urétéral détermine également la situation de l'orifice urétéro-vésical. Si le bourgeon urétéral naît trop haut ou trop bas sur le canal de Wolff, l'orifice urétéral est en situation ectopique. A l'autre extrémité, plus la pénétration du bourgeon urétéral est éloignée du centre de l'ébauche rénale, plus le parenchyme est dysplasique. Ces aspects embryologiques permettent de comprendre l'association fréquente d'une dysplasie rénale et d'un abouchement urétéral ectopique. La dysplasie peut être partielle, développée en regard d'un des deux pyélons d'une duplication totale. Les lésions de dysplasie rénale observées lorsqu'il existe des valves de l'urètre semblent plus en rapport avec une anomalie associée au niveau des orifices urétéraux qu'avec la stase induite par l'obstacle urétral.

#### **2.4.3. Aspects cliniques et radiologiques**

Les signes cliniques sont peu spécifiques, l'infection urinaire est le mode de découverte le plus fréquent. Une "pseudo-incontinence", témoignant d'un abouchement ectopique extra vésical, peut être révélatrice chez la fille. L'absence de structure rénale visible dans une fosse lombaire lors d'une échographie anténatale est également un mode de révélation.

L'imagerie varie en fonction des anomalies de la voie excrétrice:

- En échographie, le rein est petit. Des lésions de dysplasie sont suspectées lorsqu'il existe une différenciation cortico-médullaire, avec un parenchyme plus échogène que le foie, et des micro- ou macrokystes;
- L'urographie montre un défaut de concentration ou une absence de sécrétion associés à des anomalies morphologiques des voies excrétrices, simplifiées et/ou dilatées.

Le rein peut ne pas être individualisable avec l'imagerie, faisant porter à tort le diagnostic d'agénésie rénale. Lorsqu'il existe un système double, la reconnaissance d'un pyélon supérieur muet en regard d'une zone de parenchyme dysplasique peut également être difficile.

- Dysplasie multikystique (figure 1) : elle correspond à un rein de taille variable, souvent volumineux, avec des kystes également de taille variable, juxtaposés les uns après les autres.

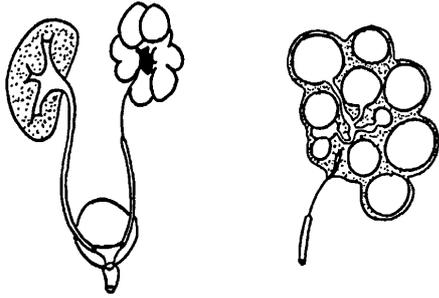


Figure 1 : Dysplasie multikystique.

Les kystes peuvent être indépendants, ou communiquer par des structures tubulaires. L'uretère est soit atrétique, soit perméable, communiquant ou non avec les kystes par l'intermédiaire de tubules. Au centre de la masse et entre les kystes, il existe du tissu fibreux comportant des éléments dysplasiques. L'atteinte est en général unilatérale, mais peut être associée à une autre malformation controlatérale.

L'hypothèse physiopathologique actuellement retenue, est celle d'une forme très sévère de sténose infundibulo-pyélique ou urétérale, survenant précocement pendant la vie intra-utérine. La stase urinaire provoque le développement dysplasique du parenchyme rénal. Il existe ainsi une continuité pathogénique entre les malformations de la jonction pyélo-urétérale, les sténoses infundibulaires avec hydrocalices et la dysplasie multikystique, qui représente la forme majeure des sténoses infundibulo-pyéliques.

De nombreux cas sont dépistés par l'échographie anténatale, qui met en évidence l'existence de formations transsoniques de taille et de nombre variables, juxtaposées, disposées sans organisation particulière, et séparées par des septa échogènes sans parenchyme rénal individualisable et sans dilatation des voies excrétrices sous-jacentes.

A la naissance, l'existence d'une masse abdominale mobile, lobulée, sans retentissement sur l'état général, peut être révélatrice si la formation multikystique est volumineuse. L'échographie confirme la présence de multiples formations liquidiennes séparées par des septa échogènes, sans communications, ce qui doit permettre de la différencier d'une obstruction de la jonction pyélo-urétérale. L'urographie montre un rein muet avec parfois une prise de contraste au niveau des septa et des parois des kystes. La cystographie peut retrouver un reflux dans un uretère borgne. Cette séméiologie est modifiée si la dysplasie multikystique se développe sur l'un des pyélons d'une duplication totale : en échographie, la zone correspondant au parenchyme sain peut être méconnue, ce qui justifie la réalisation d'une urographie avant toute intervention. Enfin, si le rein est d'emblée de petite taille, il peut être difficile de le mettre en évidence.

Lorsque le diagnostic est méconnu à la période néonatale, deux évolutions sont possibles : la diminution progressive de taille des kystes s'accompagne d'une atrophie secondaire de la masse rénale. Si des kystes volumineux persistent, des calcifications pariétales peuvent apparaître. L'hypertension artérielle est rare, la dégénérescence maligne exceptionnelle.

### **3. Anomalies de position**

Pendant la vie foetale, le métanéphros est en position pelvienne. Il va progressivement subir une rotation le mettant en position frontale et une migration en regard de la fosse lombaire.

#### **3.1 Dystopie rénale**

C'est l'anomalie de rotation du rein :

- absence de rotation (fréquente): jonction pyélo-urétérale antérieure ;
- excès de rotation: jonction pyélo-urétérale postérieure ;
- rotation inverse: jonction pyélo-urétérale externe.

La malrotation peut être uni- ou bilatérale, associée à une ectopie ou à une fusion entre les deux reins. Le diagnostic est porté sur l'urographie qui montre un bassinnet un peu agrandi, parfois déformé, qui se projette, de face, sur les groupes caliciels. L'uretère à son origine est écarté du rachis. La réalisation d'incidences obliques aide à déterminer le type de malrotation. L'association à une malformation de la jonction pyélo-urétérale est fréquente et peut être révélatrice.

#### **3.2 Ectopie rénale**

Le rein peut être en ectopie haute, ectopie basse ou ectopie croisée.

##### **3.2.1. Rein intrathoracique**

C'est une anomalie rare touchant essentiellement le rein gauche chez le sujet mâle. L'ectopie peut être intrathoracique vraie à travers un défaut diaphragmatique, ou sous le feuillet fibreux d'une éventration.

Le mode de découverte le plus fréquent est la mise en évidence d'une opacité basithoracique postérieure gauche. L'échographie permet de suspecter le diagnostic: elle montre la vacuité de la fosse lombaire et l'existence d'une structure rénale au-dessus de la rate. L'urographie confirme le diagnostic.

##### **3.2.2. Ectopie basse**

L'ectopie peut être lombaire basse, iliaque ou pelvienne (fréquente). Elle est uni- ou bilatérale, et peut survenir sur un rein unique. La présence d'une dystopie associée est fréquente, de même que l'existence d'une obstruction de la jonction pyélo-urétérale. La découverte peut être fortuite ou être en rapport avec l'exploration d'une masse abdomino-pelvienne. Le risque de lésion au cours d'un traumatisme doit être pris en compte. En échographie un rein en ectopie iliaque basse peut être difficile à reconnaître parmi les structures digestives. Au niveau du pelvis, la réplétion vésicale aide au diagnostic. En urographie, la constatation d'une fosse lombaire vide implique la réalisation de clichés obliques pour ne pas méconnaître un pyélogramme se projetant sur le rachis.

##### **3.2.3. Ectopie croisée**

Les deux reins sont situés du même côté. L'uretère du rein ectopique croise la ligne médiane et se termine dans la vessie par un orifice en position normale. L'ectopie croisée peut être simple ou double. Lorsqu'elle est simple, l'existence d'une fusion rénale entre les deux parenchymes est fréquente. Le mode de découverte peut être motivé par l'exploration d'une masse abdominale.

### **3.3 Fusion entre les deux reins**

Les reins fusionnés se caractérisent par l'existence d'un isthme parenchymateux ou fibreux entre les deux reins: ectopie rénale croisée avec fusion, rein en "fer à cheval", rein discoïde. Toutes ces fusions sont associées à d'importantes variations de la vascularisation avec artères multiples et ectopiques et à des anomalies de la voie excrétrice, souvent obstructives.

#### **3.3.1. Symphyses rénales sur ectopie croisée**

Le rein ectopique est fusionné à l'autre rein. Il y a plusieurs types de fusion:

- le rein sigmoïde: le bord interne du pôle supérieur du rein ectopique est fusionné avec le bord interne du pôle inférieur du rein en place. L'axe des deux reins est vertical;
- le rein en Ç L È: le rein ectopique est transversal, pré rachidien, fusionné par un pôle avec le pôle inférieur du rein en place.

#### **3.3.2. Le rein "en fer à cheval"**

Les deux reins sont fusionnés par un isthme pré rachidien, pré-vasculaire, fibreux ou parenchymateux, réunissant le plus souvent leurs pôles inférieurs. Ils sont verticalisés, rapprochés de la ligne médiane, plus bas que des reins normaux. Les cavités sont dystopiques par défaut de rotation, avec une jonction pyélo-urétérale antérieure ou externe. Les orifices urétéraux sont normaux.

Les signes cliniques permettant la mise en évidence d'un rein en "fer à cheval " sont souvent peu spécifiques: infection urinaire, ou en rapport avec une anomalie de la voie excrétrice associée: obstruction de la jonction pyélo-urétérale, fréquente, lithiase. Des douleurs abdominales lors de l'hyperextension du rachis seraient plus évocatrices. Le rein en "fer à cheval " peut s'intégrer dans un syndrome malformatif plus complexe ou dans le cadre d'une aberration chromosomique (syndrome de Turner, trisomie 18).

L'échographie permet de noter la verticalisation des reins, et l'isthme parenchymateux est facile à voir en avant des vaisseaux. S'il s'agit seulement d'un pont fibreux, le diagnostic peut être plus difficile. En urographie, les pôles inférieurs des reins sont rapprochés, l'arbre caliciel est oblique en bas et en dedans. Le groupe caliciel inférieur se projette sur le rachis. Les uretères ont un trajet en avant des bassinets et de l'isthme parenchymateux. Le reflux vésico-urétéral est fréquent et doit être recherché par une cystographie.

#### **3.3.3. Rein discoïde ou en "galette "**

Les deux reins sont fusionnés par leurs deux pôles et forment une masse parenchymateuse en ectopie pelvienne. Il peut exister deux uretères à abouchement normal. Les bassinets peuvent être communicants avec un ou deux uretères.

## 4. Malformations des calices

### 4.1 Diverticule pré-caliciel (figure 2) : kyste pyélogénique

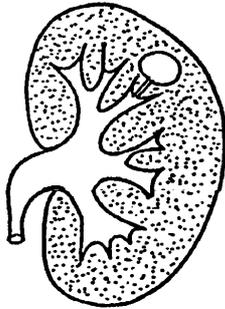


Figure 2 : Diverticule pré-caliciel.

C'est une cavité intraparenchymateuse remplie d'urine et bordée par un épithélium transitionnel qui communique avec le fornix ou avec la tige d'un calice normal par un canal très étroit. Il siège habituellement au pôle supérieur du rein. Il est plus souvent unique que multiple. Il s'agit probablement d'une anomalie de division d'un bourgeon urétéral primitif qui, au lieu de donner un petit calice, aboutit à la formation d'un kyste communicant. Certains auteurs évoquent la rupture possible d'un kyste simple dans un calice. Le diverticule précaliciel est presque toujours asymptomatique. Il peut cependant être volumineux et se compliquer d'infection et de lithiase, surtout en cas d'obstruction inflammatoire du collet.

En échographie, il existe une image liquidienne se projetant en bordure du sinus rénal. L'urographie montre une image d'addition se remplissant de façon synchrone avec les cavités excrétrices, qui se projette en dehors de la ligne interpapillaire de Hodson, ce qui permet de le différencier d'un hydrocalice.

### 4.2 Hydrocalice

C'est la dilatation isolée d'un calice par sténose de la tige calicielle. Cette sténose peut être intrinsèque ou extrinsèque:

- la sténose intrinsèque correspond à une hypoplasie infundibulaire: elle peut être isolée et n'intéresser qu'une tige calicielle, ou en toucher plusieurs et s'étendre au bassinet (sténose infundibulo-pyélique). Le rein multikystique serait la forme majeure d'une hypoplasie très étendue. L'urographie montre une dilatation calicielle en amont d'une sténose de la tige. Lorsque l'hydrocalice est compliqué (infection, lithiase), il est difficile de faire la part entre une véritable sténose congénitale et une fibrose rétractile secondaire de la tige calicielle, avec stase d'amont.
- la compression extrinsèque de la tige calicielle supérieure par une artère polaire constitue le *syndrome de Fraley*. La présence d'une empreinte vasculaire au pied de la tige calicielle supérieure est fréquente et n'a de signification pathologique que si il existe une dilatation d'amont avec stase du produit de contraste.

#### 4.3 Méga-polycalicose

C'est une hypoplasie des pyramides de Malpighi avec ectasie passive et multiplication des petits calices. En urographie, les tiges calicielles sont courtes et larges; le bassinet et l'uretère ne sont pas dilatés. Les contours du rein sont normaux. Il faut différencier cet aspect d'une dilatation calicielle en rapport avec une anomalie de la jonction pyélo-urétérale. La réalisation d'une épreuve d'hyper-diurèse, en montrant l'absence d'obstacle fonctionnel, peut aider à faire la distinction.

### 5. MALFORMATION DE LA JONCTION PYÉLO-URÉTÉRALE (FIGURE 3)

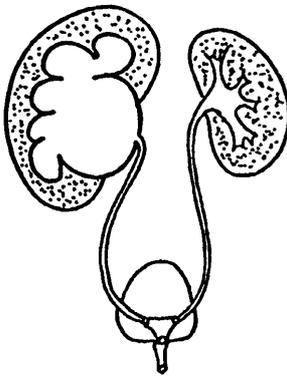


Figure 3 : Syndrome de la jonction pyélo-urétérale.

C'est le dysfonctionnement obstructif de la jonction pyélo-urétérale, qui peut correspondre à plusieurs anomalies :

- fonctionnelles (50 %) : disparité de calibre entre le bassinet et l'uretère sans obstacle visible. Le péristaltisme pyélique est mal transmis à l'uretère; il existe des anomalies histologiques de la musculuse;
- organiques (50 %) : sténose fibreuse (20 %), insertion haute de l'uretère, plicature, repli valvulaire, polype fibreux. Le croisement avec une artère polaire est fréquent (20 %), mais le plus souvent, il n'est pas responsable de l'obstruction.

L'atteinte peut être uni- ou bilatérale, asymétrique. L'association avec les autres malformations rénales est fréquente. Les cavités pyélo-calicielles sont plus ou moins dilatées en amont de la jonction en fonction de la sévérité de l'obstruction. Parallèlement, le rein est plus ou moins gros, très volumineux dans les obstructions sévères. La dilatation peut toucher de façon égale le bassinet et les calices, ou prédominer sur celui-là ou ceux-ci. L'atteinte du parenchyme est variable (figure 4), allant du parenchyme conservé (A, B, C) à une mince lame atrophique entourant les cavités dilatées (D, E). Des kystes dysplasiques peuvent se développer dans ce parenchyme atrophique (F). Quand ces kystes sont volumineux, ils réalisent la forme hydronéphrotique du rein multikystique (Felson).



*Figure 4 : Etat du parenchyme dans les dilatations hydronéphrotiques.*

Les circonstances de découverte ont été modifiées par l'échographie anténatale: l'existence d'une pyélectasie dont le diamètre est supérieur à 10 mm implique un bilan morphologique plus complet à la naissance, avec au minimum la réalisation d'une échographie postnatale. Dans les autres cas, le diagnostic est porté devant des signes non spécifiques: infection urinaire, ou plus évocateurs: douleurs intermittentes d'une fosse lombaire. Un traumatisme peut également être un mode de découverte, et être à l'origine d'une décompensation aiguë de l'obstruction, d'autant plus que la taille du bassinet le rend plus vulnérable. La présence de caillots peut majorer l'obstacle, avec une dilatation majeure initiale. Il ne faut pas juger de la valeur fonctionnelle du rein à la phase initiale, mais après une période de récupération.

#### *Imagerie :*

L'échographie montre la dilatation pyélo-calicielle avec un aspect communicant des cavités (aspect en "oreille de Mickey"). Toute dilatation du bassinet supérieure à 10 mm est suspecte. Un simple bassinet extra-sinusal peut être difficile à éliminer. Il faut apprécier l'épaisseur du parenchyme rénal et confirmer le niveau de l'obstacle en montrant l'absence de dilatation de l'uretère en arrière de la vessie.

Les aspects urographiques varient en fonction du degré d'obstruction :

- aspect de néphrogramme en "coquillage", en "lâcher de ballons" dans les obstructions graves, avec absence de sécrétion; dans ces formes majeures, la ponction directe du bassinet peut permettre son opacification, confirmant le diagnostic.
- signe du "croissant de Dunbarr ", qui correspond à la stagnation d'urine opacifiée dans les tubes collecteurs à la périphérie des calices dilatés ; la présence de ce signe est un bon élément en faveur de la persistance d'une valeur fonctionnelle du rein en stase. Il faut poursuivre l'examen et réaliser des clichés retardés.
- retard d'excrétion avec dilatation des cavités, aspect en "boule" des calices, perte de la concavité du bord inférieur du bassinet. La réalisation d'un cliché en procubitus favorise les passages urétéraux et permet de montrer la disparité de calibre entre le bassinet et l'uretère.
- défaut d'adaptation au débit urinaire avec dilatation des cavités au cours d'une épreuve d'hyperdiurèse (test au furosémide) qui permet de démasquer une forme intermittente.

La réalisation d'une scintigraphie au DTPA (acide diéthylènetriamine pentacétique) avec épreuve d'hyperdiurèse permet également de chiffrer le degré d'obstruction.

A la période néonatale, les formes intermittentes ou modérées, sans retard de sécrétion, justifient une surveillance simple en imagerie. Les formes sévères avec conservation de la fonction rénale relèvent d'une pyéloplastie chirurgicale. Les formes graves, avec dilatation majeure et fonction rénale altérée peuvent être traitées soit par néphrostomie percutanée transitoire, soit par pyéloplastie d'emblée : en fonction de l'évolution, une décision de néphrectomie secondaire peut être posée.

## 6. MALFORMATIONS DE L'URETÈRE

Les sinuosités fœtales ne constituent pas une malformation: ce sont des replis de l'urothélium de l'uretère lombaire, sans fibre musculaire, sans obstruction, qui involuent en postnatal.

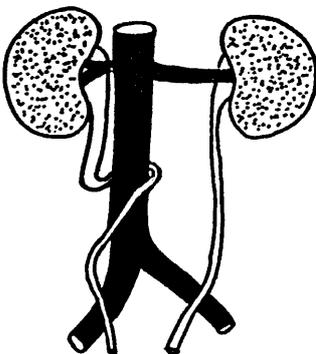
### 6.1 Uretère rétrocave

Le trajet lombaire de l'uretère droit est anormal: il passe en arrière, puis en dedans, et enfin en avant de la veine cave inférieure (figure 5).

C'est une anomalie de formation de la veine cave inférieure par défaut de développement de la veine supracardinale. Exceptionnellement, l'uretère rétrocave peut être gauche, en cas de veine cave double ou de situs inversus.

Les signes cliniques sont absents ou modérés, en fonction du degré d'obstruction.

L'urographie montre une dilatation pyélo-calicielle en général peu importante. L'uretère, dans son segment proximal, est dilaté. En regard de L3-L4, il se recourbe en dedans, avec un aspect en " J " renversé. Le segment rétrocave est fin ou mal visible. L'uretère sous-jacent est médialisé et de calibre normal.



*Figure 5 : Uretère rétrocave*

Il existe d'autres malformations urétéro-vasculaires : uretère rétro-iliaque, croisement rétro-ovarien ou rétrospermatique, croisement avec l'artère ombilicale.

### 6.2 Sténoses et valves de l'uretère

Ce sont des sténoses ou replis de l'urothélium contenant des fibres musculaires. Ces obstacles siègent sur l'uretère lombaire. Quand ils siègent haut, ils posent des problèmes nosologiques avec une sténose basse de la jonction pyélo-urétérale. Quand ils siègent bas, ils sont difficiles à différencier des méga-uretères obstructifs.

### 6.3 Atrésie urétérale

C'est une solution de continuité de la lumière urétérale. Elle est rarement isolée, avec une dilatation urétéro-pyélo-calicielle sus-jacente. Elle est le plus souvent associée avec une aplasie rénale ou surtout une dysplasie multikystique.

### 6.4 Méga-uretère primitif obstructif

C'est la dilatation congénitale de l'uretère en amont d'un segment terminal obstructif, d'apparence macroscopique normale, avec un abouchement normal, dans une vessie normale, sans obstacle cervico-urétral .

L'élément obstructif siège sur la partie terminale de l'uretère. Sa longueur est en moyenne de 1,5 cm. Les lésions responsables sont variées : hypertrophie collagénique pure, anomalies des fibres musculaires (défaut de fibres musculaires longitudinales, prédominance de fibres circulaires, dysembryoplasie fibro-épithéliale, collier scléreux). L'aspect histologique peut être rigoureusement normal, témoin d'un obstacle entièrement fonctionnel. Au-dessus de l'obstacle, l'uretère se dilate, puis s'allonge et forme des boucles. La paroi est épaissie. Le péristaltisme est conservé. Le retentissement parenchymateux est moins marqué que dans les autres obstacles.

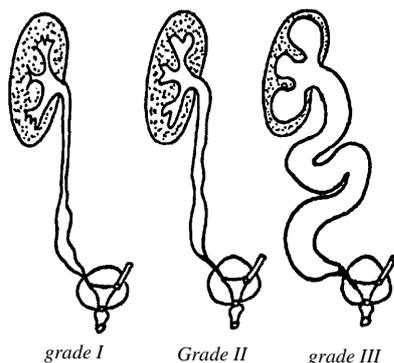


Figure 6 : Différents types de méga-uretères.

Il est habituel de distinguer trois types:

- type 1 : méga-uretère pelvien ou ilio-pelvien respectant la partie haute lombaire et les cavités pyélo-calicielles;

- type 2 : méga-uretère total avec dilatation d'ensemble sans sinuosité;
- type 3 : dolicho-méga-uretère sinueux.

Sur le plan évolutif, un méga-uretère obstructif primitif est susceptible de régresser spontanément dans les premières années de la vie : les indications thérapeutiques, à la période néonatale, sont moins interventionnistes que pour les syndromes de la jonction pyélo-urétérale.

Le méga-uretère primitif *obstructif* doit être distingué des autres méga-uretères primitifs (méga-uretère en amont d'un abouchement anormal au niveau de la vessie : orifice ectopique, urétérocèle) et des méga-uretères secondaires:

- méga-uretère secondaire à un obstacle sous-jacent: valves de l'urètre, vessie neurogène;
- méga-uretère par reflux vésico-urétéral +++.

Les circonstances de découverte sont similaires à celles des obstructions de la jonction pyélo-urétérale, avec une proportion importante de cas dépistés par une échographie anténatale: celle-ci montre une dilatation du haut appareil, mais n'est pas toujours performante pour situer le niveau de l'obstacle, ce qui impose le bilan postnatal.

Le diagnostic de méga-uretère obstructif repose sur plusieurs examens :

L'échographie montre la dilatation pyélo-urétérale, avec conservation du péristaltisme au niveau du bas uretère dilaté en arrière de la vessie. Il faut également apprécier le retentissement sur le haut-appareil.

L'urographie doit confirmer ces aspects: il faut préciser la morphologie du bas uretère, dont l'extrémité est effilée, en Ç queue de radis È, bien visible sur une incidence oblique. La persistance du méga-uretère à vessie vide est un élément capital du diagnostic.

La réalisation d'une cystographie complète les explorations pour s'assurer de l'absence d'obstacle cervico-urétral, ou de reflux vésico-urétéral. Ce reflux peut toutefois être associé à un véritable méga-uretère primitif obstructif. Il peut aggraver le pronostic, et justifier la réalisation d'une réimplantation vésico-urétérale.

## **7. DUPLICATIONS DE LA VOIE EXCRÉTRICE**

Ce sont des anomalies très fréquentes, souvent asymptomatiques. Sur le plan embryologique, le bourgeon urétéral, né du canal de Wolff, pénètre le blastème rénal o□ il forme les cavités excrétrices et les tubes collecteurs. S'il existe une division prématurée du bourgeon urétéral, cela entraîne la formation d'une duplication incomplète. Si un bourgeon surnuméraire naît du canal de Wolff, il en résulte une duplication complète.

### 7.1 Duplications partielles (bifidités)

C'est le dédoublement incomplet de la voie excrétrice supérieure avec deux uretères qui se rejoignent à un niveau variable : pyélique, lombaire, iliaque, pelvien ou intramural. Les deux uretères se rejoignent au carrefour de jonction. Ce carrefour peut être le siège de troubles du péristaltisme avec un reflux d'une branche dans l'autre (reflux urétéro-urétéral - phénomène du "yo-yo"). La portion terminale est commune avec un seul orifice vésical en position normale.

L'uretère bifide à branche borgne correspond à une bifidité dont l'un des deux uretères a arrêté son développement et n'a pas atteint le rein. La branche borgne doit être distinguée d'un diverticule urétéral.

### 7.2 Duplications complètes (figure 7)

Le dédoublement des deux uretères est complet. Dans leur portion intramurale, les deux uretères cheminent dans une même gaine et sont vascularisés par la même artère. L'uretère supérieur est celui qui s'abouche le plus bas dans la vessie et l'uretère inférieur est celui qui s'abouche le plus haut (loi de Weigert et Meyer).

Le système caliciel supérieur est simplifié avec deux ou trois petits calices directement branchés sur l'uretère. Le système inférieur est plus complet avec deux ou trois tiges calicielles et un bassinnet dont l'axe est oblique en haut et en dehors, et qui est écarté du rachis. Le rein est plus grand qu'un rein normal (+2 à +4 DS) avec parfois une incisure médiane, correspondant au parenchyme de chacune des voies excrétrices.

La découverte d'une duplication complète non compliquée est souvent fortuite, au cours d'explorations réalisées pour une infection urinaire.

En échographie, le diagnostic est souvent difficile : présence d'une zone d'échogénicité similaire au cortex, divisant le sinus hyper-échogène en deux parties inégales. Cet aspect peut également correspondre à une simple hypertrophie d'une colonne de Bertin.

L'urographie permet d'affirmer la duplication complète lorsque les deux trajets urétéraux sont visibles au niveau de leur segment intramural vésical.

Quand la duplication est compliquée, la pathologie du système supérieur diffère des anomalies du système inférieur :

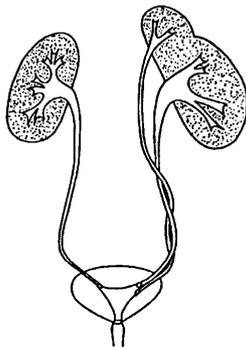


Figure 7 : Duplication totale

- Pathologie du système supérieur (figure 8) :

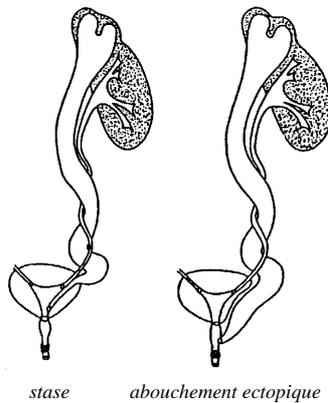


Figure 8 : Duplication et abouchement ectopique avec stase.

- La stase du système supérieur: l'orifice urétéral est bas situé dans le trigone ou au niveau du col vésical avec un trajet très long responsable d'un obstacle fonctionnel et d'un méga-uretère obstructif. Cela peut être associé à une urétérocèle intra-vésicale (cf. infra). La dilatation d'amont est plus ou moins marquée.

- L'abouchement ectopique de l'uretère du pyélon supérieur peut se faire dans l'urètre supra-sphinctérien (sans ou avec urétérocèle ectopique) et, chez le garçon, dans la vésicule séminale, chez la fille, dans l'urètre sous-sphinctérien, à la vulve et dans le vagin.

- La dysplasie du parenchyme supérieur est fréquente et d'autant plus sévère que l'ectopie urétérale est plus marquée. Ce parenchyme est alors peu ou pas fonctionnel. La dysplasie peut avoir un aspect multikystique. Quand le parenchyme en regard du pyélon supérieur est atrophique, la mise en évidence peut être difficile. Il doit être systématiquement recherché devant l'existence de signes cliniques évoquant un abouchement ectopique.

- Pathologie du système inférieur (figure 9) :

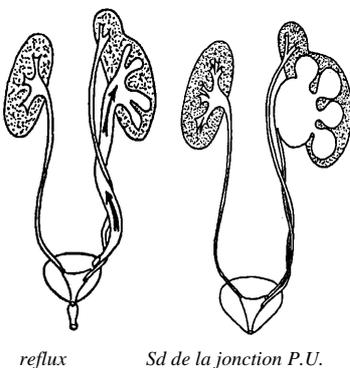


Figure 9 : Pathologie de reflux et syndrome de jonction.

- Le reflux vésico-urétéral: l'orifice vésical est souvent en ectopie intravésicale haute, avec un trajet intramural court, ce qui favorise la survenue du reflux. Celui-ci peut induire une

néphropathie de reflux de gravité variable, avec une atrophie secondaire du pôle inférieur du rein. Ce reflux, s'il survient lors d'une urographie, peut donner le change avec une sécrétion du pyélon inférieur.

- La malformation de la jonction pyélo-urétérale est la seconde complication survenant sur le pyélon inférieur. Elle peut être associée à un reflux dans ce système.

## 8. URÉTÉROCÉLES

C'est la hernie intravésicale de la portion sous-muqueuse dilatée d'un uretère, entre le hiatus du détrusor et son abouchement dans la vessie.

### 8.1 Classification

Il y a quatre types principaux d'urétérocèles en fonction de leur survenue sur un uretère unique ou sur un système double, et de leur topographie intravésicale ou ectopique, à cheval sur le col :

#### 8.1.1. Urétérocèles intravésicales (figure 10)

L'orifice de l'uretère est intravésical, souvent sténosé (urétérocèle "sténotique") et la portion sous-muqueuse de l'uretère dilaté fait une hernie "pseudokystique" plus ou moins volumineuse dans la vessie, sans intéresser le col.

L'urétérocèle intravésicale simple (sur uretère unique) est la plus fréquente (urétérocèle orthotopique de type adulte d'Ericsson). L'urétérocèle intravésicale sur l'uretère supérieur d'une duplication totale est plus rare.

La dilatation de la voie excrétrice est en général modérée et les lésions de dysplasie rénale sont absentes ou discrètes, avec un parenchyme fonctionnel.

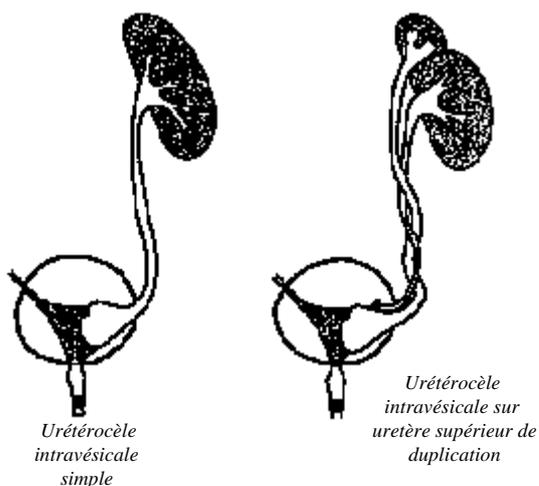


Figure 10 : Urétérocèle.

### 8.1.2. Urétérocèles ectopiques (figure 11)

L'orifice de l'uretère est ectopique sur ou sous le col, ou dans l'urètre sous-cervical, mais sus-sphinctérien. La longue portion sous-muqueuse dilatée fait hernie dans la vessie et réalise une urétérocèle à cheval sur le col, dite ectopique ou extra vésicale.

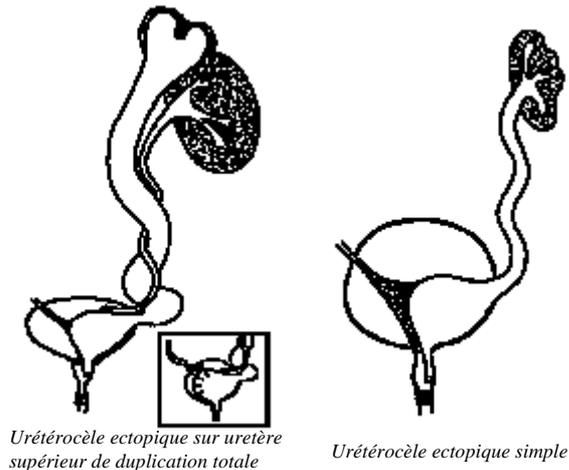


Figure 11 : Urétérocèles ectopiques.

L'urétérocèle ectopique sur uretère supérieur de duplication totale (urétérocèle de type infantile d'Ericsson) est la plus fréquente. L'urétérocèle ectopique simple, développée sur un uretère unique, est rare.

La dilatation de la voie excrétrice sus-jacente et la dysplasie du parenchyme rénal correspondant sont associées à des degrés divers et le rein est peu ou non fonctionnel.

## 8.2 Circonstances de découverte

Le signe révélateur essentiel reste l'infection urinaire. La symptomatologie peut être plus évocatrice: dysurie par urétérocèle obstructive, ou accouchement à la vulve chez la fille. Le diagnostic anténatal est assez rare : le dépistage d'une dilatation du haut appareil implique un bilan postnatal qui permet de reconnaître l'urétérocèle. En fonction de retentissement, celle-ci pourra être affaïssée par endoscopie, ou nécessiter une réimplantation de l'uretère.

## 8.3 Aspects en imagerie

### 8.3.1. Urétérocèle intra-vésicale

Elle peut être développée sur un système simple (fréquent) ou sur l'uretère supérieur d'une duplication totale.

L'échographie montre la dilatation intramurale de l'uretère terminal, séparé de la lumière vésicale par une fine ligne échogène. Il peut être difficile d'affirmer sa topographie exacte, à distance du col. Le caractère contractile de l'urétérocèle au cours de l'examen doit être précisé. Au niveau du haut appareil, il faut rechercher des signes en faveur d'une duplication.

Urographie : l'aspect varie en fonction de la taille de l'urétérocèle. Si elle est petite, elle s'opacifie en même temps que la vessie, sous la forme d'une structure ronde, opaque, entourée d'un liseré clair, bien visible en début d'examen, réalisant l'aspect en "tête de serpent". Si l'urétérocèle est volumineuse, il existe souvent une stase supérieure et un retard de sécrétion : en début d'examen, l'urétérocèle apparaît comme une lacune claire intra-vésicale entourée par le contraste. Elle s'opacifie secondairement, en restant séparée du contraste de la vessie par un liseré clair.

Au niveau du haut appareil, il existe soit un système simple, non ou peu dilaté, soit une duplication, avec un parenchyme fonctionnel au niveau du pôle supérieur.

La cystographie est systématique pour rechercher un reflux ou une anomalie associée. Au temps mictionnel, elle peut révéler un prolapsus de l'urétérocèle dans l'urètre.

#### **8.4 Urétérocèle ectopique**

Elle est le plus souvent développée sur l'uretère supérieur d'une duplication totale.

L'échographie montre l'urétérocèle séparée de la cavité vésicale par une ligne échogène. La base d'implantation est large, plongeant vers le col. En temps réel, il n'y a pas de contraction visible au niveau de la paroi de l'urétérocèle. En regard du haut appareil, il existe une dilatation des cavités du pôle supérieur en cas de duplication, ou de l'ensemble des cavités si le système est simple. Le parenchyme rénal correspondant à l'urétérocèle peut également être dysplasique, et il est alors plus difficile de le mettre en évidence.

Urographie: l'urétérocèle se présente sous la forme d'une lacune intravésicale, à bords nets. Sa base d'implantation, large, correspond à la ligne trigono-cervicale du côté atteint. Cette lacune n'est pas entièrement entourée par l'urine opaque de la vessie, et peut s'estomper lorsque la vessie est pleine. Au niveau de la fosse lombaire sus-jacente, lorsqu'il existe une sécrétion, il faut rechercher les signes indirects permettant de suspecter une duplication car le pyélon supérieur n'est pas fonctionnel: pyélogramme simplifié, avec seulement deux groupes caliciels, orientation en haut et en dehors de l'axe des calices et du bassinet qui est écarté du rachis, empreintes sur l'uretère inférieur secondaires au méga-uretère supérieur. Il n'y a pas de parallélisme strict entre la taille de l'urétérocèle et la dilatation sus-jacente.

Si l'urétérocèle est développée sur un système simple, il n'y a aucune sécrétion visible du côté de l'urétérocèle.

La cystographie est là aussi systématique, à la recherche d'anomalies associées. Le cathétérisme rétrograde permet parfois d'opacifier directement l'urétérocèle dont l'abouchement est ectopique. Au temps mictionnel, il peut exister un prolapsus de l'urétérocèle dans l'urètre.

## 9. ABOUCHEMENTS ECTOPIQUES DE L'URETÈRE

Ils se définissent par un abouchement extra vésical d'un uretère. Plus la terminaison est ectopique, plus le rein a des chances d'être dysplasique et ectopique.

### 9.1 Aspects anatomo-cliniques

- *Chez la fille*, les abouchements ectopiques sont 5 à 6 fois plus fréquents que chez le garçon. Dans 75 à 80 % des cas, il s'agit de l'abouchement ectopique de l'uretère supérieur d'une duplication totale. La terminaison de l'uretère peut se faire dans l'urètre (35 %), à la vulve près du méat (30 %), dans le vagin (25 %), au niveau des résidus wolffiens, canal de Gartner, épiphore, oophore (5 %), et même très exceptionnellement dans le rectum.

Cet abouchement ectopique, quand il est sous-sphinctérien urétral, vulvaire ou vaginal, provoque un écoulement permanent d'urine : c'est la "pseudo-incontinence", survenant alors que l'enfant contrôle parfaitement ses mictions. Ce signe, de même que l'existence de vulvo-vaginites à répétition, doit systématiquement faire rechercher un abouchement ectopique.

- *Chez le garçon*, l'abouchement ectopique est plus rare. Il peut s'agir de l'uretère supérieur d'une duplication totale en cas d'ectopie haute (col vésical, urètre sus-montanal), mais, plus l'orifice ectopique est éloigné de sa position normale, plus grande est la fréquence d'un abouchement anormal de l'uretère d'un système simple. L'abouchement ectopique se fait soit dans l'urètre postérieur au-dessus du sphincter strié (55 %), soit dans le tractus génital (45 %) : vésicule séminale, canal déférent, épididyme.

Il n'y a jamais de pseudo-incontinence chez le garçon, car il n'existe pas de dérivé wolffien sous-sphinctérien. Le signe d'appel est fréquemment une orchio-épididymite survenant dans la petite enfance.

### 9.2 Diagnostic

Le diagnostic d'un uretère à abouchement ectopique peut être difficile car le parenchyme rénal correspondant est souvent dysplasique, de petite taille, non sécrétant.

L'échographie peut montrer, au niveau du pelvis, une structure tubulaire ou pseudokystique indépendante de la vessie et qui doit être différenciée d'une urétérocèle. Cette image peut correspondre à l'uretère dilaté, à un kyste du canal de Gartner chez la fille, à une grosse vésicule séminale chez le garçon. L'examen de la fosse lombaire recherche des signes de duplication. Si la fosse lombaire est vide, il ne faut pas conclure systématiquement à une agénésie rénale, car le rein dysplasique peut être petit et/ou ectopique.

En urographie, la sécrétion est souvent faible ou absente. La recherche de signes en faveur d'une duplication méconnue avec pyélon supérieur muet doit être soigneuse.

La cystographie peut mettre en évidence un reflux permictionnel si l'abouchement est urétral.

Parfois, le diagnostic n'est pas affirmé par l'imagerie. L'urétro-cystoscopie, la vaginoscopie peuvent également être prises en défaut et c'est l'exploration chirurgicale qui permet de préciser la disposition anatomique exacte.

## **10. MALFORMATIONS DE LA VESSIE**

### **10.1 Diverticule vésical**

Le diverticule solitaire juxta-urétéral de "Hutch" correspond à la hernie de la muqueuse vésicale à travers une faiblesse du hiatus urétéral. Il se rencontre en dehors de toute obstruction cervico-urétrale ou de dysfonctionnement vésico-sphinctérien. Il peut se ballonner et devenir compressif sur le bas uretère, responsable d'une stase urinaire supérieure. Il peut également entraîner l'orifice urétéro-vésical, et être alors à l'origine d'un reflux.

### **10.2 Malformations de l'ouraque**

L'ouraque correspond à l'oblitération et à la régression de l'allantoïde, unissant le pôle supérieur de la vessie à la face profonde de l'ombilic. Lorsque cette involution est incomplète, plusieurs anomalies sont possibles :

- La persistance de la perméabilité du canal de l'ouraque correspond à un fistule urinaire ouverte à l'ombilic. La cystographie permet d'en faire le diagnostic.
- le kyste de l'ouraque est une formation non communicante située en région sus-pubienne est sus-vésicale. Ce kyste peut être quiescent, ou se surinfecter. L'échographie retrouve une masse sus-vésicale, en général médiane, d'allure kystique ou parfois hétérogène, à parois irrégulières, qui peut faire également discuter un abcès appendiculaire ou une pathologie annexielle.
- Le diverticule de l'ouraque peut être rétro-ombilical ou vésical, réalisant un prolongement ouraquien médian et supérieur sur le dôme vésical.

### **10.3 3 Extrophie vésicale**

Elle se définit par une aplasie plus ou moins complète de la paroi abdominale sous-ombilicale ainsi que de la paroi antérieure de la vessie, du col et de l'urètre, de la verge ou du clitoris.

Si l'extrophie est complète, il persiste une plaque vésicale trigonale, en continuité avec la peau. Les orifices urétéraux siègent au niveau de cette zone. Le col et l'urètre sont incomplets, limités à leur partie postérieure. Il existe un écartement des deux pubis. Le bilan en imagerie doit apprécier le degré de stase urinaire supérieure éventuelle, ainsi que la valeur fonctionnelle des reins.

L'extrophie peut être mineure, se résumant à une fistule urinaire vésicale antérieure, ou à un épispadias.

La forme majeure correspond à l'extrophie cloacale, avec malformation anorectale associée et fistule recto-urinaire.

## 11. PATHOLOGIE DE L'URÉTRE DU GARÇON

### 11.1 Les valves de l'urètre postérieur

Les valves de l'urètre postérieur sont des replis membraneux congénitaux obstructifs. Elles ne touchent que le garçon.

Selon la classification de YOUNG, il peut exister trois types de valves (figures 12, 13) :

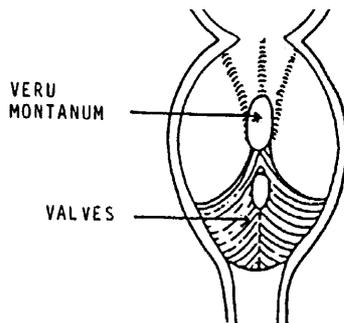


Figure 12 : Valves de type I.

- Type I : Ce sont des replis membraneux qui naissent à la partie inférieure du veru montanum et s'insèrent en descendant sur les parois antéro-latérales de l'urètre. Leur bord médian se redresse verticalement, d'où leur aspect en "nid de pigeon", qui les fait comparer aux valvules sigmoïdes cardiaques ; lors de la miction, les deux valves s'accolent et deviennent ainsi obstructives.

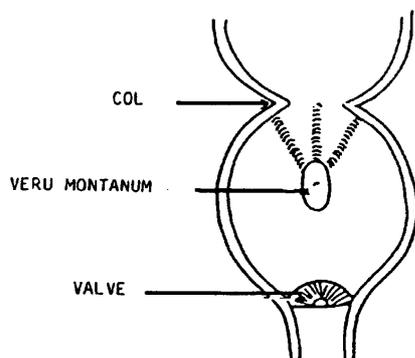


Figure 13 : Valves de type III.

- Type II : Ces valves sont beaucoup plus discutées ; la plupart des auteurs n'admettent pas leur existence. Il s'agirait de deux replis naissant à la partie supérieure du veru montanum. En fait, la mise en évidence de ces replis correspondrait aux freins

- Type III : Il s'agit d'un diaphragme percé en son centre, situé au-dessous du veru montanum.

### **11.2 Présentation clinique et circonstances de découverte**

Elles sont fonction de l'âge :

- chez le fœtus, les valves peuvent être suspectées devant un oligo-amnios avec une grosse vessie et parfois une dilatation bilatérale des cavités pyélo-calicielles ; il peut également exister une ascite urinaire anténatale. La suspicion de valves de l'urètre postérieur doit faire réaliser un bilan postnatal précoce, de façon à apprécier le retentissement sur le haut appareil, et poser les indications thérapeutiques
- chez le nouveau-né et le nourrisson, une grosse vessie peut être retrouvée. La survenue d'un pneumothorax spontané néonatal doit systématiquement faire rechercher un obstacle sur les voies urinaires. Il serait dû à un défaut de maturation pulmonaire.
- chez l'enfant plus grand, le tableau est très différent; il s'agit d'un "prostatisme" survenant chez un enfant : il existe une dysurie, l'enfant urine goutte à goutte, avec une pollakiurie ; d'autres fois, les valves vont être découvertes au cours de l'exploration d'une insuffisance rénale ou d'une infection urinaire.
- chez le grand enfant, le tableau est moins évocateur: il peut s'agir d'une incontinence, d'une énurésie, d'une anomalie du jet, d'une insuffisance rénale, d'un retard staturo-pondéral.

Le traitement consiste en une résection endoscopique des valves.

### **11.3 Aspects en imagerie**

L'échographie peut montrer des signes de vessie de lutte, avec une paroi épaissie. L'urètre postérieur est parfois visible sur les coupes récurrentes pelviennes, sous la forme d'une structure médiane transsonique faisant suite à la vessie.

Le diagnostic repose sur la cystographie, réalisée par voie sus-pubienne. Lors de l'opacification de l'urètre, il existe une disparité de calibre au niveau de l'urètre postérieur, avec une rétro-dilatation de la portion sus-jacente.

### **11.4 Appréciation du retentissement :**

#### **11.4.1. Retentissement sur la vessie**

En cas d'obstacle sous-vésical dont les valves sont l'exemple le plus typique, le retentissement vésical est variable et passe par deux stades : vessie de lutte, puis vessie de stase.

- La vessie de lutte : l'obstacle urétral entraîne une augmentation de la pression per-mictionnelle intravésicale. Pour maintenir un débit urinaire normal le muscle dérusor s'hypertrophie. Le jet urinaire est souvent très fin mais puissant, les mictions sont fréquentes et peu abondantes (pollakiurie).

- Sur le plan échographique, il est noté une réduction de la lumière vésicale, un épaississement de la paroi vésicale qui peut être mesuré avec exactitude.

- Sur le plan radiologique, il existe une réduction de la capacité vésicale, un épaississement de la paroi vésicale (appréciation de la distance qui sépare la lumière vésicale des gaz intestinaux)

péri-vésicaux), une trabéculatation qui correspond à l'hypertrophie des faisceaux musculaires lisses du détrusor (vessie à colonnes), une sacculation qui correspond à des hernies intramuqueuses vésicales entre les colonnes musculaires hypertrophiées sous l'effet de la pression intravésicale.

- La vessie atone, de stase: le muscle vésical s'épuise en maintenant un débit urinaire constant à pression très élevée. A un moment variable, mais qui peut être très précoce, il se décompense. La pression mictionnelle et le débit urinaire chutent, le volume vésical augmente parfois considérablement. La vessie se dilate et le muscle vésical s'amincit. La miction est très faible et ne se fait plus que par regorgement, goutte à goutte avec un résidu permanent.

Sur le plan radiologique, la vessie est très grande, atone avec une paroi très mince ; c'est une vessie flasque de rétention chronique. la miction est souvent très difficile à obtenir; la mise en évidence et le diagnostic de l'obstacle sous-vésical sont souvent difficiles.

- La vésicalisation de l'urètre : au cours de l'évolution, le col peut prendre plusieurs aspects : soit il reste hypertonique et la saillie de la lèvre postérieure du col marque bien la limite entre la vessie et l'urètre postérieur dilaté; soit il se relâche et il n'existe aucune limite nette entre la vessie et l'urètre postérieur dilaté: l'urètre est vésicalisé.

#### **11.4.2. Retentissement sur le haut-appareil**

- La stase urinaire supérieure est variable. L'obstruction est liée à la sténose de la jonction urétéro-vésicale par le détrusor hypertonique. Si cette stase est sévère, les cavités pyélocalicielles sont dilatées avec des dolicho-méga-uretères.

- Le reflux vésico-urétéral est une complication grave ; il est d'autant plus sévère que les valves sont plus serrées et que l'enfant est plus jeune.

La jonction urétéro-vésicale est normalement fermée, mais elle peut être forcée par l'hyperpression vésicale. Étant donné le défaut de maturation de la jonction (4 fois plus courte chez le nouveau-né que chez grand enfant), elle est facilement forcée et le retentissement en période pré et postnatale est très important et précoce.

En imagerie, il faut s'attacher sur l'urographie intraveineuse et sur l'échographie à bien apprécier l'épaisseur du parenchyme rénal, ce qui a une valeur pronostique importante. En échographie, l'appréciation de lésions éventuelles de dysplasie est difficile : elles peuvent être suspectées lorsque le cortex est très échogène.

Le retentissement des valves de l'urètre postérieur sur le haut appareil est capital : c'est l'élément majeur du pronostic. Le reflux a un caractère péjoratif. Il faut traiter les valves et juger secondairement de la dilatation résiduelle du haut-appareil.

#### **11.5 Le polype de l'urètre postérieur**

C'est une tumeur bénigne, hamartomateuse, naissant au niveau du veru montanum. Il se présente comme une petite formation arrondie, pédiculée, mobile, en "battant de cloche". Sa situation est variable selon le temps mictionnel. Il peut remonter dans la vessie au repos ; lors de la miction, entraîné par le flux urinaire, il descend dans l'urètre postérieur. Son pédicule s'insère toujours sur le veru montanum.

Il se révèle cliniquement soit par des signes évocateurs d'obstruction : dysurie, pollakiurie, rétention aiguë d'urine, soit par des signes moins spécifiques : hématurie, infection urinaire.

Sur le cliché d'urographie, il existe au niveau de la vessie une petite image lacunaire médiane juste en regard de l'orifice du col.

Lors de la miction, cette image se prolabe dans l'urètre postérieur. Elle apparaît sous la forme d'une petite formation ronde, lacunaire, appendue à un long pédicule qui est attaché sur le veru montanum, au niveau de la convergence des deux freins supérieurs.

L'urétroscopie confirme le diagnostic.

Le traitement est la résection endoscopique, rarement la résection par abord transvésical.

### **11.6 Les kystes des glandes de Cowper**

Les glandes de Cowper sont de petites glandes péri-urétrales situées dans le diaphragme uro-génital le long de l'urètre bulbaire. Elles communiquent avec l'urètre par de petits canaux pairs et symétriques. Leur sécrétion sert de lubrifiant pour l'urètre.

Les kystes des glandes de Cowper se forment en amont d'une sténose canaliculaire ou ostiale. Ils se développent habituellement dans la lumière urétrale, plus rarement dans l'épaisseur du diaphragme uro-génital.

Le kyste peut s'ouvrir dans l'urètre donnant un canal béant, pseudo diverticulaire, appendu à la face ventrale de la partie postérieure de l'urètre bulbaire.

Cliniquement les kystes des glandes de Cowper sont souvent asymptomatiques et de découverte fortuite. Parfois, il existe une symptomatologie urétrale : dysurie, pollakiurie, douleurs périnéales, urétrorragie. Ces signes sont discrets. Plus rarement, ils se manifestent précocement par une obstruction urétrale sévère avec retentissement important sur le haut appareil urinaire.

La cystographie mictionnelle montre une cavité diverticulaire appendue au plancher de l'urètre bulbaire qui s'opacifie au cours de la miction, ce qui signe son caractère communicant avec l'urètre. Elle reste séparée de lui par une mince paroi.

### **11.7 Diverticule et valves de l'urètre antérieur**

Les diverticules sacculaires de l'urètre antérieur sont des protrusions de la muqueuse à la face ventrale de l'urètre antérieur. Le collet qui sépare la cavité diverticulaire de l'urètre est large, sauf à son extrémité distale où il existe un repli membraneux parfois très étendu. Lorsque la miction est déclenchée l'urine vient plaquer cette membrane contre la paroi de l'urètre d'aval et provoque une obstruction. Ce repli membraneux qui correspond à la limite antérieure du diverticule est interprété par certains auteurs comme une valve de l'urètre antérieur. Diverticules et valves ne seraient que des degrés différents d'une même malformation.

Cliniquement, un gonflement à la face inférieure de la verge lors de la miction avec un écoulement d'urine post-mictionnel est caractéristique. Une surinfection est possible, ainsi que la formation d'une lithiase donnant une petite masse indurée, douloureuse, avec pollakiurie et

hématurie. Le caractère obstructif des diverticules peut se manifester par une dysurie, une rétention, une infection urinaire et parfois chez le nourrisson par une insuffisance rénale.

En imagerie, il existe une ectasie de l'urètre antérieur, le plus souvent dans sa portion scrotale, avec une cavité sessile largement ouverte. La limite antérieure est très nette et le raccordement de la cavité se fait à angle aigu avec l'urètre pénien.

L'aspect d'une valve est voisin : la cavité inférieure n'est pas individualisée; il existe essentiellement une disparité de calibre nette.

### **11.8 Les épispadias**

L'épispadias est une fissure dorsale de l'urètre. Le méat urétral siège à la racine ou à la partie moyenne de la face dorsale de la verge. On distingue deux grands types d'épispadias, suivant que le sphincter urétral est intact ou qu'il participe à la malformation.

- Dans le premier type, le siège de l'orifice peut être balanique et, plus fréquemment, pénien entre le sillon balano-préputial et la racine de la verge. Au delà de l'orifice, l'urètre reste présent sous forme d'une profonde gouttière.
- Dans le deuxième type, l'orifice est péno-pubien, l'urètre est ouvert en totalité, l'orifice correspond au col vésical ; il n'y a donc plus de moyen de continence vésicale. En fait, cette forme, véritable déhiscence antérieure de la partie inférieure de la paroi abdominale, est une forme de transition avec l'extrophie vésicale. Ainsi on parle d'épispadias lorsque la déhiscence est limitée à l'urètre et Extrophie lorsque l'ouverture s'étend à la vessie.

Cliniquement, la verge courte, large, couchée sur l'abdomen. Le méat est en général large et lorsqu'il est proche de la vessie, il laisse apparaître le veru montanum. Le prépuce dorsal manque totalement. Dans les formes postérieures, l'urine s'écoule en permanence. Il existe, comme dans l'extrophie vésicale, un écartement du pubis et souvent une cryptorchidie.

L'abdomen sans préparation montre une déhiscence de la symphyse pubienne, d'autant plus marquée que l'épispadias est postérieur. La cystographie montre un urètre masculin, avec une portion antérieure très courte et un méat à la face dorsale de la verge.

### **11.9 Les hypospadias**

C'est l'ectopie du méat urétral à la face inférieure, ventrale, de la verge en un point variable sur le raphé médian entre le périnée et le gland. La fréquence est d'environ 1 pour 500 garçons.

- Dans les formes antérieures, le méat est balanique ou balano-préputial. Cette malformation est bénigne et n'appelle généralement pas de correction chirurgicale. La complication essentielle est représentée par la sténose du méat urétral.

- Les hypospadias postérieurs : le méat peut être pénien, péno-scrotal ou scrotal.

Le diagnostic est évident dès l'examen, avec deux anomalies toujours retrouvées :

- le méat en position ventrale sur la verge,

- le dédoublement du prépuce réalisant un tablier plus ou moins large.

L'opacification montre un urètre de type masculin, avec deux parties, postérieure et antérieure. La portion antérieure est très courte.

Il faut rechercher les anomalies associées de la verge : torsion de la verge, coudure de la verge, conséquence d'une bride fibreuse tendue de la fossette naviculaire au méat hypospade. elle est d'autant plus marquée que le méat est plus postérieur : en cas d'hypospadias scrotal, il existe un enlèvement de la verge entre les deux replis scrotaux donnant à la malformation le nom d'hypospadias vulviforme. Cette forme pose directement le problème d'une ambiguïté sexuelle. Il faut absolument rechercher une cavité diverticulaire en arrière de la portion bulbair, correspondant alors à une cavité vaginale. Le diagnostic exact repose sur le caryotype, les dosages hormonaux, l'endoscopie voire l'exploration cœlioscopique.

### **11.10 Les duplications de l'urètre**

Les duplications urétrales sont caractérisées par l'existence d'un urètre surnuméraire :

#### **11.10.1. Dans la duplication épispade**

L'urètre surnuméraire s'ouvre à la face dorsale de la verge.

Quand la duplication est complète, il existe deux orifices vésicaux ; l'urètre accessoire passe au-dessus et en avant du col vésical, puis il a un trajet parallèle à celui de l'urètre normal en restant en avant et au-dessus pour s'aboucher à la face dorsale de la verge. Dans la duplication incomplète, l'urètre se divise en deux, l'urètre dorsal et l'urètre accessoire. Cette disposition anatomique semble très rare. Dans la duplication à sinus borgne, la partie postérieure de l'urètre surnuméraire est atrétique.

La symptomatologie clinique est variable : incontinence si l'orifice vésical est large, miction normale à deux jets.

L'opacification montre un dédoublement du canal urétral, avec un urètre accessoire filiforme cheminant au-dessus et parallèlement à l'urètre principal. Si la duplication est complète et perméable, ceci peut être vu lors de la miction. Il est souvent nécessaire de faire une opacification rétrograde de l'urètre accessoire, en particulier lorsque cet urètre est à sinus borgne. Le traitement consiste à enlever le canal surnuméraire.

#### **11.10.2. Dans la duplication hypospade**

Les deux canaux sont situés à la face inférieure des corps caverneux, L'un s'ouvre sur le gland en position normale, l'autre est hypospade. Les opacifications mictionnelles et/ou rétrogrades doivent permettre de reconnaître les différentes formes :

- La duplication peut être complète mais cette forme est extrêmement rare.
- La duplication incomplète se caractérise par la division de l'urètre postérieur en deux canaux. Elle peut se compliquer de sténose au niveau du méat hypospade, et/ou au niveau de la bifurcation.
- La duplication à sinus borgne de l'urètre accessoire est fréquente, le plus souvent asymptomatique, n'entraînant que rarement une suppuration. Lorsque la duplication est très postérieure, scrotale, il existe souvent une sténose en regard du confluent des deux

urètres. La reconstruction chirurgicale peut être difficile, car l'urètre principal est le plus hypospade.

## **12. LE SYNDROME DE PRUNE-BELLY**

Le syndrome de Prune Belly associe une aplasie abdominale, une ectopie testiculaire et une dilatation de tout l'appareil urinaire d'origine dysplasique. Il touche presque exclusivement le garçon.

Cliniquement, il existe :

- une aplasie de la paroi abdominale ; c'est l'élément le plus évident du syndrome : la peau apparaît flasque, fripée, distendue, comparable à un "pruneau d'Agen" ;
- l'ectopie testiculaire est toujours présente; son absence doit faire mettre en doute le diagnostic ;
- les manifestations urinaires associent, à des degrés variables, infection urinaire et insuffisance rénale.

Sur le plan uro-radiologique, il existe :

- une méga-vessie flasque, souvent associée a un diverticule ou à une fistule de l'ouraque;
- des méga-uretères allongés et sinueux;
- un urètre postérieur dilaté avec une disparité de calibre nette par rapport à l'urètre antérieur filiforme. Cet aspect simule des valves mais il n'y a pas de valve. la dilatation est purement dysplasique.

## LES INSUFFISANCES RENALES AIGUËS CHEZ L'ENFANT

### Les symptômes évocateurs d'une insuffisance rénale sont:

Pâleur liée à l'anémie, oedèmes, oligoanurie, HTA, vomissements, léthargie. L'hypervolémie peut entraîner des convulsions, coma, troubles du comportement, décompensation cardiaque... L'insuffisance rénale aiguë peut être liée à une cause prérénale, rénale ou post rénale  
Causes Pré Rénales : perfusion insuffisante ( hypovolémie, insuffisance cardiaque, thrombose ).

#### Causes rénales:

- Glomérulonéphrites aiguës
- Troubles vasculaires locaux:  
Le syndrome hémolytique et urémique: SHU  
La thrombose des veines rénales
- Nécroses tubulaires
- Néphrites interstitielles

Causes post rénales: obstructions, reflux, calculs...

#### Causes pré-rénales

Toute baisse de perfusion rénale, suite à une sepsis, une hypovolémie, une hypotension, ou une hypoxie peuvent se compliquer rapidement chez le nourrisson d'insuffisance rénale, qui compliquera la prise en charge du patient. Une restauration de la volémie permet en général de restaurer la fonction rénale. On recherchera naturellement les causes d'hypovolémie: déshydratation, hémorragie, diarrhée, ileus avec troisième secteur.....

Dans les maladies hépatiques chroniques, au stade de cirrhose, le flux sanguin est redistribué et la correction de l'insuffisance rénale pré-rénale est difficile. c'est le syndrome hépatorénal.

#### Causes rénales

### La Glomérulonéphrite aiguë. Démarche clinique en dix étapes

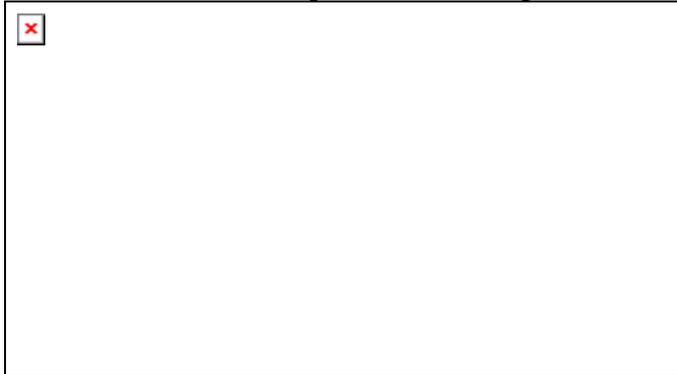
1. Evoquer l'insuffisance rénale devant l'apparition soudaine de prise de poids, avec oedème, hématurie( $\mu$  ou M), HTA chez une enfant à partir de 3 ans jusqu'à l'âge adulte. Les oedèmes sont liés à la rétention hydrosodée, mais parfois aussi à un syndrome néphrotique; Pâleur, asthénie, convulsions. Si rétention sévère, risque de décompensation cardiaque, oedème pulmonaire.
2. Rechercher un antécédent de pharyngite / angine dans les 1 à 3 semaines qui précèdent, ou encore d'une cellulite ou autre infection à streptocoque.
3. Objectiver la chute du débit urinaire
4. Analyse d'urines: hématurie, cylindres hématiques, protéinurie
5. Prise de sang: hypocomplémentémie initiale, urée élevée, créatinine variable, hyperkaliémie, hyperphosphorémie, hypocalcémie..
6. Bactériologie: rechercher le streptocoque: culture, ASLO. Sensibilité et spécificité insuffisante.
7. Mettre le patient en restriction sodée, au repos, diurétiques (Furosémide), anti-hypertenseurs, kayexalate. Parfois dialyse péritonéale.
8. Antibiothérapie, Pénicilline. De principe, pas d'évidence absolue.
9. Rapide correction de la complémentémie (mois), de la protéinurie (3 mois) , de l'hématurie (dans l'année)

#### 10. Guérison dans 95% des cas

Critères de mauvais pronostic:

- Persistance d'une hypocomplémentémie > 4 semaines
- Persistance d'une protéinurie (> 1g/24 h) , au delà de 3 mois
- Persistance d'une hématurie au delà de 1 an.

NB: La GNA chez l'enfant ne suit pas toujours une infection streptococcique, mais aussi des infections virales (MNI, Varicelle, ...). On la rencontre également en cas d'endocardite ou de shunt ventriculo-cardiaque infectés (strepto viridans, staphylocoque coagulase - )



La GNA survient en général chez un enfant entre 4 et 10 ans

#### Le Syndrome Hémolytique et Urémique:

1. C'est La plus fréquente cause d'IRA chez le nourrisson . Cause également d'insuffisance rénale chronique secondaire. Avant 4- 5 ans; plus rare chez le grand enfant . Survient souvent en été, suite à une gastroentérite. Rôle de consommation de viande peu cuite - contaminée ( "Hamburger disease")
2. La maladie est liée à une microangiopathie thrombotique rénale. Lésions endothéliales artériolaires et capillaires, épaissement des parois, dépôts de fibrine, thromboses, nécrose corticale. Rôle des toxines bactériennes.
3. Prodromes: T°, vomissements, douleurs abdominales, diarrhée sanglante récente.( Salmonella, Shigella, Coli entéropathogène, souche 0157:H7, ...) mais aussi Bartonella, virus... ). On estime qu'un enfant sur dix qui présente une gastroentérite à Coli 0157:H7 présentera un SHU. Le SHU survient environ 8 à 10 jours plus tard.
4. Symptômes cliniques: Pâleur intense, oligoanurie, prise de poids, convulsions, léthargie, irritabilité, ictère ou sub-ictère.
5. Triade :
  - *Anémie hémolytique*: anémie, réticulocytose, schizocytes. Elévation de la bilirubine non conjuguée et des LDH. Les schizocytes sont des globules rouges déchiquetés et déformés par leur passage au niveau des vaisseaux obstrués. A rechercher au *frottis sanguin*. Transfusions nécessaire chez 80% des patients.
  - *Thrombopénie* avec éventuelles pétéchies, franche diathèse hémorragique rare
  - *Insuffisance Rénale Aiguë*: pâleur, prise de poids, oligoanurie.
6. Examen d'urines (si disponible) : hématurie, protéinurie.

7. Bilan sanguin: Augmentation de l'urée, créatinine, hyperkaliémie, + les signes d'anémie hémolytique (cfr supra) , autres signes d'IR.
8. La phase d'oligoanurie avec insuffisance rénale dure  $\pm$  8 jours.
9. Une dialyse péritonéale est instaurée pour correction de l'hypervolémie, hyperkaliémie, IRA, jusqu' à reprise de la diurèse . Elle est nécessaire chez 50% des patients.
10. Pronostic lié à l'importance et à la longueur de la phase oligoanurique: En cas de durée plus prolongée, risque d' insuffisance rénale terminale, ou du moins de complications d'HTA permanente, protéinurie, diminution GFR . Mortalité de 3 à 5%.

Recommandations: ne pas manger de viande crue ou mal cuite, surtout en été. Laver ses mains après avoir manipulé de la viande crue. Consommer la viande fraîche dans les 48 heures. Décongeler la viande au frigo ou au microonde, pas à T° ambiante.

### **La thrombose des veines rénales**

- Rare
- Survient en période néonatale suite à shock, asphyxie, sepsis
- Plus tard associée au syndrome néphrotique, cardiopathies, produits de contraste
- Hématurie brutale, néphromégalie et douleurs dans les flancs, unilatérale, parfois bilatérale.
- Confirmation par US doppler
- Atrophie rénale consécutive chez le nourrisson, possible récupération chez le plus grand enfant

### **Néphrites interstitielles aiguës**

Mêmes causes que chez l'adulte. T°, rash, hyperéosinophilie . IRA et tubulopathie.

- Toxiques, Médicaments
- Infections aiguës, virales
- métaboliques: hypercalciurie, ac urique, ac oxalique ,cystinose, néphronophtise
- idiopathiques

### **Nécrose Tubulaire Aiguë**

- Métaux lourds
- Médicaments
- Hémolyse massive
- Schock
- Ischémie, réanimation

## NEPHROPATHIES GLOMERULAIRES

Glomérulonéphrite aiguë post streptococcique (vr supra, IRA)

Glomérulonéphrites chroniques de l'enfant

Purpura rhumatoïde + Photo

Une protéinurie est pathologique si elle dépasse 50mg/24h. Protéinurie glomérulaire (albumine) ou tubulaire ( bêta 2 microglobuline, Retinol-binding Protéine,...)

**Glomérulonéphrites chroniques de l'enfant** (cfr cours Néphro adulte)

- **Extra -Membraneuse** . Liées à l'infection par le virus de l'hépatite B, en phase de réplication virale active (HBeAg & HBsAg +). Dans ce cas, guéri en même temps que la séroconvesion HBe. Lupus érythémateux, D-Pénicillamine, ... Protéinurie et hématurie, syndrome néphrotique. Complément normal. HTA rare. Essai de traitement de la cause: Lamivudine, Interféron si Hépatite B.
- **Néphrite Lupique:** LED rare avant la puberté. Atteinte rénale quasi systématique. Marqueurs autoimmuns - ANA. Lupus band test . R/ Immunosuppresseur
- **Membrano-prolifératives:** Adolescence. Protéinurie, hématurie variable, hypocomplémentémie. Associée à l'hépatite C et au déficit en Alpha 1 antitrypsine, phénotype ZZ.
- **Glomérulonéphrite à IgA,** maladie de Berger

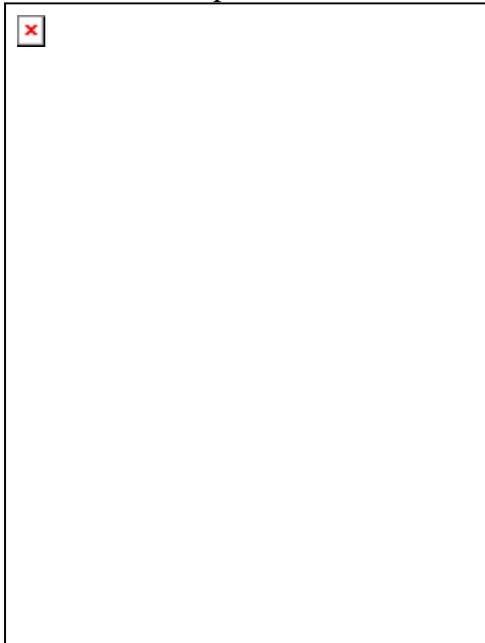


Glomérulonéphrite à IgA. Petite zone de prolifération.

### **Purpura Rhumatoïde- Purpura Anaphylactoïde - Purpura d'Henoch Schönlein**

1. La plus fréquente des vasculites de l'enfant, ( pics entre 5 & 10 ans)
2. Evolution par poussées unique ou successives durant les 3 premiers mois, parfois plus tard.
3. Eruption purpurique prédomine sur les membres inférieurs et les fesses. Tronc en général épargné.
4. Douleurs abdominales, parfois rectorragies, invaginations. (= indication de stéroïdes)
5. Hématurie ( $\mu$  ou M) , protéinurie légère, parfois syndromes néphrotiques.  
L'atteinte rénale survient dans les premières semaines et guéri dans > 95% des cas..  
Rare persistance de glomérulonéphrite progressive . Dans ce cas , risque d'évolution rapide vers IR.  
Réponse parfois aux stéroïdes/azathioprine
6. Arthrites, arthralgies (chevilles, genoux)
7. Résolution du rash en quelques semaines, et guérison complète dans l'année
8. Pas de marqueur biologique = diagnostic clinique
9. Traitement  
Repos, décharge articulaire  
Aspirine et AINS en cas de symptômes articulaires  
Corticoïdes en cas de douleurs abdominales sévères ou de glomérulonéphrite progressive

Patient avec Purpura d'Henoch Schoenlein



## **Acute renal failure in the newborn**

**DEFINITION** — Acute renal failure (ARF) is defined as the sudden impairment of kidney function (estimated from the glomerular filtration rate [GFR]) that results in the lack of excretion of waste products. The serum creatinine at birth is equal to the concentration in the mother (usually less than 1.0 mg/dL [88 micromol/L]). It then falls over time to a lower normal value. Newborns are considered to have renal failure if the serum creatinine concentration is >1.5 mg/dL (133 micromol/L) [1,2] .

ARF may be oliguric (urine volume less than 1 mL/kg per h) or nonoliguric, depending upon the severity of the reduction in GFR and the degree of tubular reabsorption. At a given GFR, the urine output will be higher when there is less tubular reabsorption.

**INCIDENCE** — Information is sparse on the incidence of ARF in newborns. In the few reports that are available in small numbers of patients, the incidence of ARF has ranged from 0.4 percent of live births to 3.5 percent of hospital admissions, to 8 percent of admissions to a neonatal intensive care unit [3,4] . Most newborns with ARF are preterm and/or critically ill. (See "Etiology" below).

**PATHOPHYSIOLOGY** — Renal embryogenesis is completed by the 35th week of gestation, resulting in 0.6 to 1.2 million nephrons in each kidney. However, several factors make newborn infants, especially those born preterm, more susceptible to renal failure than older infants or children. These include:

- Developmental immaturity that limits the function of the immature kidney.
- Hemodynamic changes that occur at birth and in the early neonatal period that affect the kidney.
- An increased risk of hypovolemia because of large insensible water losses.

Several changes in renal function occur in the perinatal period. Renal blood flow (RBF) increases substantially soon after birth because renal vascular resistance decreases and systemic blood pressure increases. As a proportion of cardiac output, RBF increases from 2 to 4 percent in the fetus to approximately 10 percent by one week after birth (the normal adult value is approximately 20 percent). Interference with this transition may lead to diminished renal function.

Autoregulation of RBF, in which small changes in systemic pressure produce parallel changes in renal vascular resistance so that RBF is maintained, is set at a lower range of blood pressure than in adults. This reduces a newborn's ability to compensate for significant hemodynamic changes and may lead to compromised renal function. Impaired autoregulation can predispose to ARF when the blood pressure is reduced [5-7] .

Urine concentrating ability is limited in the newborn compared to the older infant. The maximum urine concentration that can be achieved increases from 400 mosmol/kg in the first few days after birth to 1200 mosmol/kg at one year of age. The reasons for poor urine concentrating ability in infants include low corticomedullary solute gradient, decreased formation of cyclic AMP in response to antidiuretic hormone (ADH), a short loop of Henle, and interference by prostaglandins [8-10] . (See "Chapter 4B: Countercurrent mechanism").

Limited urine concentrating ability increases the risk of volume depletion if intake is reduced and/or fluid loss is increased. There is also an impairment in maximum reabsorption of sodium that may be mediated in part by reduced responsiveness to aldosterone [5-7]. The fraction of the filtered sodium that is excreted (FENa) is as high as 5 percent in preterm infants compared to less than 2 percent in older children.

Another source of fluid loss is insensible water loss through the skin, which may be high in newborns who have a greater body surface area for their mass compared to older children and adults. Insensible losses are increased by radiant warmers or phototherapy.

**ETIOLOGY** — The causes of ARF in newborns are distributed as follows (show table 1) [11] :

- Prerenal failure, due to inadequate renal perfusion — 85 percent
- Intrinsic renal failure, due to intrarenal pathology — 11 percent
- Postrenal failure, due to obstruction to the flow of urine — 3 percent

**Perinatal asphyxia** — Perinatal asphyxia is the most common cause of ARF in newborns, which results mostly from impaired renal perfusion. As many as 61 percent of severely asphyxiated infants may develop ARF that is predominantly nonoliguric [4,12-14]. In a report of 33 term infants with severe asphyxia, ARF was classified as nonoliguric, oliguric, and anuric in 60, 25, and 15 percent of cases, respectively [12]. (See "Systemic effects of perinatal asphyxia").

The mechanisms of ARF in perinatal asphyxia include diminished renal blood flow because of hypovolemia and hypotension, which can lead to impaired GFR and tubular function. Pulmonary disorders frequently accompany perinatal asphyxia, which may lead to hypoxemia, hypercapnia, and acidosis. These abnormalities result in increased secretion of catecholamines, adenosine, renin and aldosterone, and antidiuretic hormone (ADH). Increased catecholamines, adenosine, and angiotensin cause preglomerular vasoconstriction and postglomerular dilatation, which decreases GFR. The activated renin-angiotensin system and increased ADH secretion aggravate salt and water retention with oliguria. The use of mechanical ventilation may decrease venous return and cardiac output, which contributes to hypovolemia and hypotension [15-17].

**Prerenal disease and acute tubular necrosis** — Decreased renal perfusion can cause a direct fall in GFR without any intrinsic renal disease (called prerenal disease or functional oliguria) and can also lead to ARF associated with tubular damage, a disorder called acute tubular necrosis (ATN) or, previously, vasomotor nephropathy [18]. Almost all of the pathophysiology of ATN has been studied in experimental models and adults. As a result, some links will be provided for further information in the adult section.

The most common causes of prerenal disease/ATN are hypovolemia, hypoxemia, and septicemia. Each of these factors can induce hypotension, with secondary renal vasoconstriction due to activation of the renin-angiotensin and sympathetic nervous systems. The net effect is a reduction in RBF, GFR, and renal oxygen delivery that can predispose to tubular injury [18-21]. (See "Pathogenesis and etiology of postischemic acute tubular necrosis").

Additional factors may contribute among septic patients, including the release of cytokines such as tumor necrosis factor, and activation of neutrophils by endotoxin and by FMLP, a three amino acid (fMet-Leu-Phe)

chemotactic peptide in the bacterial cell walls [20,21] . (See "Pathogenesis and etiology of postischemic acute tubular necrosis", section on Sepsis).

Similar changes can be induced by prolonged hypothermia and certain medications [18,22] . These include prostaglandin synthesis inhibitors (eg, indomethacin), angiotensin converting enzyme inhibitors (eg, captopril), neuromuscular blocking agents (eg, pancuronium), and nephrotoxic drugs (eg, gentamicin). Renal vasodilator prostaglandins are most important in settings of decreased renal perfusion in which they help to maintain RBF. Blocking prostaglandin synthesis in such patients can lead to ARF. (See "NSAIDs: Acute renal failure and nephrotic syndrome").

**Renal vascular thrombosis** — Bilateral renal vascular thrombosis can result in intrinsic renal failure. A more common manifestation of less severe renal vascular thrombosis is hypertension. (See "Neonatal hypertension").

**Renal artery thrombosis** — Renal arterial abnormalities often are due to thrombosis associated with umbilical artery catheter (UAC) placement [23-26] . Thrombi that form on the tip or surface of the catheter can partially or completely occlude the abdominal aorta, thereby decreasing renal perfusion. These thrombi may embolize to the renal artery, resulting in areas of infarction and increased renin release [27] . (See "Neonatal hypertension").

Thrombi are common in newborns with UACs and usually are asymptomatic [24,26] . However, bilateral renal artery thrombosis can cause ARF [28,29] .

**Renal vein thrombosis** — Renal vein thrombosis (RVT) is uncommon, with an incidence estimated as 2.2 per 100,000 live births [30] . Approximately one-half of affected infants are preterm [30] . Bilateral RVT usually is associated with irreversible renal failure.

Predisposing conditions are those associated with hemoconcentration or diminished renal perfusion including diarrhea, sepsis, perinatal asphyxia, polycythemia, administration of contrast media, congenital nephrotic syndrome, homozygous protein C deficiency, homocystinuria, or a diabetic mother [31] . RVT commences in the small renal veins and subsequently propagates via larger interlobar veins to the main renal vein and inferior vena cava [32] . The adrenal glands also may be affected.

RVT typically presents with a palpable flank mass, often accompanied by hypertension and reduced urine output. Affected infants have gross or microscopic hematuria, proteinuria, and diminished renal function. Associated hematologic findings often include thrombocytopenia, anemia, fragmented red blood cells, laboratory findings of disseminated intravascular coagulation, and leucocytosis.

**Renal and urinary tract abnormalities** — The preceding discussion has emphasized renal failure developing after delivery in presumably normal kidneys. A similar picture can be produced by any severe renal or urinary tract abnormalities, although the renal disease is not really acute. Examples include polycystic kidney disease, multicystic dysplastic kidneys, renal agenesis, and urinary tract obstruction.

**CLINICAL PRESENTATION** — ARF is suspected in newborns who have an elevated or rising serum creatinine and/or anuria/oliguria.

- Oligoanuria is defined as no urine output noted by 48 hours of age or a diminished urine output (urine volume less than 1.0 mL/kg per hour). Although the time of the first void is variable, at least 50 percent of newborns void by eight hours of age and nearly all before 24 hours [33]. However, the presence of urine does not rule out ARF since some infants are nonoliguric [34]. This could reflect volume expansion and/or tubular dysfunction, as seen in obstructive uropathy and other disorders.
- An elevated or rising serum creatinine (>1.5 mg/dL [133 micromol/L]) is an indicator of a reduction in GFR, which is the hallmark of ARF. (See "Serum creatinine" below).

ARF also may be associated with a number of other laboratory abnormalities, including hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acidosis:

- Hyponatremia — Hyponatremia almost always results from the intake of water that cannot be excreted due, for example, to ARF.
- Hyperkalemia — Potassium excretion generally remains at near-normal levels in patients with renal disease as long as both aldosterone secretion and distal flow are maintained. Thus, hyperkalemia usually develops in a newborn who is oliguric or who has an additional problem, such as increased tissue breakdown or impaired aldosterone secretion due to congenital adrenal hyperplasia.
- Metabolic acidosis — Acid-base balance is normally maintained by renal excretion of the acid load (approximately 1 meq/kg per day), derived mostly from the generation of sulfuric acid during the metabolism of sulfur-containing amino acids. Elimination of this acid load is achieved by the urinary excretion of hydrogen ions. Thus, ARF may lead to hydrogen retention and metabolic acidosis.
- Hyperphosphatemia — The kidney also plays a major role in phosphate excretion. Thus, ARF, particularly if moderate to severe, can lead to hyperphosphatemia.
- Hypocalcemia — Hypocalcemia is a less common problem that can be caused by hyperphosphatemia and other factors. (See "Neonatal hypocalcemia").

Variable degrees of edema are common in newborns with ARF, who are usually critically ill. This can result from capillary leak, heart failure, or renal failure itself.

**DIAGNOSIS** — As mentioned in the preceding section, ARF should be suspected in a newborn with no urine output noted by 48 hours of age, a diminished urine output (less than 1.0 mL/kg per hour), or an elevated serum creatinine concentration (>1.5 mg/dL [133 micromol/L]).

**Serum creatinine** — Estimation of the GFR, usually by measurement of the serum creatinine concentration, is used clinically to assess the extent of renal impairment and to follow the course of the disease. It is important to recognize that estimation of the GFR has no diagnostic utility; as described below, the urinalysis is an important initial diagnostic tool to determine the underlying cause of ARF.

The serum creatinine concentration at birth is similar to that in the mother (usually less than 1.0 mg/dL [88 micromol/L]). It declines to normal values (serum creatinine 0.3 to 0.5 mg/dL [27 to 44 micromol/L]) in approximately one week in term infants and two to three weeks in preterm infants. However, the serum

creatinine concentration may increase after birth, especially in very preterm infants [35] . This effect appears to be mediated by tubular reabsorption of creatinine [35] , a finding not seen in older children and adults in whom creatinine excretion is determined solely by the GFR and tubular creatinine secretion, not reabsorption. (See "Assessment of kidney function: Serum creatinine; BUN; and GFR").

This was illustrated in two studies of very preterm infants with birth weights  $\leq 1500$  g or gestational age  $< 28$  weeks [36] .

In the first study of infants with birth weights  $\leq 1500$  g admitted to a single tertiary center in the United States, infants were excluded if they were anuric/oliguric, treated with indomethacin, amphotericin, inotropes (eg, epinephrine, dobutamine, dopamine), diuretics, or high ventilator settings, had major anomalies, or received a five-minute Apgar score below five (show calculator 1). The following findings were noted in 138 infants who met inclusion criteria:

- Serum creatinine decreased steadily from day two ( $0.75 \pm 0.22$  mg/dL [ $66.3 \pm 19.4$  micromol/L]) to day six ( $0.67 \pm 0.22$  mg/dL [ $59.2 \pm 19.4$  micromol/L]).
- In a subset analysis, infants with birth weights  $< 1000$  g, had an initial increase in serum creatinine and serum creatinine values did not differ between days 2 and 6 of life.
- In this study, 89 percent of patients received gentamicin, 48 percent xanthines, and 21 percent received respiratory support (eg, mechanical ventilation of continuous positive airway pressure [CPAP]).

The second study included 161 of 172 infants with a gestational age  $< 28$  weeks admitted to a single British tertiary center from 2001 to 2004 [37] . Most of the infants were mechanically ventilated and 30 infants died. Overall, serum creatinine increased in the first two days of life, peaked between 48 and 96 hours of age, and decreased over time to stable values by the fifth week of life. Peak serum creatinine values increased with decreasing gestational age. The mean peak values (10th and 90th percentile values) based upon gestational age are as follows:

- 22 to 24 weeks gestation (n = 33) — 1.5 mg/dL (1.2 and 1.8 mg/dL) [132 micromol/L (106 and 162 micromol/L)]
- 25 to 26 weeks gestation (n = 55) — 1.4 mg/dL (1.0 and 1.7 mg/dL) [127 micromol/L (89 and 151 micromol/L)]
- 27 to 28 weeks gestation (n = 73) — 1.2 mg/dL (1.0 and 1.5 mg/dL) [110 micromol/L (87 and 134 micromol/L)]

Based upon these data, we diagnosis acute renal insufficiency when the creatinine concentration is  $> 1.5$  mg/dL (133 micromol/L) or increasing by at least 0.2 to 0.3 mg/dL (17 to 27 micromol/L) per day. A BUN  $> 50$  mg/dL (17.9 mmol/L) is also consistent with ARF but can result from increased urea production due, for example, to increased tissue breakdown.

**EVALUATION** — The next step is to determine the cause of ARF, which is made on the basis of a careful history and physical examination and laboratory and imaging studies.

**History** — The history should include prenatal conditions such as oligohydramnios, polyhydramnios, renal abnormality detected on antenatal ultrasound examination, and antenatal medications. Neonatal conditions that may be associated with ARF include prematurity, perinatal asphyxia, respiratory distress syndrome, sepsis, umbilical artery catheterization, drug administration at or soon after birth, volume depletion, delayed first urine output, and an abnormal urine stream in males. Family history should be obtained for conditions including congenital nephrotic syndrome, polycystic kidney disease, diabetes insipidus (which can cause marked hypovolemia and hyponatremia if the urinary losses are not replaced), or any other renal disease. These disorders are discussed in the appropriate topic reviews.

**Physical examination** — Findings on the physical examination that may be associated with ARF include edema, elevated or diminished blood pressure, enlarged or absent kidneys, and a distended bladder. Dysmorphic features should also be noted, including meningomyelocele, anal atresia, prune belly syndrome, or facial and limb deformities associated with oligohydramnios resulting from decreased fetal urine production.

**Urinalysis** — The urinalysis is the most important noninvasive test in the diagnostic evaluation, since characteristic findings on microscopic examination of the urine sediment suggest certain diagnoses.

- The urinalysis is relatively normal in prerenal disease, most cases of urinary tract obstruction, and some cases of ATN.
- The presence of muddy brown granular casts and epithelial cell casts is highly suggestive of ATN (show sediment 1A-1C). However, the absence of these urinary findings does not exclude the diagnosis.
- The presence of red blood cells, tubular cells, and proteinuria indicates intrinsic renal disease. However, microscopic hematuria should be interpreted cautiously, as it commonly occurs in urine samples obtained by bladder catheterization.

**Complete blood count** — A complete blood count should be performed to identify hematologic abnormalities. Infants with ARF due to thrombotic complications such as bilateral renal vein thrombosis may have polycythemia or thrombocytopenia.

**Urine sodium excretion** — Measurement of the urine sodium concentration is helpful in distinguishing prerenal from intrinsic renal disease. The gold standard in the studies that evaluated the diagnostic accuracy of the urine sodium concentration was the response to volume repletion. Recovery of renal function within 48 hours was considered diagnostic of prerenal disease, while persistent renal failure was considered to represent intrinsic renal disease. (See "Fluid challenge" below).

- The urine sodium concentration usually is less than 20 to 30 meq/L in prerenal disease. Since the kidney is sensing underperfusion and tubular function is intact, the kidney is responding appropriately by limiting sodium excretion and preventing further volume loss.

- In contrast, the urine sodium concentration is typically above 30 to 40 meq/L with intrinsic renal disease. This can occur because tubular function is impaired, as in ATN. It also represents the normal value in infants who are not volume depleted and therefore not sodium avid, as in those with renal and urinary tract abnormalities.

However, there is substantial overlap in the urine sodium concentration, due in part to variations in the urine volume. As an example, a child with diabetes insipidus will have a low urine sodium concentration even though sodium excretion may not be reduced.

The urine sodium concentration also may be misleading if measured after the administration of volume expanders or inotropic agents, which can restore renal perfusion in an infant with prerenal disease, or after the administration of diuretics, which directly impair sodium reabsorption.

**FENa** — The potentially confounding effect of the urine volume on the urine sodium concentration can be removed by calculating the fractional excretion of sodium (FENa) ([show calculator 2](#) or, for standard units, [show calculator 3](#)). The FENa, which represents the fraction of the filtered sodium load that is excreted, is calculated from the following equation:

$$\text{FENa, percent} = \frac{\text{UNa} \times \text{PCr}}{\text{PNa} \times \text{UCr}} \times 100$$

where UCr and PCr are the urine and plasma creatinine concentrations, respectively, and UNa and PNa are the urine and plasma sodium concentrations, respectively. Note that the urine volume is not part of the equation.

A related formula called the renal failure index (RFI) is similar to the FENa except that the plasma sodium concentration is not included. This formula is similar to and as useful as the FENa but will not be discussed further here.

The FENa is a more accurate screening test than the urine sodium concentration alone to differentiate between prerenal and intrinsic ARF. However, values of FENa overlap in newborns with and without ARF, which limits its clinical usefulness compared to older children and adults [\[2,38\]](#).

- In general, a value below 2 percent suggests prerenal disease, since the reabsorption of almost all of the filtered sodium represents an appropriate response to decreased renal perfusion. FENa values in prerenal newborns are higher than those in older children (less than 2 percent versus less than 1 percent) because of their decreased ability to reabsorb sodium.
- A value above 2.5 to 3 percent usually indicates intrinsic disease in the absence of diuretic therapy [\[31,39\]](#).

The FENa appears to be less useful in preterm infants, although data are limited. One report evaluated 72 oliguric infants 25 to >37 weeks gestation [\[40\]](#). The following findings were noted:

- FENa >3 percent differentiated intrinsic from prerenal ARF in infants >31 weeks gestational age

- FENa >6 percent was consistent with intrinsic ARF in infants 29 to 30 weeks gestational age
- Because of overlap, the FENa was not useful in infants <28 weeks gestation

**Urine osmolality** — Term infants are able to concentrate the urine to more than 400 mosmol/kg. Hypovolemia is a potent stimulus to the release of antidiuretic hormone; as a result, prerenal disease is typically associated with a urine osmolality above 400 mosmol/kg. Such a concentrated urine suggests prerenal disease, while lower values in a hypovolemic newborn are consistent with intrinsic renal disease, which impairs concentrating ability (as may occur with ATN, dysplastic kidneys, or obstructive uropathy), but do not exclude prerenal disease [6] .

Urine specific gravity is too variable to be used as a diagnostic tool. This is because proteins and glucose alter the correlation between osmolality and specific gravity, and their regulation is not as stable in newborns as in older children.

**Renal imaging** — Renal ultrasound examination is the initial imaging study to evaluate newborns with ARF. Depending upon the clinical circumstances, voiding cystourethrography and radionuclide scintigraphy may be useful.

**Renal ultrasound** — Renal ultrasound examination is used to document the presence of one or two kidneys, delineate renal size and shape, help evaluate the renal parenchyma for the presence of echogenicity or cysts, and to help detect urinary tract obstruction. The absence of hydronephrosis and hydroureter and a normal size bladder with normal emptying rules out urinary tract obstruction. Simultaneous Doppler examination allows assessment of renal blood flow and can help diagnose occlusion of the major renal vessels.

**Voiding cystourethrogram** — A voiding cystourethrogram (VCUG) should be performed to rule out vesicoureteral reflux in newborns with renal anomalies detected on ultrasound. In infants with urinary tract obstruction, a VCUG is also used to identify associated reflux and to evaluate the anatomy of the ureters and bladder.

**Radionuclide scintigraphy** — Radionuclide scintigraphy can be used to demonstrate renal structure and function. Renal function and blood flow can be assessed using isotopes such as DTPA or MAG 3 that are handled by glomerular filtration. The renal cortex can be evaluated using isotopes such as technetium-99m-dimercaptosuccinic acid (DMSA) that bind to renal tubules.

Although these studies are difficult to accomplish in sick infants, they are essential in newborns with prolonged anuria to evaluate ischemic renal damage (cortical necrosis) or urinary tract obstruction.

**INITIAL APPROACH** — The initial approach to an infant with oliguria or anuria should consist of:

- Catheterization of the bladder, which will exclude obstruction of the lower urinary tract and may yield urine for analysis.
- Fluid challenge which, if it leads to correction of the oliguria, is strongly suggestive of prerenal ARF, the most common cause of ARF in newborns. (See "Fluid challenge" below).

- Fluids containing potassium should be discontinued or minimized, and the dose of medications excreted by the kidneys should be adjusted.

Treatment should be directed at specific causes, if identified. As noted above, a renal ultrasound examination is essential to exclude urinary tract obstruction. Infants with urinary tract obstruction require consultation with a pediatric urologist and may need surgical intervention.

Thrombolytic therapy should be considered in infants with ARF and bilateral renal vein thrombosis.

**Fluid challenge** — A fluid challenge should be given to all infants with oligoanuria, except those with obvious volume overload or heart failure. This will identify prerenal failure, the most common etiology, which may progress to ATN if not treated promptly.

The fluid challenge consists of the intravenous administration of 10 to 20 mL/kg of isotonic saline given over one to two hours. A positive response, which indicates a prerenal cause, is an increase in urine output to  $\geq 1$  mL/kg per hour. The fluid challenge should be repeated in infants who do not respond to the initial infusion and do not have clinical signs of fluid overload.

We do not infuse colloid such as albumin or fresh frozen plasma, except when clearly indicated (eg, fresh frozen plasma for a bleeding diathesis). Saline is equally effective and avoids complications associated with colloid, including the risk of infection and leakage of protein into the lungs leading to pulmonary edema [41].

In infants who respond, the urine output should be maintained by adequate fluid maintenance and replacement that takes into account ongoing urinary and insensible losses, and allows for other losses due to a radiant warmer, phototherapy, and nasogastric or surgical drainage.

Absence of a response to a repeated challenge generally indicates intrinsic renal failure. Such infants require conservative treatment, including fluid restriction, careful monitoring of fluid balance and serum electrolytes, and dialysis when needed. In addition, furosemide (1 to 2 mg/kg) is given for signs of fluid overload. In some cases, a higher dose (up to 5 mg/kg) may be needed.

From the standpoint of renal function, giving furosemide simply to induce a diuresis is of limited value, since recovery of renal function requires an increase in GFR that results from resolution of the underlying cause of renal failure. This process is not generally affected by increasing the urine output with a loop diuretic. However, increased urine output facilitates the management of affected newborns because it allows administration of an increased volume of fluid including parenteral nutrition, thus improving nutritional status.

**Dopamine** — In infants with heart failure or with hypotension that does not respond to volume repletion, dopamine infusion may increase renal blood flow and urine output by raising systemic blood pressure. In newborns without heart failure or hypotension, dopamine infused at low doses (1 to 3 mcg/kg per minute) increases renal blood flow and, via reduced tubular reabsorption, can raise the urine output. However, despite apparent benefits and the widespread use of low dose dopamine in this setting, there is at present little evidence for a renal protective effect in critically ill newborns and potential harm from adverse effects [42].

**MANAGEMENT** — The treatment of ARF that does not respond to fluid challenge, as described above, depends upon the underlying etiology, severity, and complications. The general approach consists of

- Maintenance of fluid and electrolyte balance
- Avoidance of life-threatening complications
- Adequate nutritional support
- Treatment of the underlying cause

**Fluids** — Fluid administration should be limited to estimated insensible water losses plus the urine output. Infants with renal failure should be weighed every 12 hours and fluid administration adjusted accordingly.

Daily insensible loss in newborns increases with decreasing birth weight, as follows [34,43,44] :

- >2500 g — 15 to 25 mL/kg
- 1500 to 2500 g — 15 to 35 mL/kg
- <1500 g — 30 to 60 mL/kg

Infants cared for under radiant warmers rather than incubators may need 25 to 100 percent more fluid. In addition, the daily fluid increment typically required by infants receiving phototherapy is approximately 20 mL/kg.

**Hyperkalemia** — Depending upon the severity and the rate of onset, hyperkalemia can be mild and asymptomatic or so severe as to constitute a medical emergency. Electrocardiographic findings associated with hyperkalemia consist of peaked T waves, which typically is the earliest change, followed by flattened P waves, increased PR interval, and widening of the QRS complex. Bradycardia, supraventricular or ventricular tachycardia, and ventricular fibrillation may occur. Muscle weakness is another potential manifestation that can be difficult to distinguish from that seen with severe illness alone.

A plasma potassium concentration above 6 to 7 meq/L is potentially life-threatening. Immediate therapy is warranted if electrocardiographic changes are present, regardless of the degree of hyperkalemia.

The following modalities are listed according to their rapidity of action; all may be beneficial (show table 2):

- Reversal of the effect of hyperkalemia on the cell membrane by infusion of 10 percent calcium gluconate (0.5 to 1.0 mL/kg IV over five minutes). Calcium is generally given only for severe, life-threatening hyperkalemia.
- Promotion of potassium movement from the extracellular fluid (ECF) into the cells. This can be achieved by the administration of sodium bicarbonate (1 to 2 meq/kg IV over 5 to 10 minutes), particularly if the infant is acidemic, and the administration of insulin as a bolus (0.05 units/kg human regular insulin with 2 mL/kg of 10 percent dextrose in water), followed by a continuous infusion of insulin (0.1 units/kg per hour with 2 to 4 mL/kg per hour of 10 percent dextrose in water).

If these modalities are ineffective, stimulation of cellular potassium uptake can also be achieved with beta adrenergic receptor agonists, such as albuterol (4 to 5 mcg/kg IV over 20 minutes or 2.5 mg by nebulization) or salbutamol (4 mcg/kg IV).

The above interventions only transiently lower the plasma potassium concentration. Additional therapy is required to remove potassium from the body. The first step is to increase the urine output with furosemide (1 mg/kg per dose) in infants with adequate urine output.

In severely oliguric or anuric patients, Kayexalate, an ion exchange resin, can be administered in a dose of 1 g/kg dissolved in saline for rectal administration or in 10 percent dextrose in water for enteral administration. Exchange resins should be avoided, if possible, in small preterm infants who may develop gastric bezoars or cecal perforation. Other complications include bowel opacification, hypernatremia, fluid retention, and constipation [34,45] .

Renal replacement therapy should be considered if these measures fail to improve hyperkalemia. (See "Renal replacement therapy" below).

**Metabolic acidosis** — In addition to the treatment of hyperkalemia, metabolic acidosis should be corrected if the plasma bicarbonate concentration falls below 16 meq/L or the arterial pH is less than 7.20 to 7.25. Bicarbonate therapy is not warranted if the acidosis is primarily respiratory.

Correction of metabolic acidosis is accomplished by administering sodium bicarbonate in a dose that can be estimated from the following formula:

Bicarbonate dose

$$= (16 - \text{serum bicarbonate concentration}) \times 0.4 \times \text{body weight (kg)}$$

An alternative approach is to give bicarbonate empirically in a dose of 1 to 2 meq/kg.

Depending upon the severity of metabolic acidosis, the bicarbonate dose can be given intravenously over five to 10 minutes or added to the intravenous fluids and given over several hours. Rapid correction by bolus infusion should be avoided because of the risk of hypertension, fluid overload, and intracranial hemorrhage.

**Hypocalcemia and hyperphosphatemia** — Hypocalcemia generally is not treated with intravenous calcium gluconate unless the patient is symptomatic or the hypocalcemia is severe.

Among patients who are hyperphosphatemic, lowering the serum phosphate concentration will also tend to raise the serum calcium. Phosphorus intake should be restricted which, in infants taking enteral feedings, can be accomplished by using a formula low in phosphorus. Oral phosphate binders such as calcium carbonate can be used to decrease intestinal absorption.

**Hyponatremia** — Hyponatremia in newborns is almost always due to dilution that results from the intake of water that cannot be excreted. Therapy generally consists of restricting free water intake, which usually results in a gradual return of the serum sodium to normal levels. However, if neurologic signs such as seizures or lethargy

develop or if the serum sodium concentration is extremely low ( $<120$  meq/L), urgent partial correction is needed with hypertonic saline. Additional correction of hyponatremia should be based upon calculations of the sodium deficit, which is equal to the product of the volume of distribution of the serum sodium concentration (the total body water) times the sodium deficit per liter (ie, 140 minus the serum sodium concentration) ([show table 2](#)). (See "Fluid and electrolyte therapy in newborns", section on Hyponatremia).

**Nutrition** — Nutritional support is essential for infants with ARF and should consist of a minimum of 50 kcal/kg per day. Infants who are able to take enteral feedings should be given a formula that has a low renal solute load and low phosphate content. However, the need for fluid restriction makes it difficult to meet the caloric needs of an oliguric infant. As a result, daily loss of 0.2 to 1 percent of body weight usually persists beyond the first week of age [45]. The weight loss is not reversed until the clinical condition improves and nutrition is adequate.

Most affected infants are critically ill and require parenteral nutrition. Such infants should receive amino acids up to a maximum of 1.5 g/kg per day and intravenous lipid solution up to a maximum of 2 g/kg per day. The concentration of glucose and solutes such as sodium, potassium, calcium, and phosphorus depend upon the infant's weight, serum electrolyte concentrations, the severity of the renal failure, and whether or not the patient is on dialysis.

**Hypertension** — Approximately 10 to 20 percent of infants with ARF have hypertension. This is usually due to fluid overload. Treatment is similar to infants without ARF.

**Renal replacement therapy** — Renal replacement therapy should be considered if appropriate fluid and electrolyte balance and adequate nutrition cannot be maintained because of persistent oliguria or anuria. We consider renal replacement therapy in infants who, despite appropriate therapy, have severe acidosis (serum bicarbonate concentration  $<12$  meq/L), hyperkalemia (plasma potassium concentration  $\geq 8$  meq/L), hyponatremia (serum sodium concentration  $\leq 120$  meq/L), or volume overload with heart failure, pulmonary edema. Dialysis is performed rarely in severe hypertension that is not responsive to medications and is associated with central nervous system signs such as seizures or with heart failure.

The question of whether to institute renal replacement therapy in a newborn with no expectation of recovery of renal function or with severe multisystem failure is difficult. Decisions should be made after considerable discussion with the neonatologist, nephrologist, other consultants as needed, and the family.

Available renal replacement modalities for the management of ARF in newborns include hemodialysis, peritoneal dialysis, and hemofiltration (with or without dialysis). The choice of modality is influenced by the clinical presentation, the presence or absence of multisystem failure, and the indication for renal replacement therapy [46].

Hemodialysis and peritoneal dialysis each provide specific benefits [47]:

- Hemodialysis offers a more rapid change in plasma solute composition and more rapid removal of excessive body water. However, this may not be tolerated by hemodynamically unstable patients and is technically challenging in newborns.

- Peritoneal dialysis is less efficient in altering blood solute composition and in fluid removal. However, it can be applied continuously and is therefore well tolerated by hemodynamically unstable patients. Unlike hemodialysis and hemofiltration, systemic heparinization is not required.

Peritoneal dialysis is preferred in newborns, even in those of low birth weight [48,49]. It is safe and effective and technically simpler and less expensive than hemodialysis and hemofiltration, requiring only minimal equipment. It can be initiated immediately after the dialysis catheter is placed and can be done as soon as three days after major abdominal surgery [50].

Morbidity and mortality are high in newborns undergoing peritoneal dialysis and are related to the infant's underlying diagnosis and clinical condition. In one series, 31 infants with renal failure (n = 20) or metabolic disorders (n = 11) underwent dialysis at less than 60 days of age, and 19 (61 percent) died [51]. Complications included peritonitis, obstruction of the dialysis catheter, leaking dialysate, and inguinal or umbilical hernias. Five of the 12 survivors remained on chronic dialysis awaiting renal transplantation.

The use of continuous venovenous hemodiafiltration (CVVHD) is increasing in newborns. Compared with peritoneal dialysis and hemodialysis, CVVHD allows more precise fluid and metabolic control, decreases hemodynamic instability, and, in patients with sepsis or multiorgan system failure, enhances the removal of cytokines [52,53].

**PROGNOSIS** — The prognosis of ARF in newborns depends upon the underlying condition and its severity and reversibility. Mortality is high and a substantial number of patients develop chronic renal failure. In a review of ARF in neonates, mortality was as high as 60 percent in patients with oliguric ARF and up to 86 percent in those with congenital heart disease or urinary tract anomalies [4]. Among the survivors of oliguric ARF caused by asphyxia, vascular thrombosis, hypotension, and toxins, 40 percent had persistently low creatinine clearance. In comparison, the prognosis was excellent in newborns with nonoliguric renal failure.

Other small series have evaluated subsets of newborns with ARF [1,16,54]. The following illustrate the range of findings:

- Among 14 newborns with ARF due predominantly to hypoxemia and hypotension, five died during the acute phase [16]. Five of the nine survivors had residual renal damage.
- In a series of 16 newborns, ARF was due to perinatal asphyxia in nine, renal anomalies in four, and congenital heart disease in three [1]. Four infants died, all with oliguric renal failure; all were anuric four or more days and had no uptake on radionuclide scintigraphy. The serum creatinine concentration in the survivors was normal.

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## GRAPHICS

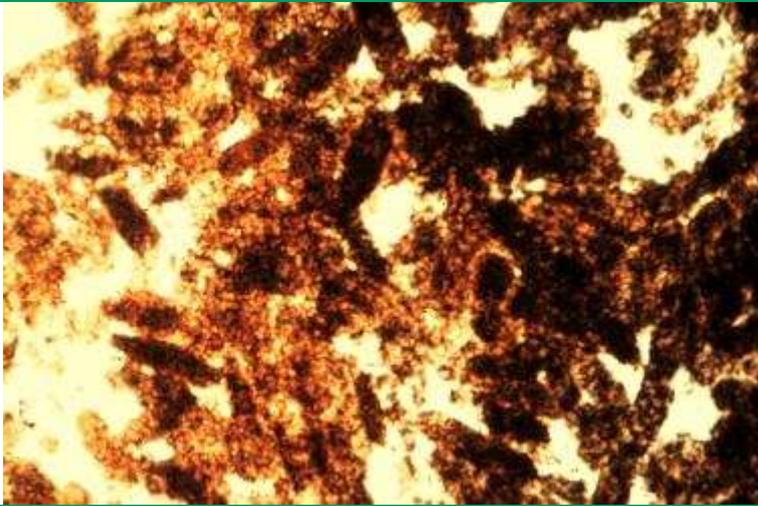
### Causes of acute renal failure in newborns

<b>Prerenal</b>
Hypovolemia
Hypotension
Hypoxemia
Heart failure
Dehydration
Septicemia
Hypoalbuminemia
Perinatal asphyxia/respiratory distress syndrome
Congenital heart disease/cardiac surgery
Polycythemia
Pharmacologic agents*
<b>Post-renal</b>
Posterior urethral valves
Bilateral obstructive uropathy
Neurogenic bladder
<b>Intrinsic renal</b>
Acute tubular necrosis
Corticomedullary necrosis
Renal venous/arterial thrombosis
Acute pyelonephritis
Hemoglobin/myoglobin
Disseminated intravascular coagulation
Isoimmune hemolytic disease with massive hemoglobinuria
Congenital renal anomalies (renal agenesis, cystic disease/dysplasia, polycystic kidney disease, congenital nephrotic syndrome)
Infections (eg, pyelonephritis)
Intrauterine infections (eg, candidiasis, toxoplasmosis)
Toxic nephropathy due to pharmacologic agents

\* Includes agents such as prostaglandin inhibitors (indomethacin), angiotensin-converting enzyme inhibitors (captopril), and vasodilators. Drugs such as aminoglycosides, amphotericin, and radiocontrast agents cause prerenal as well as intrinsic renal failure.

## Urine sediment in ATN

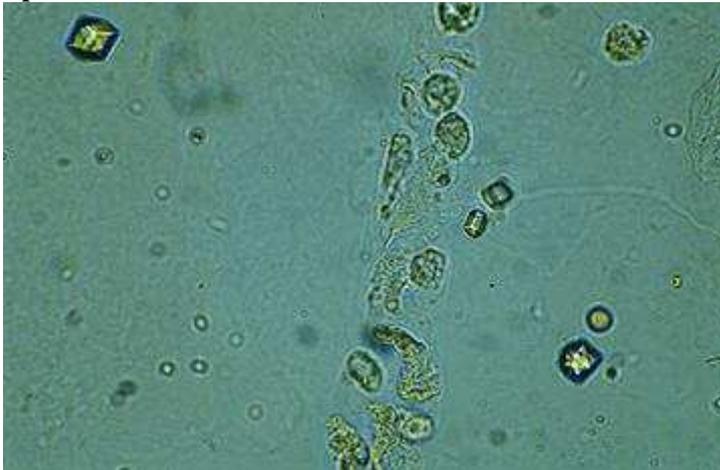
### Sediment in ATN



Urine sediment showing multiple, muddy brown granular casts. These findings are highly suggestive of acute tubular necrosis in a patient with acute renal failure. *Courtesy of Harvard Medical School.*

### Epithelial cell cast I

#### Epithelial cell cast



Epithelial cell cast containing cells that are larger than white cells. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Epithelial cell cast



Epithelial cell cast with free epithelial cells (arrow) in the urine sediment. Renal tubular epithelial cells are larger than white cell and have a single, large central nucleus. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Treatment of electrolyte disturbances

#### Acidosis

Sodium bicarbonate dose =  $(16 - (\text{serum bicarbonate concentration})) \times 0.4 \times \text{BW (kg)}$

#### Hyponatremia

Sodium chloride dose =  $0.8 \times \text{BW (kg)} \times (\text{Desired serum Na}^+ - \text{Actual serum Na}^+)$

#### Hypocalcemia

10 percent calcium gluconate 0.5 to 1.0 mL/kg over 5 to 10 minutes with cardiac monitoring

#### Hyperkalemia

Sodium bicarbonate 1 to 2 mEq/kg over 5 to 10 minutes

10 percent calcium gluconate 0.5 to 1.0 mL/kg over 5 to 10 minutes with cardiac monitoring

Bolus of 2 mL/kg 10% dextrose in water plus 0.05 units/kg regular insulin, followed by infusion of 2 to 4 mL/kg per hour 10% dextrose in water plus 0.1 units/kg per hour regular insulin

Salbutamol 4 mcg/kg over 20 minutes or albuterol 4 to 5 mcg/kg over 20 minutes

Furosemide 1 mg/kg if urine output is present

BW: body weight.

## **Clinical presentation, evaluation and diagnosis of acute renal failure in children**

**INTRODUCTION** — Acute renal failure (ARF) is defined by a rapid decline in glomerular filtration rate, resulting in the disturbance of renal physiological functions including [1-3] :

- Impairment of nitrogenous waste product excretion
- Loss of water and electrolyte regulation
- Loss of acid-base regulation

ARF is an important contributing factor to the morbidity and mortality of critically ill infants and children [4] .

An overview of ARF in children is presented in this topic review. The prevention and management of ARF in children and the approach to ARF in newborns are presented separately.

**PATHOGENESIS AND ETIOLOGY** — The causes of acute renal disease can be related to the renal anatomy most affected by the disorder [5] as follows:

- Vascular — Blood from the renal arteries is delivered to the glomeruli.
- Glomeruli — Ultrafiltration occurs at the glomeruli forming an ultrafiltrate, which subsequently flows into the renal tubules.
- Renal tubule — Reabsorption and secretion of solute and/or water from the ultrafiltrate occurs within the tubules.
- Urinary tract — The final tubular fluid, the urine, leaves the kidney, draining sequentially into the renal pelvis, ureter, and bladder, from which it is excreted through the urethra.

Any process that interferes with any of these structures and/or functions can cause renal disease. The causes of ARF can therefore be categorized as prerenal, renal, or postrenal [6] .

**Prerenal** — Prerenal azotemia results from either:

- Volume depletion due to bleeding (surgery, trauma, gastrointestinal bleeding), gastrointestinal (vomiting, diarrhea), urinary (diuretics, diabetes insipidus), or cutaneous losses (burns).
- Decreased effective arterial pressure and/or effective circulating volume seen in heart failure, shock, or cirrhosis.

**Intrinsic renal disorders** — Intrinsic renal disease includes disorders that involve the renal vascular, glomerular, and/or tubular/interstitial pathology.

**Vascular** — Vascular causes of ARF include thrombosis (arterial and venous), hemolytic-uremic syndrome, malignant hypertension, and vasculitis.

**Glomerular** — The principal glomerular cause of ARF is acute glomerulonephritis, which is commonly postinfectious. ARF can be observed with most of the glomerulonephritides that can occur in childhood.

**Tubular and interstitial disease** — Acute tubular necrosis (ATN) results from ischemia due to decreased renal perfusion or injury from tubular nephrotoxins. All causes of prerenal azotemia can progress to ATN if renal perfusion is not restored and/or nephrotoxic insults are not withdrawn.

The administration of nephrotoxic agents, including aminoglycosides, amphotericin B, and contrast agents, is a common cause of tubular disease. ARF can also be induced by the release of heme pigments, as with myoglobinuria due to rhabdomyolysis and hemoglobinuria due to intravascular hemolysis.

In children, acute interstitial nephritis most commonly results from a reaction to a drug that is thought to be hypersensitive in nature [7] .

**Postrenal** — Postrenal ARF is due to bilateral urinary tract obstruction unless there is a solitary kidney. In neonates, urinary tract obstruction, due to posterior urethral valves is the most common cause of postrenal failure. Children with chronic obstructive uropathies are also at significant increased risk of ARF from ischemic and toxic insults.

**EPIDEMIOLOGY OF ARF** — Although the overall precise incidence and prevalence of ARF has been difficult to ascertain, a retrospective review from England estimated a yearly incidence for ARF in children as 0.8 per 100,000 population [6] . This incidence is about one-fifth of that found in adults. There are indications that the overall incidence of renal failure in children is rising with increased availability of advanced pediatric medical technology including bone marrow, hepatic, and cardiac transplantation, congenital heart disease surgery, and in the care of the very low birth weight infants [1,3,6] .

**Causes of ARF** — As the prevalence of ARF has changed with the advances in medicine, so has the prevalence of different causes of ARF changed. This is especially true in tertiary care centers where many children with pre-existing chronic diseases are at increased risk for ARF due to ischemia, drug toxicity, or infection [8] .

This is illustrated in the following retrospective study of 248 patients cared for at a single tertiary referral center from 1998 to 2001 in the United States [8] .

- Approximately two-thirds had an underlying comorbid condition.
- The most common causes of ARF included ischemia (21 percent), nephrotoxic drugs (16 percent), sepsis (11 percent), and unknown (11 percent).
- Primary renal diseases accounted for only 7 percent of cases (17 cases) and included glomerulonephritis (9 cases), pyelonephritis (5 cases), and hemolytic uremic syndrome (3 cases).
- A quarter of the patients were neonates (0 to 30 days of age). In 27 percent of this group, ARF was caused by ischemia due to congenital cardiac disease.

In contrast, a review of seven reports primarily from Asia (India [3 reports], New Zealand [1 trial], Singapore [1 trial]), found a higher incidence of primary renal disease (43 percent) causing ARF in children [9] . The following were the most common causes of ARF ranked in order of incidence:

- Acute tubular necrosis (ATN), (23 percent)
- Hemolytic uremic syndrome (HUS), (21 percent)
- Glomerulonephritis (13 percent)
- Intrinsic renal disease (9 percent), causes not specified
- Postoperative (7 percent)
- Sepsis (6 percent)
- Ischemia/prerenal (4.5 percent)
- Urinary tract obstruction (3 percent)
- Miscellaneous causes (13.8 percent) including metabolic disorders, renal venous thrombosis, hepatorenal syndrome, complication of organ transplantation

A case series of 311 children cared for at a single tertiary center in Thailand from 1982 to 2004 also demonstrated primary renal disease was more likely to cause ARF [10] . In this report, the etiology of ARF included sepsis (21 percent), hypovolemia (12 percent), poststreptococcal glomerulonephritis (12 percent), systemic lupus erythematosus (10 percent), and other infectious diseases (9 percent).

In these studies, the most common cause of ARF in children was ATN due to either decreased renal perfusion (due to ischemia and sepsis) or nephrotoxic agents. In children, hypovolemia from excessive fluid losses from vomiting, diarrhea, burns, trauma is the usual cause of decreased renal perfusion [4] .

**CLINICAL PRESENTATION** — A careful history and physical examination can frequently identify events and/or disease processes that underlie ARF and suggest an underlying diagnosis:

- A history of vomiting, diarrhea, hemorrhage, sepsis and/or decreased oral intake resulting in hypovolemia, associated with decreased urine output suggests ARF due to prerenal disease or ATN.
- Physical examination findings that include tachycardia, dry mucous membranes, sunken eyes, orthostatic blood pressure changes, and decreased skin turgor suggest hypovolemia, resulting in ARF due to prerenal disease or ATN.
- Bloody diarrhea with oliguria (defined as less than 500 mL/1.73 m<sup>2</sup> per day in children and less than 0.5 mL/kg per hour in infants) or anuria (absent urine) is consistent with the hemolytic-uremic syndrome.
- A history of pharyngitis or impetigo, a few weeks prior to the onset of gross hematuria suggests post-infectious glomerulonephritis.

- Nephrotic syndrome, heart failure, and liver failure may result in edema and other signs of specific organ dysfunction.
- Hemoptysis in the presence of renal impairment suggests a diagnosis of pulmonary-renal syndrome, which includes Goodpasture's syndrome or Wegener's granulomatosis.
- Skin findings, such as purpura, malar rash, or petechiae, and/or joint pain favor a diagnosis of systemic vasculitis, such as systemic lupus erythematosus or Henoch Schönlein purpura [11].
- Anuria or oliguria in a newborn suggests a major congenital malformation or genetic disease, such as posterior urethral valves, bilateral renal vein thrombosis, or autosomal recessive kidney disease.
- In the hospital, ATN resulting from hypotension (due to sepsis or intraoperative events) or from the administration of nephrotoxic medications (such as aminoglycosides or amphotericin-B) is the common cause of ARF [6,8,12-15].

Among patients who develop ARF in the hospital, the day of onset can be determined in the patient in whom the serum creatinine concentration is measured daily. Suppose, for example, that a child has had a stable serum creatinine concentration, which then begins to rise progressively on day five. In such a patient, there must have been some insult on day four or a cumulative insult that has become clinically apparent (most often aminoglycoside therapy). Careful perusal of the patient's chart may identify the precipitating event on day four (eg, hypotension, radiocontrast exposure).

**EVALUATION AND DIAGNOSIS** — In addition to a careful history and physical examination, the initial evaluation includes an estimation of the glomerular filtration rate, examination of the urine, and the use of other modalities.

**Serum creatinine concentration** — Estimation of the glomerular filtration rate (GFR), usually by the serum creatinine concentration and less often by the creatinine clearance, is used clinically to assess the degree of renal impairment and to follow the course of the disease. It is important to realize that estimation of the GFR has no diagnostic utility.

Measurement of the serum creatinine concentration alone is sufficient in most patients with a relatively constant body mass and diet. On account of maternal contributions in the newborn and increased muscle mass with age, the normal range of serum creatinine concentrations varies by age in children [16]:

- Newborn - 0.3 to 1.0 mg/dL (27 to 88 micromol/L)
- Infant - 0.2 to 0.5 mg/dL (18 to 35 micromol/L)
- Child - 0.3 to 0.7 mg/dL (27 to 62 micromol/L)
- Adolescent - 0.5 to 1.0 mg/dL (44 to 88 micromol/L)

Even if absolute values remain in the normal range, a sequential increase in the serum creatinine concentration strongly suggests a decrease in the glomerular filtration rate.

There are several exceptions to this rule, including the presence of certain drugs (such as cimetidine) that increase the serum creatinine concentration or substances that interfere with the serum assay. When adjusting medication doses for children with progressive ARF, the creatinine clearance should be estimated to be less than 10 mL/min per 1.73 m<sup>2</sup> [16].

Several formulas that utilize easily obtained values have been developed that help estimate the GFR in patients with chronic renal failure. In children, the most commonly used formula to estimate creatinine clearance is the Schwartz formula [17]. However, this formula can only be used in patients with stable renal function.

**Serum BUN/creatinine ratio** — In adults and older children, the serum BUN/creatinine ratio is normal at 10 to 15:1 in ATN, and may be greater than 20:1 in prerenal disease due to the increase in the passive reabsorption of urea that follows the enhanced proximal transport of sodium and water. Thus, a high ratio is highly suggestive of prerenal disease. This ratio is not useful in infants and smaller children as their serum creatinine levels are much lower.

**Urinalysis** — The urinalysis is the most important noninvasive test in the diagnostic evaluation, since characteristic findings on microscopic examination of the urine sediment strongly suggest certain diagnoses (show table 1).

As examples:

- A normal or near-normal urinalysis, characterized by few cells with little or no casts or proteinuria, suggests prerenal disease, urinary tract obstruction, and some cases of acute tubular necrosis (ATN).
- Muddy brown granular casts and epithelial cell casts are highly suggestive of ATN (show sediment 1A-1C). However, the absence of these urinary findings does not exclude the diagnosis.
- The finding of a red cell cast is diagnostic of glomerulonephritis, while the presence of proteinuria is generally indicative of some form of glomerular disease (show sediment 2A-2D). The concurrent presence of hematuria with red cell casts, dysmorphic red cells, heavy proteinuria, or lipiduria can also help subclassify patients into those with an active "nephritic" sediment. This is commonly associated with ARF due to glomerulonephritis.
- Pyuria with white cell and granular or waxy casts and varying levels of proteinuria is suggestive of tubular or interstitial disease or urinary tract infection (show sediment 3A-3E). White cells and white cell casts can also be seen in acute glomerulonephritis, particularly postinfectious glomerulonephritis. In this setting, however, there are also other signs of glomerular disease, such as hematuria, red cell casts, and proteinuria.
- Hematuria and pyuria with no or variable casts (excluding red cell casts) may be seen in acute interstitial nephritis, glomerular disease, vasculitis, obstruction, and renal infarction.

**Urine sodium excretion** — With ARF in children, measurement of the urine sodium concentration is helpful in distinguishing ATN from prerenal ARF due to effective volume depletion. The urine sodium concentration is usually above 30 to 40 mEq/L and below 10 mEq/L in the former and latter conditions, respectively. Since normal newborns have a relatively decreased ability to conserve sodium, prerenal disease is usually associated with somewhat increased urine sodium concentrations (less than 20 to 30 mEq/L).

However, since the urinary sodium concentration is influenced by the urine output, there is substantial overlap between ATN and prerenal disease. As an example, a given rate of sodium excretion will be associated with a lower urine sodium concentration by dilution in patients who have a high urine output.

**Fractional excretion of sodium (FENa)** — The effect of variations in urine volume can be eliminated by calculating the FENa. This is defined by the following equation:

$$\text{FENa (percent)} = \frac{\text{UNa} \times \text{PCr}}{\text{PNa} \times \text{UCr}} \times 100$$

where UCr and PCr are the urine and serum creatinine concentrations, respectively, and UNa and PNa are the urine and serum sodium concentrations, respectively.

The FENa is a screening test that differentiates between prerenal ARF and ATN in children.

- A value below 1 percent suggests prerenal disease, where the reabsorption of almost all of the filtered sodium represents an appropriate response to decreased renal perfusion.
- A value between 1 and 2 percent may be seen with either disorder.
- A value above 2 percent usually indicates ATN.
- In newborns, prerenal disease and ATN are associated with FENa values of less than 2.5 percent and greater than 2.5 to 3.5 percent, respectively, because of their decreased ability to reabsorb sodium.

The FENa is most useful in patients with severe renal failure and low urine output (oliguria). It is less accurate in those with a normal or moderately reduced GFR because the value determining a prerenal state changes continuously with the GFR. FENa may also be elevated after the administration of either a distal or loop diuretic due to the increase in urine sodium excretion. Why this occurs is discussed in detail separately.

A low FENa is not unique to prerenal disease, since it can occur in disorders associated with normal tubular function but a low GFR. These include acute glomerulonephritis, vasculitis, and acute urinary tract obstruction. It can also be seen when ATN is superimposed upon a chronic sodium-retaining state.

**Urine osmolality** — Loss of concentrating ability is an early and almost universal finding in ATN with the urine osmolality usually being below 350 mosmol/kg. However, lower values similar to those in ATN may be seen in prerenal disease and are therefore of little diagnostic help. In contrast, a urine osmolality above 500 mosmol/kg is highly suggestive of prerenal disease.

**Urine volume** — The urine volume is typically, but not always, low (oliguria) in prerenal disease due to the combination of sodium and water avidity. In comparison, patients with ATN may be either oliguric or nonoliguric.

**Response to volume repletion** — Unless contraindicated, a child with a clinical history consistent with fluid loss (such as vomiting and diarrhea), a physical examination consistent with hypovolemia (hypotension and tachycardia), and/or oliguria should be administered intravenous fluid therapy. This fluid challenge attempts to identify prerenal failure that can progress to ATN if not treated promptly. However, such fluid infusion is contraindicated in those with obvious volume overload or heart failure.

Commonly used fluids are crystalloid solutions, such as normal saline (20 mL/kg) administered over 20 to 30 minutes, which may be repeated. Restoration of adequate urine flow and improvement in renal function with fluid resuscitation is consistent with prerenal disease. However, if urine output does not increase and renal function fails to improve with the restoration of intravascular volume, invasive monitoring may be required to adequately assess the child's fluid status and help guide further therapy..

#### **Additional laboratory measurements**

**Complete blood count** — Severe microangiopathic hemolytic anemia associated with thrombocytopenia in the setting of ARF confirms the diagnosis of HUS [18,19] . Severe hemolysis, whether drug-induced or secondary to hemoglobinopathies, may also result in ATN due to massive hemoglobinuria..

**Other abnormalities** — The measurement of additional blood components may be diagnostically helpful in certain settings. As examples:

- In children with a clinical picture consistent with rapidly progressive glomerulonephritis (RPGN), the presence of anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), anti-glomerular basement membrane (GBM) antibodies, antistreptococcal antibodies, and/or hypocomplementemia is associated with certain inflammatory disorders [11,20] . (See "Hypocomplementemia in glomerular disease", see "Differential diagnosis of glomerular disease" and see "Systemic lupus erythematosus in children").
- Elevated serum levels of aminoglycosides are associated with ATN. (See "Pathogenesis and prevention of aminoglycoside nephrotoxicity and ototoxicity").
- Eosinophilia and/or urine eosinophiluria may be present in some cases of interstitial nephritis.
- Markedly elevated uric acid levels may also induce ARF. Thus, tumor lysis syndrome secondary to chemotherapy treatment of childhood leukemia or lymphoma may result in ARF due to urate nephropathy [21,22] . (See "Tumor lysis syndrome" and see "Uric acid renal diseases").

Although not diagnostically helpful, hyperkalemia, hyperphosphatemia, hypocalcemia, and acidosis can be observed in ARF:

- **Hyperkalemia.** The ability to maintain potassium excretion at near normal levels is generally maintained in patients with renal disease as long as both aldosterone secretion and distal flow are maintained. Thus, hyperkalemia generally develops in the patient who is oliguric or who has an additional problem, such as a high potassium diet and increased tissue breakdown.
- **Hyperphosphatemia.** Once the GFR falls below threshold levels, the renal excretion of phosphorus decreases, resulting in hyperphosphatemia.
- **Hypocalcemia.** Hypocalcemia can result from hyperphosphatemia, decreased calcium absorption in the gastrointestinal tract (due to inadequate renal production 1,25-vitamin D), and/or skeletal resistance to parathyroid hormone (PTH).
- **Acid-base balance** is normally maintained by the renal excretion of the daily acid load (about 1 mEq/kg per day, derived mostly from the generation of sulfuric acid during the metabolism of sulfur-containing amino acids). Elimination of this acid load is achieved by the urinary excretion of hydrogen ions. A metabolic acidosis may therefore ensue with ARF.

**Renal imaging** — Renal ultrasonography should be performed in all children with ARF of unclear etiology. It can document the presence of one or two kidneys, delineate renal size, and help survey renal parenchyma [23]. It is particularly useful in diagnosing urinary tract obstruction or occlusion of the major renal vessels. (See "Radiologic assessment of renal disease").

**Renal biopsy** — A renal biopsy is most commonly obtained when noninvasive evaluation has been unable to establish the correct diagnosis [4,6].

**RIFLE Criteria** — The Acute Dialysis Quality Initiative has developed criteria to standardize the reporting and classification of ARF in adults. Five levels of acute kidney injury are based upon degree of elevation of serum creatinine, urine output, and requirement for dialysis. In adults, the RIFLE criteria have been shown to predict mortality, renal outcome, and length and cost of hospital stay.

In one study of 150 critically ill children admitted to a single pediatric intensive care unit (PICU), the modified RIFLE criteria was used to prospectively evaluate their renal course [24]. Based upon these criteria, 123 patients (82 percent) developed acute kidney injury within the first week of admission, of which 11 required dialysis. The presence of acute renal injury on admission was not an independent risk factor for mortality, and patients who had no improvement in renal function within 48 hours of admission were at a higher risk of requiring dialysis. Standardized classification criteria, such as the RIFLE criteria, can be used as research tools to improve the understanding of ARF epidemiology and potentially identify treatable risk factors.

**SUMMARY** — The following is a summary of the above discussion on the clinical presentation, evaluation, and diagnosis of ARF in children.

**Etiology** — ARF is classified by the portion of the renal anatomy most affected by the disorder in the following manner (See "Pathogenesis and etiology" above):

- Prerenal azotemia results from either volume depletion (hypovolemia), decrease effective arterial pressure (shock), or effective circulating volume (heart failure).
- Intrinsic renal disease includes disorders that involve the renal vascular (arterial or venous thrombosis), glomerular (glomerulonephritis), tubular [acute tubular necrosis (ATN)], or interstitial pathology.
- Postrenal ARF is due to bilateral urinary tract obstruction unless there is a solitary kidney.

**Epidemiology** — The overall precise incidence and prevalence of ARF has been difficult to ascertain. The incidence of ARF in children appears to be rising with increased utilization of advanced medical technology.

Causes of ARF are changing especially in tertiary care centers in developed countries. ATN is the most common cause of ARF and there is a decreased prevalence of primary renal disease. Increasingly, children with ARF have underlying co-morbid diseases.

(See "Epidemiology of ARF" above).

**Evaluation** — The evaluation of the child with ARF first involves establishing the correct diagnosis and estimating the degree of renal dysfunction.

A detailed history and physical examination can detect specific signs or symptoms that strongly favor an underlying diagnosis. Thus, a history of fluid loss (eg, gastrointestinal losses or major blood loss) or decreased oral intake associated with a decreased urine output, combined with signs of hypovolemia (eg, tachycardia, orthostatic blood pressure changes) strongly suggest prerenal disease or ATN as the cause of ARF. (See "Clinical presentation" above).

Laboratory tests play a central role in the initial evaluation and may distinguish different causes of ARF.

- The urinalysis is the most important noninvasive diagnostic test with characteristic findings that strongly suggest certain diagnoses (show table 1). (See "Urinalysis" above).
- The serum creatinine is obtained as an estimation of glomerular filtration rate. (See "Serum creatinine concentration" above).
- Additional tests include the serum BUN/creatinine ratio, urine sodium, and fractional excretion of sodium. These tests are useful in distinguishing from ARF caused by prerenal disease versus ATN (show table 2). (See "serum BUN/creatinine ratio" above, and see "Urine sodium excretion" above).
- Renal ultrasound is the most common radiologic test. It can document the presence of one or two kidneys, delineate renal size, survey renal parenchyma, detect

urinary tract obstruction, and occlusion of major renal vessels. (See "Renal imaging" above).

- For a child with a clinical history suggestive of prerenal disease, a fluid challenge of intravenous solution should be administered to detect prerenal ARF that may progress to ATN. However, fluid administration is contraindicated in those with obvious volume overload or heart failure. (See "Response to volume repletion" above).
- A renal biopsy is most commonly obtained in patients with suspected glomerulonephritis or in those with otherwise unexplained ARF.

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## GRAPHICS

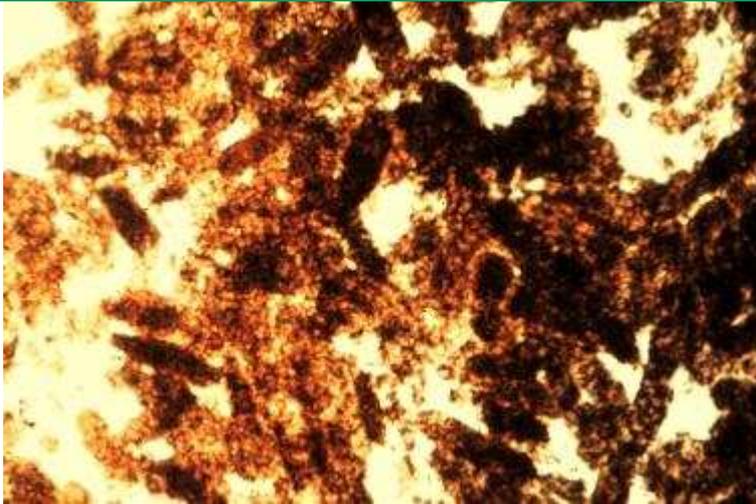
### Correlation between urinary patterns and renal disease

Urinary pattern	Renal disease
Hematuria with red cell casts, dysmorphic red cells, heavy proteinuria, or lipiduria	Virtually diagnostic of glomerular disease or vasculitis
Multiple granular and epithelial cell casts with free epithelial cells	Strongly suggestive of acute tubular necrosis in a patient with acute renal failure
Pyuria with white cell and granular or waxy casts and no or mild proteinuria	Suggestive of tubular or interstitial disease or urinary tract obstruction
Hematuria and pyuria with no or variable casts (excluding red cell casts)	May be observed in acute interstitial nephritis, glomerular disease, vasculitis, obstruction, and renal infarction
Hematuria alone	Varies with the clinical setting
Pyuria alone	Usually infection; sterile pyuria suggests urinary tract tuberculosis or tubulointerstitial disease
Few cells with little or no casts or proteinuria (normal or near-normal)	In acute renal failure, prerenal disease, urinary tract obstruction, hypercalcemia, myeloma kidney, some cases of acute tubular necrosis, or a vascular disease with glomerular ischemia but not infarction (scleroderma, atheroemboli); in chronic renal failure, nephrosclerosis, urinary tract obstruction, and tubulointerstitial disease

### Urine sediment in ATN

### Sediment in ATN

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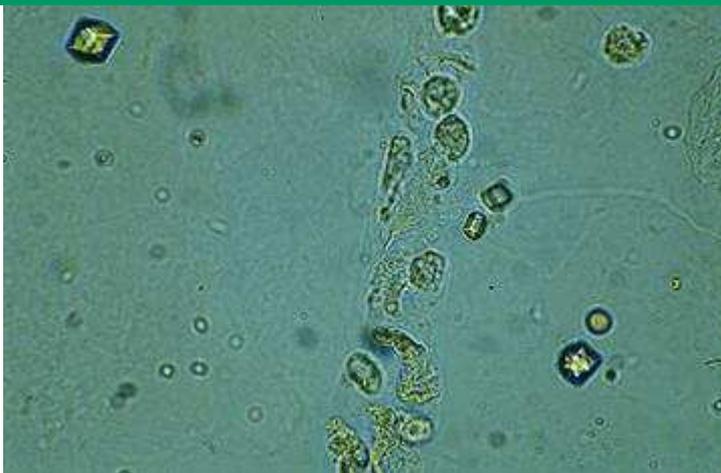


Urine sediment showing multiple, muddy brown granular casts. These findings are highly suggestive of acute tubular necrosis in a patient with acute renal failure. *Courtesy of Harvard Medical School.*

### Epithelial cell cast I

#### Epithelial cell cast

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Epithelial cell cast containing cells that are larger than white cells. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

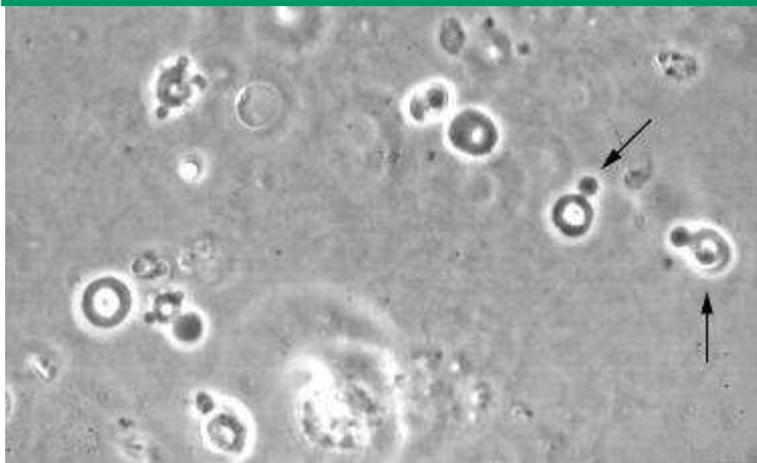
### Epithelial cell cast



Epithelial cell cast with free epithelial cells (arrow) in the urine sediment. Renal tubular epithelial cells are larger than white cell and have a single, large central nucleus. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Dysmorphic rbc I

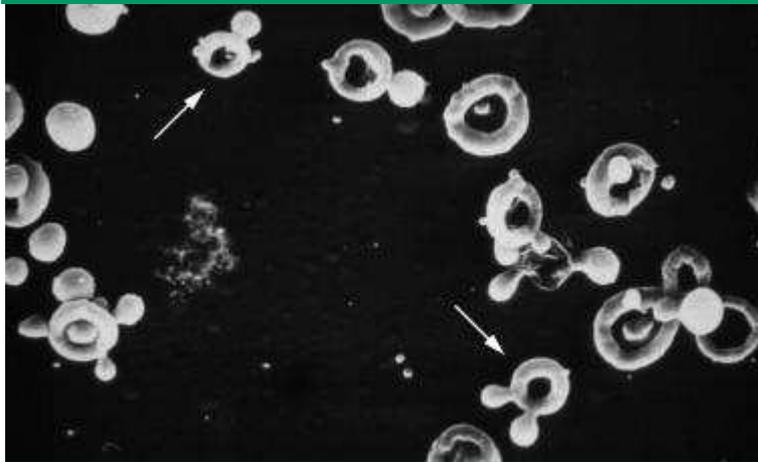
#### Dysmorphic red cells



Phase contrast microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows). *Courtesy of Hans Köhler, MD.*

## Dysmorphic rbc II

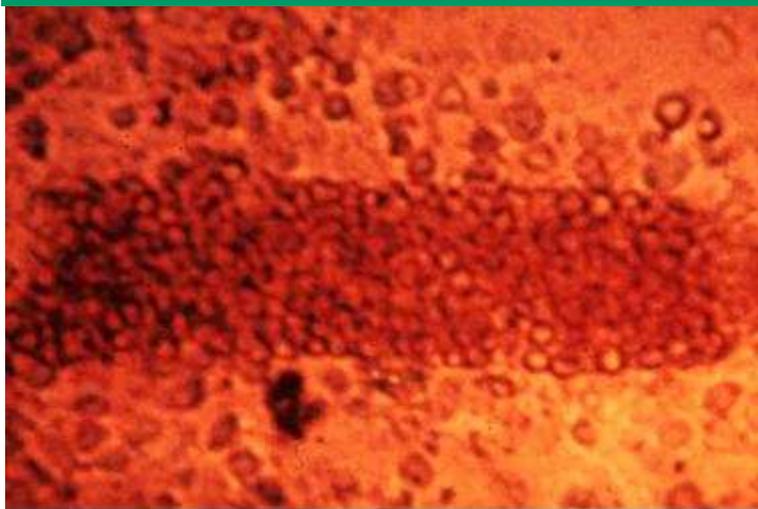
### Dysmorphic red cells



Scanning microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows). *Courtesy of Hans Köhler, MD.*

## Red cell cast

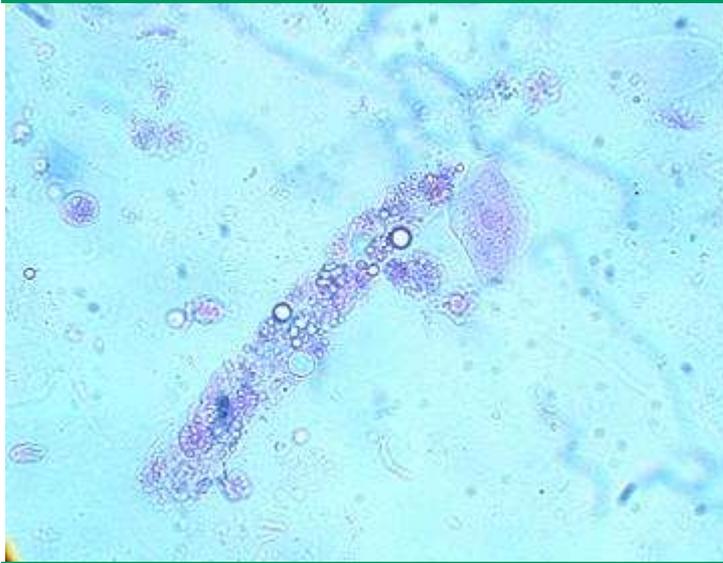
### Red cell cast



Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis. *Courtesy of Harvard Medical School.*

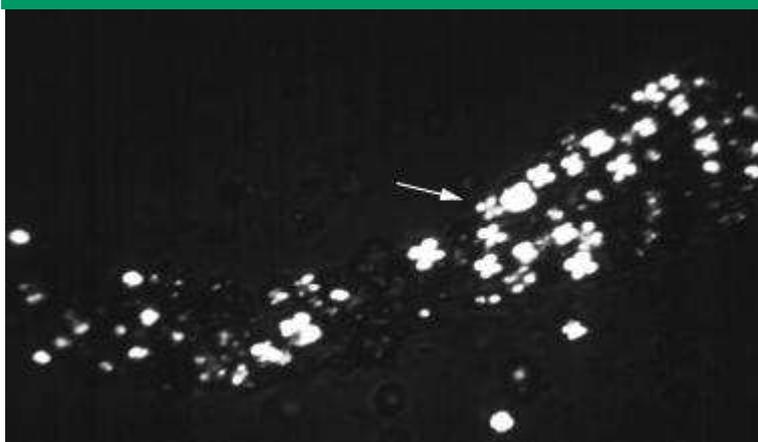
## Fatty cast

### Fatty cast



Urine sediment showing a fatty cast. The fat droplets (or globules) can be distinguished from red cells (which also have a round appearance) by their variable size (from much smaller to much larger than a red cell), dark outline, and "Maltese cross" appearance under polarized light. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

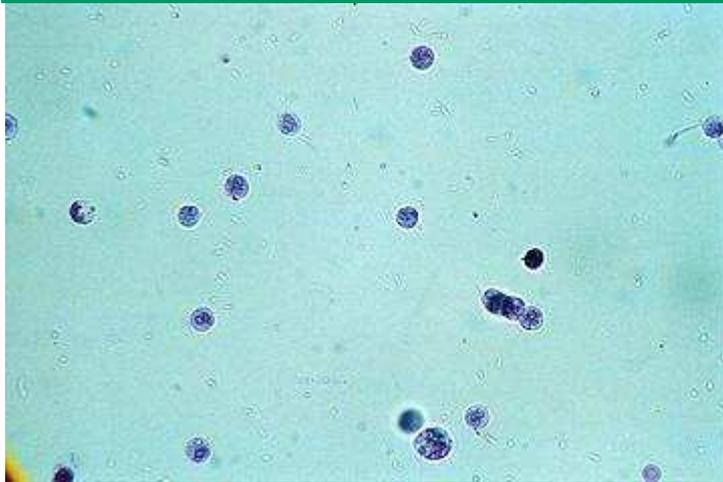
### Fatty cast



Urine sediment showing fatty cast under polarized light. The fat droplets have a characteristic "Maltese cross" appearance (arrow). *Courtesy of Harvard Medical School.*

## White blood cells

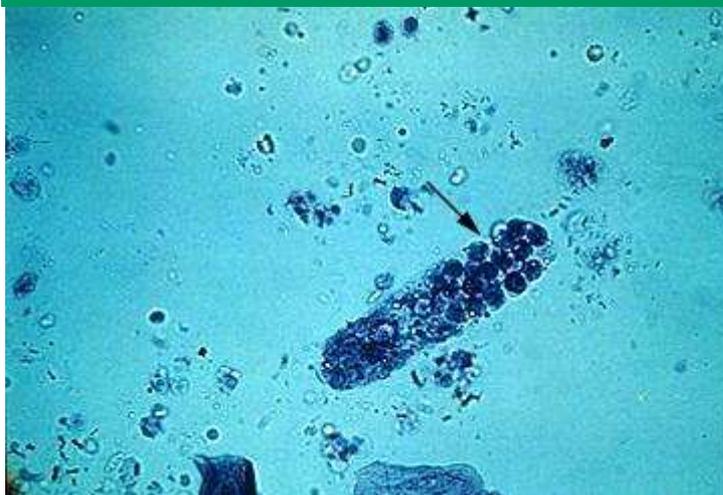
### White blood cells



White blood cells in the urine sediment with nuclei and granular cytoplasm. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

## White cell cast I

### White blood cell cast



White cell cast in which blue stained white cells (arrow) are contained within a granular cast. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

## White cell cast II

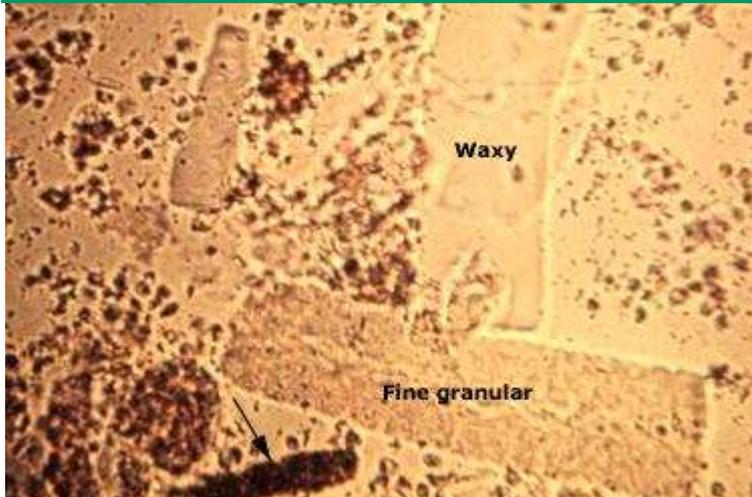
### White blood cell cast



A white blood cell cast, three-quarters of which is filled with leukocytes. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

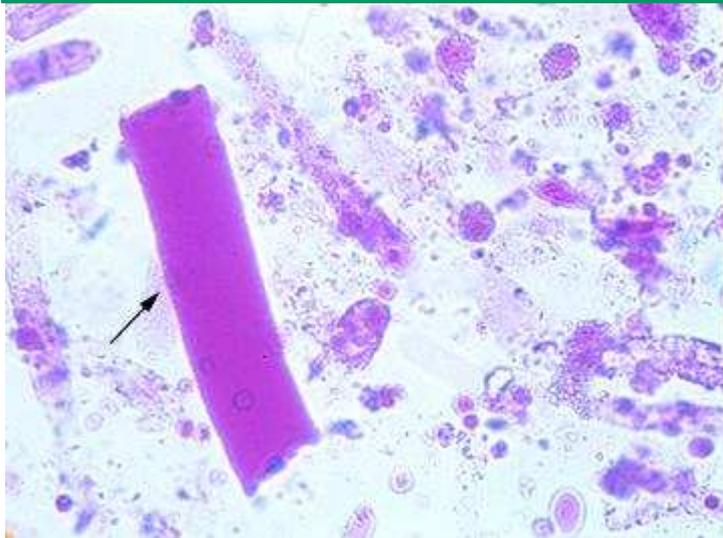
## Granular casts

### Granular and waxy casts



Urine sediment showing waxy and fine and coarse (arrow) granular casts. The broader casts are thought to form when there is stasis (due to advanced renal failure) in the wider collecting tubules into which many nephrons drain. *Courtesy of Harvard Medical School.*

### Waxy cast



Urine sediment showing a waxy cast (arrow) and many small fine granular casts. Note the cast outline and its amorphous appearance. The high optical density, smooth surface, and blunt ends of waxy casts, which appear to represent degenerated cellular or granular casts, allows them to be distinguished from hyaline casts. The latter are composed solely of precipitated Tamm-Horsfall mucoprotein. *Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.*

### Laboratory studies used to differentiate between prerenal acute renal failure (ARF) and acute tubular necrosis (ATN)

	Prerenal ARF	ATN
Urine sodium (meq/L)	<20	>30
Fractional excretion of sodium	<1 percent	>2 percent
Urine osmolality (mOsm/L)	<350	>500
Serum BUN/Cr ratio*	>20:1	<20:1

\* Used only in adolescents and older children.

# **DIALYSE PERITONEALE**

## **I. DÉFINITION**

La dialyse péritonéale est la méthode **d'épuration extrarénale** la plus simple chez l'enfant. Son principe physico-chimique repose sur la diffusion de substances dissoutes à travers une membrane semi-perméable naturelle : le péritoine.

Les substances dissoutes diffusent donc entre le sang du petit patient et le dialysat introduit dans la cavité péritonéale.

Cette diffusion est passive et bidirectionnelle selon le gradient osmotique.

**La surface d'échange est la membrane péritonéale qui est une surface à peu près égale à la surface corporelle de l'enfant.**

## **II. INDICATIONS**

1. L'insuffisance rénale aiguë : quand une évolution prolongée est à craindre.
2. En cas d'insuffisance rénale chronique : la dialyse péritonéale chronique à la maison peut s'envisager à domicile après un apprentissage en milieu hospitalier.
3. La dialyse péritonéale est une alternative à l'hémodialyse dans l'attente d'un accès vasculaire (fistule)
4. Plus rarement, la dialyse péritonéale est appliquée
  - dans certains désordres métaboliques et ioniques
  - dans des intoxications médicamenteuses par des substances dialysables
5. Hypothermie
6. Indications biologiques

### **Contre-indications :**

- Absolue : omphalocèle, hernie diaphragmatique
- Relative : chirurgie abdominale.

### III. LE MATERIEL

#### Garder étiquettes des cathéters dans le dossier médical de l'enfant ( en cas de soucis de dialyse)

<b>Matériel pour dialyse péritonéale <u>commun</u> à la méthode manuelle et machine</b>				
<b>TYPE DE MATERIEL</b>	Référence	Description	<b>LIEU DE COMMANDE</b>	<b>QTE en réserve dans le set</b>
Cathéter péritonéal TYCO TENCKHOFF – droit	à facturer 411405	2 cuffs, i.p.15,5 cm, tot. 41 cm	Baxter <sup>1</sup> (via magasin clinique)	<b>1</b> de chaque type
TENCKHOFF – droit	414201	2 cuffs, i.p.12 cm ped, tot. 30 cm		
SWAN-NECK Tenckhoff	413101	2 cuffs, i ; p ; 12 cm (DP prolongée)		

<b>TYPE DE MATERIEL</b>	<b>REFERENCE</b>	<b>LIEU DE COMMANDE</b>	<b>QTE EN RESERVE dans le set</b>
Embout en titane <u>restérilisable !!!</u> (ne pas jeter car coût 250€/pièce)	C4129	Baxter (via magasin clinique)	<b>2</b>
Raccord intermédiaire ( PD MiniCap ligne de transfert à durée de vie prolongée avec clamp de torsion)	C4482	Baxter (via magasin clinique)	<b>5</b>
Bouchons de déconnexion ( MiniCap type R , avec povidone iodée)	C4466	Baxter (via magasin clinique)	<b>1 bte</b> peuvent être périmés, il suffit d'ajouter de l'isobétadine dermique
Coquilles de protection connexion	C4211	Baxter (via magasin clinique)	<b>1bte</b> peuvent être périmés, il suffit d'ajouter de l'isobétadine dermique

#### **Matériel pour méthode manuelle**

*Méthode à utiliser au départ*

Trousse en Y double burette (150ml)	JMC 3437	Baxter (via magasin clinique) Lessines via livraison TRAVACARE 02/6501616	<b>15</b>
Poches de dialyse DPI <sup>2</sup> 1.36% luer-lock	B5346RL	Baxter (via magasin clinique)	<b>1 bte</b>

2000 ml			
Poches de dialyse DP1 2.27% luer-lock 2000 ml	B 5437RL	Baxter (via magasin clinique)	<b>1 bte</b>
Poches de dialyse DP1 3.86% luer-lock 2000 ml	B 5417RL	Baxter (via magasin clinique)	<b>Pas de stock,</b> utilisation limité → à commander si néc.
Clamp pour changement de poche	C4527	Baxter  (via magasin clinique)	1 bte  (= 12 pièces)
Clamp de ligne  (pour UV flash)	C4334	Baxter  (via magasin clinique)	1 bte  (= 12 pièces)
Dispositif de drainage de cycleur  (sac récolteur vidangeable 15l)	R5C4145P	Baxter  (via magasin clinique)	1 bte  (= 30 pièces)
Plaques de réchauffe			2

### Matériel pour méthode machine

Méthode à utiliser lorsque les dialyses se prolongent au delà d'une semaine

Machine Home Choice disponible en prêt auprès de la firme BAXTER			
Ligne de branchement 4 branches avec cassette pour Home Choice (! Boite de 30 cassettes)	C4479 (spécifique pédiat)	Baxter (via magasin clinique)	<b>Pas de stock</b> <b>! très cher</b> (27€/pièce)  → à commander si néc.
Dispositif de drainage du cycleur (=sac récolteur)	C4145P	Baxter (via magasin clinique)	Peut être périmé

### **III. 1 ) Le cathéter :**

Le cathéter est un tube souple, en silicone, qui permet l'accès à la cavité péritonéale.

Il est implanté chirurgicalement.

Il a 3 parties : - une partie externe - une partie sous-cutanée - une partie interne.

Il y a 2 cuffs : une cuff sous-cutanée et une péritonéale. Ces cuffs ont 2 rôles : éviter les fuites de dialysat et empêcher la migration des germes de l'extérieur vers la cavité péritonéale. Ces cuffs, au bout de quelques jours, assurent une fixation solide du cathéter au tissu cutané..

Il y a différents types :

- le cathéter droit,
- le cathéter en queue de cochon appelé aussi Pigtail
- le cathéter en col de cygne : le Swan Neck.

Il y a différentes tailles de cathéters pédiatriques : 12 cm, 15 cm et 20 cm.

#### Type de cathéter péritonéal disponible (i.p.=intrapéritonéal)

- TENCKHOFF – Droit ref 411405: 2 cuffs, i.p. 15.5cm, total 41cm
- TENCKHOFF – Droit ref 414201: 2 cuffs, i.p. 12 cm, total 30cm (enf 3-10kg)
- SWAN–NECK TENCKHOFF ref 413101: 2cuffs, i.p. 12cm (DP prolongée)
- Sur commande, cathéter de 20 cm ou 1 cuff

### **III. 2) Le connecteur en titane :**

Il s'agit d'une pièce de liaison inaltérable entre le cathéter et la ligne. Ce connecteur ne doit jamais être éliminé puisqu'il est restérilisable.

### **III 3) Le prolongateur ou raccord intermédiaire :**

C'est une tubulure souple, mise en place de façon stérile, qui relie le raccord en titane (vissé sur le cathéter) à la poche de dialyse.

Ce prolongateur est à changer tous les mois ou tous les 6 mois selon le modèle.

### **III. 4) Les bouchons de déconnexion.**

Ils permettent d'obturer la ligne lorsqu'il n'y a pas de dialyse en cours.

### **III. 5) Les coquilles de protection.**

### **III. 6) Les poches de dialysat :**

La poche est en plastique souple. Elle sera raccordée à la ligne.

Il faut toujours vérifier sur chaque poche : la date de péremption.

le détail de composition

la concentration en glucose.

Il existe 3 concentrations en glucose : 1.36 % poche jaune

2.27 % poche verte

3.86 % poche orange.

Le glucose agit comme agent osmotique ; il permet l'ultrafiltration c'est-à-dire la soustraction osmotique d'eau au petit patient si celui-ci est en rétention hydrique.

Il y a 2 concentrations en calcium : 1.75 mmol/litre et 1.25 mmol/litre.

Les volumes de poche sont de 2 litres.

Actuellement, il existe 4 solutions : - le Dianéal  
- le Nutrinéal  
- l'Extranéal  
- le Physionéal

a) Le Dianéal : est celui que nous utiliserons **le plus souvent**.

Son pH est à 5.7 c'est-à-dire acide.

L'agent osmotique est le glucose selon 3 concentrations précitées.

b) Le Nutrinéal : est un dialysat que nous utiliserons peu. Son intérêt est de permettre l'alimentation par la poche.

Une poche de 2 litres contient 22 gr d'acides aminés mais elle ne contient pas de glucose. Le pouvoir osmotique est toujours de 1.36%, les acides aminés exerçant ce pouvoir osmotique. On utilise une poche par jour à la place d'un repas.

c) L'Extranéal : est un polymère de glucose (Icodextrine) qui agit comme agent osmotique. L'Icodextrine permet d'obtenir « l'équivalent » d'une concentration de glucose à 4.25%. Cette concentration peut garder une ultrafiltration même pendant les péritonites contrairement au glucose seul.

Pour être efficace, l'extranéal **nécessite une stagnation de 10 à 12 h** ; son avantage est de réduire la charge en glucose et donc les risques de diabète associés à la dialyse. . En pratique, il est utilisé en cas de mauvaise ultrafiltration.

d) Le Physionéal : est utilisé uniquement pour les dialyses péritonéales **chroniques**.

Le pH de la poche est de 7.4, donc plus physiologique. *Idéal chez l'enfant, mais 20% plus cher*. Il y a aussi dans ces poches 3 concentrations en glucose 1.36 %, 2.27%, 3.86%.

Le glucose se trouve dans un compartiment supérieur en milieu acide afin d'éviter la formation de produit de dégradation du glucose pendant la stérilisation des poches (ces produits seraient irritants pour le péritoine).

### **Tampons :**

Pour toutes ces poches, le tampon utilisé est le Lactate. En dehors du Physionéal, les poches sont de pH 5.5, relativement acide et parfois irritant.

Les tampons bicarbonate ne sont pas utilisés bien que mieux tolérés car il est impossible de garder dans le dialysat, le sel de calcium.

## IV. TECHNIQUE

### IV. 1. Préparation du patient à la pose du cathéter.

- Patient à jeun
- Paramètres à suivre : poids – taille – surface corporelle
- Toujours placer un cathéter veineux central le plus vite possible, en faisant attention de préserver les sites périphériques de prélèvement chez ces enfants qui risquent un jour d'être en insuffisance rénale chronique et qui auront recours à l'utilisation des fistules d'hémodialyse.
- Placer une sonde gastrique.
- Placer une sonde urinaire.

Le patient doit descendre en salle d'opération **avec son cathéter, la pièce en titane, le prolongateur et une poche de dialyse.**

Le chirurgien décidera ou non d'une omentectomie. Dans ce cas, il réalisera plusieurs rinçages jusqu'à ce que le liquide ne soit plus sanglant.

On administre d'office une dose de Céfacidal à 50 mg/kg en I.V. à la fin de l'intervention. De l'Héparine sera aussi mise dans les poches de dialysat jusqu'au 7<sup>ème</sup> jour, à raison de 1 U/ml.

### IV 2. Cycles de dialyse péritonéale :

Il y a 3 phases :           le remplissage ou infusion  
                                  la stase ou barbotage  
                                  la vidange.

a) Le remplissage ou infusion :

La poche de dialysat chauffée est accrochée en haut d'une potence et l'écoulement se fait par gravité après ouverture du clamp. L'infusion dure 10 minutes et la mesure précise du volume infusé se fera via burette .

b) La stase :

le dialysat est au contact du péritoine, le transfert d'eau et de substances dissoutes peut s'opérer progressivement .

Le temps nécessaire pour atteindre un équilibre est de 4 heures

c) Le drainage : ou phase de vidange de la cavité péritonéale.

On placera la poche vide en bas. On ouvre le clamp et on laisse s'écouler le liquide par gravité. Le temps de drainage est de 15 minutes.

### IV. 3. Prescription de la dialyse par le médecin

Le dialysat doit être chauffé, la température idéale étant située entre 35 et 37°C.

On commence par 10 ml/kg de dialysat pour les premiers bains.

On vérifie le bon écoulement, c'est-à-dire 10 à 15 minutes d'infusion.

Après les 3 premiers échanges, on préconise d'administrer :

- 10 ml/kg/h de dialysat pendant 24h
- puis 20 ml/kg/2h pendant 24h
- puis 30 ml/kg/3h pendant 24 h
- puis 40 ml/kg/4h pendant 24 h → 50 ml/kg/4h

La dialyse ne devient efficace qu'au bout du 6<sup>ème</sup> jour en ce qui concerne le taux d'urée et de créatinine.

Il est habituel lors des premières dialyses d'avoir un bilan positif, c'est-à-dire une rétention liquidienne chez l'enfant. Cet effet est lié au plasma hypertonique de l'enfant (urée élevée). Certains utilisent du liquide hypertonique 3 x à concentration de 2,27% pour contrecarrer ce phénomène.

Dès le 4<sup>ème</sup> bain, l'infirmière doit s'assurer que le bilan devient négatif et réutiliser du glucosé à 1.36%.

En cas d'hypokaliémie liée à la fréquence des bains très rapprochés, on ajoutera une solution de KCl en ajoutant 2 à 3 mEq de KCL par litre de dialysat :

*Kaliémie > 6mEq/l : liquide sans K ; kaliémie 4 -5 mEq/l : 2-3 mEq/l de K ;*

*kaliémie < 3mEq/l : 4 -5mEq/l de K (voir Huault)*

Ne pas oublier de continuer à donner l'Héparine à raison de 1 U par ml de dialyse pendant 8 jours.

#### **IV. 3. Surveillance:**

##### **Patient :**

- poids : 2 x/jour
- monitoring cardiaque
- monitoring de pression artérielle
- bilan hydrique in – out : à vérifier 2x/jour minimum. ( à transmettre au réanimateur)
- débit urinaire horaire : calculé en ml/kg/heure
- site du cathéter veineux central
- site et pansement du cathéter de dialyse
- périmètre abdominal.

Il n'est pas nécessaire de changer le pansement de cathéter avant 5 jours mais il faut surveiller les fuites qui peuvent survenir.

##### **Biologie :**

- hémogramme – ions – urée – créat – glucose – glycémie – pH
- calcium – phosphore : 2x/jour minimum
- Crp – PS

##### **Dialysat :**

- cytologie 1x/jour
- bactériologie 2x/sem

##### **Urines émises par le patient :**

Analysées 1 x/jour : réaction, sédiment, protéines, sodium et créatinine urinaires.

#### **IV. 4 La diététique :**

En aigu, l'enfant est le plus souvent à jeun en catabolisme.

Il faut insister pour la mise en place d'un cathéter veineux central avant ou en salle d'opération pour pouvoir permettre une perfusion de glucosé hypertonique. L'alimentation parentérale est souvent nécessaire et doit être hypercalorique.

Dès que l'enfant le peut, l'apport oral de solides, puis de liquides selon son état clinique et sa diurèse sera permis. Les apports en liquide seront toujours calculés selon la diurèse, la perspiration et l'ultrafiltration obtenue.

Lors de la reprise de l'alimentation orale, le régime sera toujours vu avec le diététicien et le néphrologue pour calculer l'apport en sodium, en potassium, en calcium et en phosphore.

Par contre pour l'apport en protéines, il faut tenir compte des pertes protéiques dans la dialyse péritonéale.

On essayera toujours pour les enfants d'être hypercalorique en apportant

- des calories à raison de 110 à 150 kcal/kg/jour,
- des protéines à raison de 1 à 2.5 gr/kg/jour selon la prescription médicale
- les graisses doivent représenter 50% des apports et les sucres 35%

Les enfants prépubères recevront

20 ?? à 150 kcal/kg/jour

2,5 gr/kg/jour de protéines.

Les enfants pubères peuvent recevoir moins de calories :

70 à 100 kcal/kg/jour

2 gr/kg/jour de protéines

#### **IV. 5. Soins du système de dialyse :**

##### **a) Changement du circuit externe**

- Se change 1x/jour
- Connexion et déconnexion seront toujours stériles (type Nutrition Parentérale).
- Après libération des clamps dans les poches, il y a obligation de flusher le dialysat vers la poche de vidange (principe des vases communicants)
- Pour toute manœuvre stérile, le masque et le lavage hygiénique des mains est indispensable (Manugel)
- Les connexions et déconnexions peuvent se faire au moyen de compresses imbibées d'Isobétadine
- Les coquilles de protection doivent être placées à chaque connexion (à réimbiber d'Isobétadine si date de péremption dépassée)

##### **b) Changement du raccord intermédiaire :**

- Se change 1x/6 mois
- **Conditions d'asepsie strictes** (Masque, bonnet, tablier, lavage hygiénique, Manugel, gants stériles, champs stériles)
- Laisser tremper le bout du drain 10' dans une solution d'Isobétadine
- Connecter le raccord intermédiaire et le nouveau circuit externe

**c) Pansement du site d'insertion du cathéter péritonéal**

- Il est conseillé de ne pas le faire avant 7 jours, sauf problème, puis de changer le pansement une fois par jour, le minimum étant 1x tous les 3 jours, et plus si nécessaire.
- **Les conditions d'asepsie doivent être strictes**  
Matériel :
  - ❖ Masque
  - ❖ Remove
  - ❖ Set à pansement (avec pince et ciseaux)
  - ❖ Hibidil autour de la peau et pas d'Isobetadine qui ralentit la cicatrisation autour du drain
  - ❖ Op-site
  - ❖ Ecouvillons si nécessaire

Réalisation pratique des soins de pansement par l'infirmière.

- ❖ mettre un masque + un masque à l'enfant ( si il ne le supporte lui faire tourner la tête durant la technique)
- ❖ lavage des mains + désinfection des mains
- ❖ préparation du matériel sur le chariot de soins
- ❖ ôter les pansements
- ❖ désinfection des mains au Manugel
- ❖ - soulever légèrement le drain par l'intermédiaire d'une compresse , afin de vérifier l'intégrité du point d'insertion.  
- à l'aide d'un tampon boule, passer sur le trajet du KT, en pressant un peu vers le point de ponction, de manière à faire sortir le pus s'il y a infection. En cas d'écoulement, toujours faire un prélèvement.
- ❖ procéder à une désinfection en partant du point d'insertion vers l'extérieur. Ne pas enlever les croûtes ! Si rougeurs, NaCl 20% imbibée sur des compresses et laisser agir 10 minutes, 2x/j
- ❖ désinfecter le drain sur une longueur de 5 cm
- ❖ disposer une compresse crantée sous le drain
- ❖ placer une compresse sur le drain
- ❖ recouvrir ce système par un opsite , tout en prenant soin de placer le drain le long du corps (ne plus utiliser le gobelet)
- ❖ effectuer une fixation de type « sonde vésicale » et au besoin une boucle de sécurité. Ne pas faire de traction sinon les risques d'infection augmentent. Il existe de petites ceintures faites maison pour mettre le KT.

## V. LES COMPLICATIONS

### 1. Le mauvais drainage :

Ce mauvais drainage peut être lié :

- à la position du cathéter
- à une obstruction par des franges épiploïques aspirées par les perforations latérales du cathéter
- à la constipation.

Traitement :

- a) réinjection lente de dialysat
  - changer la position de l'enfant
  - injection forcée à la seringue : toujours faire attention aux manœuvres hyperstériles.
- b) Si échec, remplacement du drain

- c) Se méfier des oedèmes des membres inférieurs, de la vulve ou des bourses qui signifient que le cathéter s'est déplacé en dehors de la cavité péritonéale.

## 2. Les hémorragies ou la perforation intestinale :

- Très rarement observées
- Souvent liées au déplacement du cathéter péritonéal

Traitement : retrait du drain.

## 3. Les douleurs :

Peuvent être liées :

- a) à la position du drain :
- le cathéter droit étant plus source de douleur que le cathéter recourbé
  - douleur liée aux points de suture
  - douleur locale d'irritation parce que le cathéter est mal placé ; ces douleurs irradient souvent vers le pénis ou le vagin
- b) douleur à l'infusion : cas de
- péritonite
  - adhérence
  - dialysat trop « acide »
  - dialysat trop froid
- c) douleur à la vidange : douleur quand la sortie insuffisante
- Traitement : mobiliser le patient.

Les douleurs entre les dialyses sont souvent liées :

- à la distension abdominale
- parfois à l'injection malencontreuse d'air dans le péritoine : pneumopéritoine

Rappel :

Dans le traitement des douleurs, toutes les médications anti-douleur classiques peuvent être prescrites, en particulier le paracétamol, la codéine et dérivés morphiniques. On évitera l'aspirine et bien entendu, tous les anti-inflammatoires non stéroïdiens sont à proscrire en cas d'insuffisance rénale.

## 4. L'infection :

### a) L'infection du cathéter :

- la peau est irritée
- l'examen minutieux de la peau et du manchon permet de contrôler le tunnel sous-cutané
- la peau doit rester souple et non irritée
- si nécessaire, faire une culture bactérienne et traiter à la Bétadine ou au Bactroban.
- En cas de tunnelite profonde : traiter comme une péritonite et parfois retirer le drain.

### b) Péritonite et son traitement :

Il s'agit de la complication la plus sérieuse de la dialyse péritonéale.

- les symptômes sont la douleur abdominale, la température, le dialysat trouble
- la culture est positive

Toujours obtenir une protéinurie sur le dialysat (en cas d'infection se multiplie par 3 par rapport aux protéines de base du dialysat).

En cas d'infection, le dialysat contient  $>100$  GB/mm<sup>3</sup> dont 50% de polynucléaires neutrophiles.

Toujours demander une culture aérobie et anaérobie sur un milieu d'hémoculture.

Toujours faire des hémocultures périphériques. Parallèlement, prélever : sang complet, iono, CRP, ...

Faire également un prélèvement bactériologique de l'orifice du cathéter et préconiser une échographie abdominale pour trouver parfois un foyer sous-jacent.

Traitement :

- faire 3 échanges de dialysat rapides. Ne pas différer l'antibiothérapie. Instaurer d'emblée une bithérapie par antibiotique puis on adaptera le traitement selon le germe obtenu et l'antibiogramme. Deux schémas de bithérapie sont possibles : soit céphalosporine – aminoglycosides, soit vancomycine - ceftazidime ;
- savoir qu'il ne faut pas associer la pénicilline à l'aminoside en intrapéritonéal. Il y a risque d'inactivation des pénicillines.
- Remettre 500 U d'Héparine / litre de dialysat.
- Il faut donner une dose de charge pendant 4 à 6 heures puis passer à la dose d'entretien à chaque cycle comme décrit sur le tableau.
- Après 48 h à 72 h : passer en monothérapie selon l'identification du germe et l'antibiogramme.
- En cas de non réponse au bout de 48 h : ne pas hésiter à changer d'antibiotique.
- La durée du traitement doit toujours être de 2 à 3 semaines et toujours continuer 7 jours après la dernière culture stérile.
- Le dialysat doit s'éclaircir en 24 h ; la température doit diminuer en 48 h.
- En cas de non réponse au bout de 48 h : ne pas hésiter à changer d'antibiotique.

Après 2 infections : changer de cathéter.

En cas de péritonite mycotique : il faut toujours changer le cathéter.

A l'arrêt du traitement : ne pas hésiter à reconstruire les cultures de dialysat car les rechutes sont fréquentes.

En résumé, la durée totale du traitement est souvent de 21 jours. Elle sera de 21 jours en cas de germes particuliers : staphylocoque doré, germe anaérobie, plusieurs germes. Elle sera de 21 jours de bithérapie en cas de pseudomonas et de serratia.

Si l'enfant est très douloureux, n'oublions pas d'utiliser les antalgiques et de diminuer les volumes de dialysat de 25%.

Toujours rechercher : une infection du tunnel, un autre foyer, un portage bactériologique du nez, des selles ou des urines.

En cas de mycose : Ablation du cathéter entre J0 et J3. Le traitement antimycotique dure de 4 à 6 semaines et toujours 2 semaines après l'arrêt du cathéter.

Tableau des antibiotiques par classes :

- 1) céphalosporines
- 2) aminosides
- 3) glycopeptides
- 4) quinolones
- 5) pénicillines
- 6) autres

	<b>Charge 4 à 6 h de stase</b>	<b>Entretien A chaque nouveau cycle</b>
<b>1. Céphalosporine</b>		
Cefazolin (Cefacidal)	500 mg/l	125 mg/l
Ceftriaxone	250	125
Ceftazidime *	250	125
Cefotaxime	500	250
<b>2. Aminosides</b>		
Amikacine	25 mg/l	12 mg/l
Gentamycine	8	4
Metilmycine	8	4
Tobramycine	8	4
<b>3. Glycopeptides</b>		
Vancomycine**	500 mg/l	30 mg/l J1
Teicoplanine***	15 mg/kg	20 mg/l de dialysat J1 à J8
<b>4. Quinolones</b>		
Ciprofloxacine	50 mg/l péritonéale	25 mg/l

<b>5. Pénicillines</b>		
Ampicilline	500 mg/l	125 mg/l
Amphotéricine B		
Fluconazole (Diflucan)	3 à 6 mg/kg /j intrapéritonéale	
Divers		
Bactrim	SMZ 400 mg/l TMT 80 mg/l	25 mg/l 5 mg/l

\* La Ceftazidime peut être débutée en IV si signes généraux très importants : 40 mg/kg toutes les 48 heures en IV + 125 mg d'entretien dans le dialysat

\*\* Pour la Vancomycine : si signes généraux importants elle peut être utilisée par IV : utilisera une intraveineuse lente de 15 mg/kg/j puis on utilisera la dose d'entretien par 1 péritoine. Les dosages de vancomycine seront faits à 48 h, 5 jours et 10 jours

\*\*\* idem pour la Teicoplanine à raison de 10 mg/kg et continuer à la dose d'entretien de 20 mg/kg de dilaysat.

**Les péritonites réfractaires ou à rechute :**

- discuter d'un traitement local par Urokinase et Vancomycine intraluminaire à haute dose + changement de cathéter
- toujours vérifier l'orifice de sortie et du tunnel.

**Prévention de la péritonite :**

- à la pose du cathéter : donner du Cefazolin 15 mg/kg en I.V
- préférer les cathéters à double cuffs
- diriger l'orifice du cathéter vers le bas
- en cas d'ouverture accidentelle du cathéter : donner de la céfazolin intrapéritonéale pendant 2 jours
- en cas de soins dentaires : donner de l'amoxicilline à raison de 50 mg/kg per os, 1 heure avant les soins et 6 heures après les soins
- en cas d'intervention gastro-intestinale ou génito-urinaire : toujours donner de l'amoxicilline à dose de 50 mg/kg/jour en I.V. , 1 heure avant et 6 après l'intervention + de la gentamycine à raison de 1 mg/kg en I.V. 30 minutes avant le geste chirurgicale.  
SI allergie à la pénicilline : on utilisera la vancomycine à raison de 10 mg/kg 1 heure avant le geste et gentamycine 1 mg/kg en I.V. 30 minutes avant le geste.
- il faut toujours dépister et traiter tout portage de staphylocoque aureus dans le nez et faire un prélèvement chez l'enfant et chez les parents

NB : Le Ceftazidime peut être débuté en I.V. si les signes généraux sont très importants.  
On donnera une dose de 40 mg/kg toutes les 48 heures en I.V. + 125 mg/l dans le dialysat

**5. Accidents métaboliques :**

- a) Hypocalcémie : pallier à un déficit en vitamine D dans l'insuffisance rénale  
On peut : donner un bain plus riche en calcium  
donner du calcium en I.V. ou per os  
prescrire de la vit D active
- b) Hyperkaliémie : utiliser des résines échangeuses d'ions  
(voir protocole d'insuffisance rénale aiguë)  
Il s'agit de kayexalate à raison de 1 gr  
Il peut se donner par voie orale.  
Préfer le kayexalate de calcium en cas d'hypocalcémie.  
Le kayexalate peut se donner en lavement : on prépare donc  
1 gr/kg de kayexalate et on le mélange à 50 ou 70 ml de Sorbitol à 70% ou à de l'eau, mais pas au liquide physiologique qui contient trop de solvant.
- c) Hyperphosphorémie : Se contrôle par le régime alimentaire et par l'administration de calcium oral
- d) Hyperglycémie : nécessitera l'instauration d'une insulinothérapie par Actrapid en

continu, vivement conseillée dès que les glycémies sont supérieures à 2,5 gr%

#### **6. Accidents hypertensifs :**

Souvent sévères quand il y a un excès de rétention liquidienne.

Le traitement est l'utilisation d'un dialysat hypertonique. Cette utilisation doit être rigoureusement contrôlée d'une part parce que le dialysat hypertonique est très irritant pour le péritoine et d'autre part, parce que l'utilisation de substrat hypertonique entraîne l'hyperglycémie avec risque de diabète et majoration de la soif.

En cas d'hypertension artérielle aiguë, se référer au protocole de traitement sur l'hypertension.

#### **7. Traitements associés :**

- Vit. D active : Rocaltrol ou Alfaléo
- Anti-hypertenseur
- Erythropoïétine : en pratique nous utiliserons souvent le Néorecormon qui contient le dosage spécifique à la pédiatrie.
- En cas de transfusion : toujours utiliser des culots globulaires déleucocytés CMV- en pensant que ces enfants seront un jour en insuffisance rénale terminale avec nécessité d'une transplantation.

## **Clinical manifestations and diagnosis of Henoch-Schönlein purpura**

**INTRODUCTION** — Henoch-Schönlein purpura (HSP) is the most common form of systemic vasculitis in children. Ninety percent of cases occur in the pediatric age group. In contrast to many other forms of systemic vasculitis, HSP is self-limited in the great majority of cases. The disease is characterized by a tetrad of clinical manifestations:

- Palpable purpura in patients with neither thrombocytopenia nor coagulopathy
- Arthritis/arthralgia
- Abdominal pain
- Renal disease

The clinical manifestations, pathogenesis, diagnosis, and differential diagnosis of HSP will be presented here. The management of HSP and a more complete discussion of the renal manifestations of HSP are found elsewhere. (See "[Management of Henoch-Schönlein purpura](#)" and see "[Renal manifestations of Henoch-Schönlein purpura](#)").

**EPIDEMIOLOGY** — HSP is primarily a childhood disease that occurs between the ages of 3 and 15 years. In a population-based study from the United Kingdom, the annual incidence was about 20 per 100,000 in children <17 years of age with a peak incidence of 70 per 100,000 in children between the ages of 4 and 6 years [1] . In reports from Taiwan and the Czech Republic, there was a lower incidence of 10 per 100,000 in children <17 years of age with a peak incidence at 5 to 7 years of age [2,3] . Although there are no comparable epidemiologic data, HSP is less common in adults [4] .

There is a male predominance with reported male-to-female ratios of 1.2:1 to 1.8:1 [1,2,5,6] . HSP is seen less frequently in black compared to white or Asian children [1] .

HSP occurs primarily in the fall, winter, and spring but rarely in the summer months [5-7] . About half of the cases of HSP are preceded by an upper respiratory infection [8] , especially streptococcal infections [9,10] . Other infectious agents, vaccinations, and insect bites have been implicated as possible triggers for HSP [8] .

**PATHOGENESIS** — HSP is an immune-mediated vasculitis associated with immunoglobulin A (IgA) deposition. Although a variety of infectious and chemical triggers have been proposed, the underlying cause of HSP remains unknown.

The characteristic finding of HSP is leukocytoclastic vasculitis accompanied by IgA immune complexes within affected organs ([show histology 1A-1B](#)). Skin biopsies of purpuric lesions demonstrate the involvement of small vessels (primarily postcapillary venules) within the papillary dermis. The predominant cell types within the inflammatory infiltrate are neutrophils and monocytes. Immunofluorescence studies show IgA, C3, and fibrin deposition within the walls of involved vessels. IgA, C3, fibrin, IgG, and less commonly IgM also are deposited within the endothelial and mesangial cells of the kidney ([show histology 2](#)).

Attention has focused on the role of IgA and IgA immune complexes in the pathogenesis of HSP. Several studies report finding increased serum levels of IgA and IgA immune complexes, alteration in the glycosylation of IgA, and elevated levels of IgA anticardiolipin antibodies and transforming growth factor-beta in patients with HSP [6,11-15]. One unexplained peculiarity of HSP is the fact that of the two IgA subtypes (IgA1 and IgA2), only IgA1 is found in the inflammatory infiltrates of this disease [16]. Despite these reports, the precise role of IgA and the specific involvement of IgA1 in the pathogenesis of HSP remain unclear.

**CLINICAL MANIFESTATIONS** — The classic tetrad of HSP includes:

- Palpable purpura without thrombocytopenia and coagulopathy
- Arthritis/arthralgia
- Abdominal pain
- Renal disease

These clinical manifestations may develop over the course of days to weeks and may vary in their order of presentation. Purpura and joint pain are usually the presenting symptoms but this is not always the case. In the absence of the classic purpuric rash, the diagnosis of HSP may not be obvious initially. Patients who present with significant joint or abdominal symptoms without the skin manifestations may be thought to have an infectious or surgical process.

The mean age of onset of HSP is between 6 and 7 years of age [1,2,5,6]. Based upon retrospective reviews from Taiwan, Italy, and the United States, the major clinical manifestations develop with the following frequencies (show table 1) [2,5,16]:

- Purpura — All patients developed palpable purpura.
- Arthralgia/arthritis — In the American and Italian series, joint symptoms were the second most common manifestation occurring in three-quarters of the patients. In the Taiwanese study, joint complaints were present in 43 percent of patients.
- Abdominal pain — Colicky pain occurred in about half of patients and gastrointestinal bleeding in approximately 20 to 30 percent of patients.
- Renal disease — The frequency of renal involvement ranged from 21 to 54 percent.

In the retrospective Italian review of 150 children with HSP, the presenting symptom was purpura in 74 percent, arthritis in 15 percent, and abdominal pain in 12 percent of patients [5]. Similar results were seen in a Spanish retrospective review of 78 patients [6]; purpura, arthritis, and abdominal pain were the initial findings in 70, 12, and 17 percent of patients, respectively.

**Skin manifestations** — The classic rash of HSP is not the initial presenting sign in about one-quarter of affected children. As a result, it may be difficult to make the diagnosis of HSP prior to its development in patients who present with other clinical manifestations such as abdominal pain or arthritis.

The rash often begins with erythematous, macular, or urticarial wheals. The wheals then coalesce and evolve into the typical ecchymoses, petechiae, and palpable purpura ([show picture 1](#)) ([show picture 2-3](#)). The rash typically appears in crops, in a symmetrical distribution, and located in gravity/pressure-dependent areas such as the lower extremities. The buttocks are often involved in toddlers, and the face, trunk, and upper extremities in nonambulatory children.

Localized subcutaneous edema is a common feature that may be found in dependent and periorbital areas, especially in younger children (<3 years of age). Even adult patients, however, may also have this manifestation of HSP.

**Arthritis/arthralgia** — Arthritis/arthralgia, which occur in up to 84 percent of patients [5] is uncommon as the sole symptom at presentation. As previously noted, arthritis/arthralgia are the presenting symptom in only about 15 percent of patients [5] .

The arthritis is usually transient or migratory, typically oligoarticular (one to four joints), and nondeforming. It usually affects the lower extremity large joints (hips, knees, and ankles), or less commonly the upper extremities (elbows, wrists, and hands) [5,6] . There is often prominent periarticular swelling and tenderness but usually without joint effusion, erythema, or warmth. Patients may have considerable pain and limitation of motion. Younger children with lower extremity involvement may refuse to ambulate. The arthritis does not cause any chronic damage or sequelae. It may precede the appearance of purpura by one or two days.

**Gastrointestinal symptoms** — Gastrointestinal symptoms occur in about half of children with HSP and range from mild (nausea, vomiting, abdominal pain, and transient paralytic ileus) to more significant findings (gastrointestinal hemorrhage, bowel ischemia and necrosis, intussusception, and bowel perforation). Guaiac-positive stool is found in up to 56 percent of patients, but massive gastrointestinal hemorrhage is rare [17] .

Gastrointestinal symptoms typically develop within eight days of the appearance of the rash, although much longer intervals (weeks to months) have been described [18] . Gastrointestinal complaints precede the rash in about 15 to 35 percent of cases, making the diagnosis of HSP less obvious in these patients. Gastrointestinal symptoms without the appearance of cutaneous purpura at any time also have been described in case reports [19-21] .

Gastrointestinal pain associated with HSP is caused by submucosal hemorrhage and edema. Purpuric lesions may be seen on endoscopy, commonly in the descending duodenum, stomach, and colon. The terminal ileum also may be involved. Submucosal edema, ulceration, and spasm of the ileum and jejunum may be seen in small bowel series. (See "[Gastrointestinal manifestations of vasculitis](#)").

Intussusception is the most common gastrointestinal complication of HSP. Rarer gastrointestinal manifestations include acute pancreatitis, gall bladder involvement, bowel perforation, and, in children, a protein-losing enteropathy [17,22-27] .

**Intussusception** — Edema and hemorrhage can act as a pathological lead-point, contributing to the development of intussusception. Intussusception is limited to the small bowel in about 60 percent of cases, in contrast to idiopathic intussusception, which is typically ileocolic [28] . Intussusception in HSP has a reported

overall incidence of about 3.5 percent, although some retrospective series reported an incidence of only 0.4 to 0.6 percent [5,17] . This discrepancy may be due to differences in the population studied. Children demonstrating severe gastrointestinal pain and/or requiring hospitalization are presumably at greater risk.

In a retrospective review of 149 hospitalized children with HSP from two centers in Chicago, 63 patients (42 percent) presented with severe abdominal pain [29] . Four patients were diagnosed with intussusception, two of which were ileoileal intussusceptions. All four patients required surgical correction.

In patients with HSP, ultrasonography should be the initial screening test in cases of suspected intussusception. Although contrast enemas are the standard procedure in other clinical settings to diagnosis intussusception, they cannot detect ileoileal intussusception typically seen in HSP. (See "Intussusception in children").

**Renal disease** — Retrospective cohort studies report that 20 to 54 percent of patients with HSP had some degree of initial renal involvement [5,16,30,31] . Manifestations of renal disease ranged from isolated hematuria and/or proteinuria without any abnormality in renal function or blood pressure to acute nephropathy with renal insufficiency. Children who develop renal involvement usually do so within four weeks of their presentation.

In a retrospective review of 261 children with HSP (<17 years of age), renal involvement was detected in 52 patients (20 percent) within four weeks of diagnosis. Specific findings included the following [30] :

- Microscopic hematuria in 37 patients (11 percent)
- Gross hematuria in 12 patients (5 percent)
- Of the 49 patients with hematuria, 28 had proteinuria
- Nephrotic syndrome in 2 patients
- Isolated proteinuria in 2 patients

In a systematic review of the literature, 12 studies were identified that assessed the course of renal disease in children with HSP [32] . Of the 1133 patients, one-third had an abnormal urinalysis during the course of their disease. In 305 patients (27 percent), the abnormality was either isolated hematuria or proteinuria, and nephritis or nephrosis was seen in only 82 patients (7 percent). At the time of follow-up (range 6 weeks to 36 years), only 21 patients (1.8 percent) had renal impairment. Patients who had nephritis or nephrosis were at increased risk for developing renal impairment compared with all patients with HSP (RR 11.8, 95% CI 4.1 to 41.5).

The overall renal prognosis of HSP in children is considered to be excellent. Long-term follow-up studies demonstrate some risk of progressive renal disease both in children and adults, which accounts for much of the long-term morbidity in patients with HSP.

A more complete discussion on the renal manifestations of HSP, including prognosis and treatment, is found elsewhere. (See "Renal manifestations of Henoch-Schönlein purpura").

**Other organ involvement** — Other organ systems also may be involved:

- Scrotum — Reports of scrotal involvement in boys with HSP range from 2 to 38 percent [33-35] . Rarely, scrotal pain may be the presenting symptom. Clinical findings include pain, tenderness, and swelling of the involved testicle and/or scrotum.

The presentation may mimic testicular torsion. Evaluation including ultrasonography and technetium Tc99m radionuclide scanning can differentiate the two entities. In testicular torsion, these studies demonstrate decreased blood flow to the testicle, in contrast to the normal or increased flow seen in boys with HSP.

The clinical presentation of scrotal involvement in boys with HSP was reviewed in a retrospective study of 120 Korean boys diagnosed with HSP between 1992 and 2004 [36] . Twenty-six patients (22 percent) had scrotal involvement, which presented as scrotal swelling (23 patients), scrotal pain or tenderness (18 patients), and bilateral involvement (7 patients). Scrotal pain was the initial finding of HSP in two of the patients. Imaging (ultrasonography and/or radionuclide scan) was performed in 15 patients and demonstrated epididymitis in 13 and orchitis in two patients. One patient underwent surgical exploration but there was no evidence of testicular torsion.

- Central and peripheral nervous system — Single reports and case series document neurologic manifestations including headaches, seizures, focal neurologic deficits, ataxia, intracerebral hemorrhage, and central and peripheral neuropathy in children with HSP [37-39] . Most of the central nervous system findings are transient except for occasional permanent sequelae associated with hemorrhagic stroke.
- Eyes — Keratitis and uveitis, both reported in patients with HSP, are very rare sequelae of HSP and usually suggest other diseases [40] .
- Respiratory tract — In a cohort of French patients hospitalized for HSP, impaired lung diffusion capacity and mild interstitial changes on chest radiographs were found in the majority of patients (97 and 69 percent, respectively), despite the absence of significant respiratory symptoms [41] . There also are case reports of pulmonary hemorrhage in patients with HSP [42-44] .

**Adults** — Adult patients with HSP present with clinical manifestations very similar to those that occur in children. Two main distinctions exist between adults and children with HSP.

- Intussusception is extremely rare in adults.
- Adults are at increased risk for developing significant renal involvement including end-stage renal disease [4,45] .

This was best illustrated by a retrospective review of 250 French adult patients (median age: 50 years). At presentation, clinical findings included palpable purpura (96 percent), arthritis (61 percent), and gastrointestinal symptoms (48 percent) [45] . Almost one-third of patients had renal insufficiency (creatinine clearance <50 ml/min per m<sup>2</sup>) within four months of presentation. At a median follow-up of 14.8 years, persistent renal impairment was seen in 80 patients (32 percent) of the original cohort including end-stage renal

failure in 27 patients and severe renal impairment (creatinine clearance <30 ml/min per m<sup>2</sup>) in another 32 patients.

Potential explanations for the high prevalence of substantial renal impairment in this study include the fact that all patients in the study had renal disease severe enough to require renal biopsy, the long period of follow-up compared with other studies, and the possible role of co-morbidities (eg, hypertension) in contributing to the progression of renal disease.

A more complete discussion of the renal manifestations and the management of renal disease in patients with HSP is found separately. (See "[Renal manifestations of Henoch-Schönlein purpura](#)").

**Recurrence** — Recurrence of HSP is reported in about one-third of affected children [5,16,46] and generally occurs within four months of the initial episode. Recurrences tend to be milder and shorter than the initial episode, and they occur more commonly in patients with nephritis, in those with evidence of acute inflammation (eg, elevated erythrocyte sedimentation rate [ESR]), or in patients who received treatment with corticosteroids [5]. These findings suggest that patients who have a more severe course of HSP are at increased risk of recurrence.

One retrospective review from Israel reported a longer mean interval time of 13.5 months between the first and second episode of HSP than what had been reported previously [47]. In addition, there was no difference in clinical and laboratory findings between patients with recurrent disease and those without recurrence. The reasons for these differences between study results are unclear.

**DIAGNOSIS** — The diagnosis of HSP is usually based upon clinical manifestations of the disease. The diagnosis is straightforward when patients present with the classic signs and symptoms, especially palpable purpura of the lower extremities and buttocks. In patients with incomplete or unusual presentations, a biopsy of an affected organ (eg, skin or kidney) that demonstrates leukocytoclastic vasculitis with a predominance of IgA deposition confirms the diagnosis of HSP.

**Biopsy** — In pediatric patients, biopsy is reserved for patients with an unusual presentation of HSP (ie, no rash, or an atypical rash) or those with significant renal disease.

In adult patients, because of the lower incidence of HSP beyond the pediatric age group, confirmation of the diagnosis by biopsy is more important

**Skin** — Biopsies of the skin, which sample the small blood vessels of the superficial dermis, are usually adequate to make the diagnosis of HSP. Light microscopy studies (hematoxylin and eosin stains) demonstrate the classical leukocytoclastic vasculitis in postcapillary venules with IgA deposition that is pathognomonic of HSP ([show histology 1A-1B](#)) [48]. The biopsy should contain skin lesions that are less than 24 hours old because in more chronic lesions, vessel damage leads to non-specific leakage of all isotypes of immunoglobulin. Immunofluorescence studies, essential to confirming the diagnosis of HSP, generally require biopsy of a second skin site.

**Kidney** — Renal biopsy is reserved for patients in whom the diagnosis is uncertain or if there is clinical evidence of severe renal involvement. In the kidney, HSP is characterized by IgA deposition in the mesangium (show histology 2). The glomerular involvement beyond mesangial IgA deposition varies. Light microscopy changes may range from isolated mesangial proliferation to severe crescentic glomerulonephritis. In addition to IgA deposition, immunofluorescence studies demonstrate IgG, fibrin, C3, and properdin in the glomeruli. In general, the extent of renal injury parallels the clinical severity of renal disease. (See "Renal manifestations of Henoch-Schönlein purpura").

**Laboratory tests** — No laboratory test is diagnostic for HSP. Serum IgA levels have been reported to be elevated in 50 to 70 percent of patients with HSP [6,12,49] .

Findings on routine blood tests (eg, complete blood cell count, serum chemistries, and urinalysis) are non-specific. Results generally reflect the triggering condition: HSP following bacterial infections is more likely to be characterized by leukocytosis (white cell count >20,000 cells/mm<sup>3</sup>) and an elevated erythrocyte sedimentation rate (ESR). HSP after viral illnesses, on the other hand, often demonstrates no evidence of systemic inflammation. Patients may have a normochromic anemia because of occult or overt gastrointestinal bleeding.

Demonstration of a normal platelet count and coagulation studies (prothrombin time) are imperative to distinguish HSP from other diseases that present with purpura on account of thrombocytopenia or coagulopathy.

Urinalysis should be performed in all patients with HSP. In general, the findings reflect the degree of renal involvement and may include the presence of red or white cells, cellular casts, and proteinuria. Serum creatinine should be obtained in all adult patients with HSP because of the increased risk of significant renal disease. In children, renal disease is less prevalent, so serum creatinine need not be obtained unless there are abnormalities on the urinalysis. Renal involvement often becomes detectable after other manifestations of HSP, so urinary screening should be continued beyond the acute presentation. (See "Renal manifestations of Henoch-Schönlein purpura").

**Imaging studies** — Imaging studies generally are performed in patients with significant abdominal symptoms. Plain abdominal radiography may demonstrate dilated loops of bowel consistent with decreased bowel motility. Abdominal ultrasonography can detect increased bowel wall thickness, hematomas, peritoneal fluid, and intussusception [6,28,29] .

If intussusception is considered, ultrasonography rather than contrast enemas should be the initial screening test. Ileoileal intussusception is seen in more than half of the cases of intussusception in patients with HSP. Contrast enemas, usually indicated in children with signs of an intussusception, do not detect ileoileal intussusception.

In boys who present with scrotal symptoms, Doppler flow studies and/or radionuclide scans can distinguish scrotal pain caused by HSP from testicular torsion. In testicular torsion, these studies demonstrate decreased blood flow to the testicle. In boys with HSP, testicular blood flow is normal or increased. (See "Other organ involvement" above).

**Classification criteria** — A variety of classification criteria have been proposed primarily for use in research protocols and outcome studies. They have not been validated for clinical diagnosis.

In 1990, the American College of Rheumatology (ACR) Classification established criteria to classify seven types of vasculitides including HSP [50,51] . The ACR criteria for the diagnosis of HSP are as follows:

- Palpable purpura
- Age at onset  $\leq 20$  years
- Acute abdominal pain
- Biopsy, which showed granulocytes in the walls of small arterioles and/or venules

These criteria were based upon a comparison between 85 patients with HSP and 722 adult patients with other forms of vasculitis. Two or more of the criteria had a sensitivity and specificity of approximately 90 percent in separating adult patients with HSP from those with other causes of vasculitis.

In 2005, pediatric consensus criteria were developed by the European League against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PReS) [52] . These criteria are more representative of clinical practice in which a clinician is more likely to seek features to distinguish HSP from gastroenteritis or appendicitis than from Wegener's granulomatosis. The criteria included palpable purpura without thrombocytopenia and coagulopathy as a mandatory finding and one or more of the following:

- Diffuse abdominal pain
- Arthritis or arthralgia
- Any biopsy with predominant immunoglobulin A (IgA) deposition

**DIFFERENTIAL DIAGNOSIS** — In the presence of the classic presentation of palpable purpura with normal coagulation studies and platelet count, plus either abdominal pain or arthritis/arthralgia, the diagnosis of HSP is generally straightforward [52] . However, the diagnosis is more difficult if there is an incomplete presentation of HSP or if the skin manifestations are initially absent. In these circumstances, other causes for purpura, arthritis, abdominal pain, and renal disease need to be considered.

**Purpura** — Petechiae and purpuric rashes may be associated with septicemia, idiopathic thrombocytopenic purpura, hemolytic uremic syndrome, leukemia, and coagulopathies (eg, hemophilia). Platelet count and coagulation studies differentiate HSP from these entities.

There are several conditions that can present with purpura with normal platelet counts and coagulation studies.

- Acute hemorrhagic edema of infancy (AHEI) — AHEI is a leukocytoclastic vasculitis described in children between the ages of 4 months to 2 years [53-55] . It is a self-limited disease that presents with fever, purpura, ecchymosis, and inflammatory edema of the limbs and resolves in one to three weeks ([show picture 3](#)). Involvement of the kidney and the gastrointestinal tract is uncommon.

Biopsy of the skin demonstrates a leukocytoclastic vasculitis with occasional IgA deposition. It is unclear whether this condition overlaps clinically with HSP or is a separate entity.

- Hypersensitivity vasculitis — Hypersensitivity vasculitis is an inflammation of the small vessels that occurs after exposure to drugs or infection, or without an identifiable trigger [51]. Patients present with fever, urticaria, lymphadenopathy, and arthralgias, but not usually glomerulonephritis. Histopathology shows a leukocytoclastic vasculitis primarily of the postcapillary venules but IgA deposition is absent. (See "[Hypersensitivity vasculitis in children](#)").
- Other small vessel vasculitides — There are a number of causes of small vessel vasculitis (including HSP) that may present with asymmetric polyneuropathy, palpable purpura, and/or pulmonary-renal involvement. These diseases include primary vasculitides (eg, Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome), and conditions secondary to a connective tissue disorder (eg, systemic lupus erythematosus [SLE]) or to an infectious disease (eg, hepatitis B or C). In general, these diseases, which mimic HSP, are uncommon in children.

Laboratory evaluation including serum complement levels, antinuclear antibodies, anti-double stranded deoxyribonuclease (anti-dsDNA), and antineutrophil cytoplasmic antibodies, may differentiate HSP from the other causes of small vessel vasculitis. Light microscopy examination of a purpuric lesion will demonstrate leukocytoclasia in many small vessel vasculitides, but it is the predominance of IgA deposition that conclusively characterizes HSP. (See "[Classification and incidence of childhood vasculitis](#)" and see "[Classification of and approach to the vasculitides in adults](#)", section on Small vessel vasculitis).

**Arthritis and arthralgia** — In about 15 percent of patients with HSP, arthritis or arthralgia may be the presenting manifestation, usually preceding the skin manifestations by only one day. Until a patient develops the classical purpura of HSP, other causes of joint complaints must be considered.

Autoimmune diseases such as systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis (JRA) [also called juvenile idiopathic arthritis (JIA)], and rheumatic fever may present with similar joint symptoms to HSP. Assays for serum complement, antinuclear and anti-dsDNA antibodies, and rheumatoid factor may help to differentiate HSP from SLE and JRA. Evidence of a recent Group A beta-hemolytic streptococci (eg, anti-streptolysin O titers) and the clinical course distinguish acute rheumatic fever from HSP. (See "[Systemic lupus erythematosus in children](#)", see "[Clinical manifestations and diagnosis of polyarticular onset juvenile rheumatoid arthritis](#)", see "[Pauciarticular onset juvenile rheumatoid arthritis](#)" and see "[Clinical manifestations and diagnosis of acute rheumatic fever](#)").

Septic arthritis and toxic synovitis also may present with joint symptoms similar to those seen in patients with HSP. These typically involve only one or two joints, unlike the polyarthritis seen in HSP. In most circumstances these conditions are easily distinguished from HSP by an experienced clinician.

Additionally, in septic arthritis, affected joints are warm and erythematous, unlike those in HSP. Joint aspiration may be needed to differentiate the two. In the case of toxic synovitis, another self-limited disease with transient joint findings that resolve without long-term sequelae, evolution of the other manifestations of HSP will help differentiate the two conditions. (See "[Overview of the causes of limp in children](#)").

**Abdominal pain** — Distinguishing acute abdominal catastrophes such as appendicitis from HSP before the development of purpura may be very difficult. Although the rash of HSP usually precedes gastrointestinal manifestations, and seldom lags by more than a few days, evaluation for potential acute abdomen cannot be delayed. Serial examinations and radiologic studies are used to evaluate for causes of abdominal pain that require surgical intervention. This also can include patients with HSP who develop gastrointestinal complications such as intussusception, bowel infarction or perforation. (See "Causes of acute abdominal pain in children").

**Renal disease** — Patients with IgA nephropathy or Berger's disease present with similar immunologic and histopathologic findings as patients with HSP. As is true of patients with HSP, manifestations of IgA nephropathy vary from microscopic hematuria to acute renal failure. Although patients with IgA nephropathy do not have the other clinical characteristics of HSP, these two entities might share a similar pathogenesis. (See "Causes and diagnosis of IgA nephropathy").

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "Patient information: Vasculitis"). We encourage you to print or e-mail this topic, or to refer patients to our public web site [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

**SUMMARY** — Henoch-Schönlein Purpura (HSP) is the most common systemic vasculitis of childhood. It is a self-limited disease and is characterized by a tetrad of clinical manifestations that vary in their occurrence and order of presentation. (See "Clinical manifestations" above).

- Palpable purpura without thrombocytopenia and coagulopathy
- Arthralgia and/or arthritis
- Abdominal pain
- Renal disease

#### **Epidemiology and pathogenesis**

- HSP occurs primarily between the ages of 3 and 15 years. The annual incidence is 10 to 20 per 100,000 in children <17 years of age with a peak incidence in children between 4 to 6 years of age. Approximately, 10 percent of HSP cases occur in adults. (See "Epidemiology" above).
- The underlying cause of HSP is unknown. It is thought that HSP is a result of an immune-mediated vasculitic disorder. (See "Pathogenesis" above).

#### **Diagnosis and differential diagnosis**

- The diagnosis of HSP is usually based upon clinical manifestations of the disease. In patients with an incomplete or unusual presentation, biopsy of the affected organ (eg, skin or kidney) demonstrating predominantly IgA deposition supports the diagnosis of HSP. (See "Diagnosis" above).

- There are no diagnostic tests for HSP. All patients in whom the diagnosis is considered should have a CBC, prothrombin, and urinalysis. The presence of thrombocytopenia or a coagulopathy excludes the diagnosis of HSP. A serum creatinine should be obtained in children with an abnormal urinalysis. Serum creatinine should be obtained in all adult patients with HSP because of the increased risk of significant renal disease. (See "Laboratory tests" above).
- Abdominal ultrasonography is indicated in patients with severe abdominal pain. It can detect increased bowel wall thickness, hematomas, peritoneal fluid, and intussusception. Contrast studies may miss intussusception in patients with HSP. (See "Imaging studies" above).
- The diagnosis is more difficult if there is an incomplete presentation of HSP or if the skin manifestations are absent at presentation. In these circumstances, other causes for purpura, arthritis, abdominal pain, and renal disease must be considered. (See "Differential diagnosis" above).

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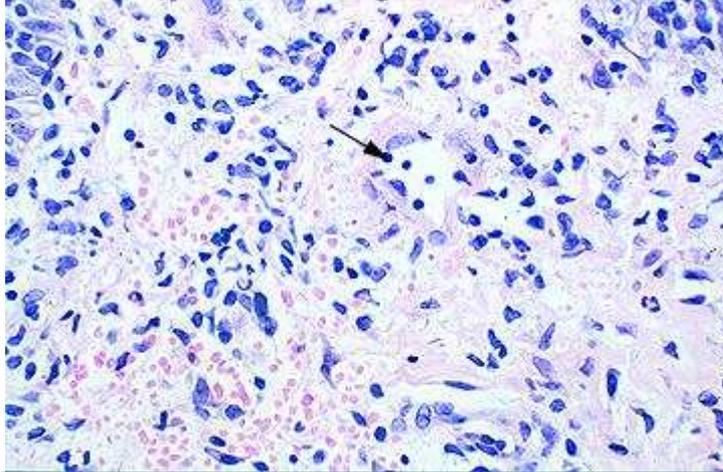
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## GRAPHICS

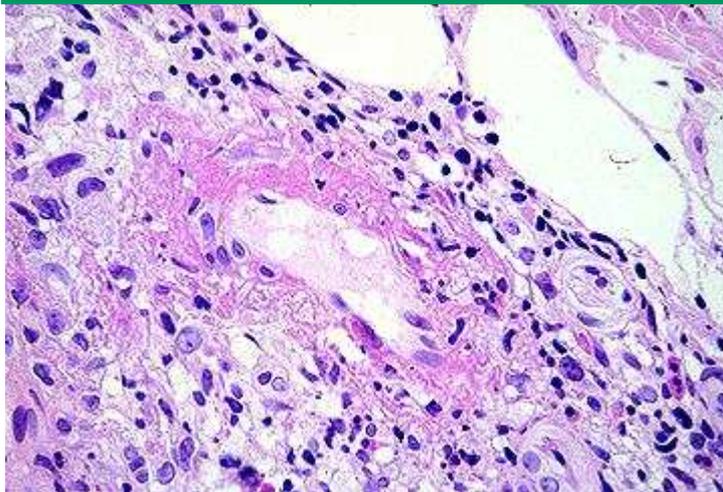
### Leukocytoclastic vasculitis I

#### Leukocytoclastic vasculitis



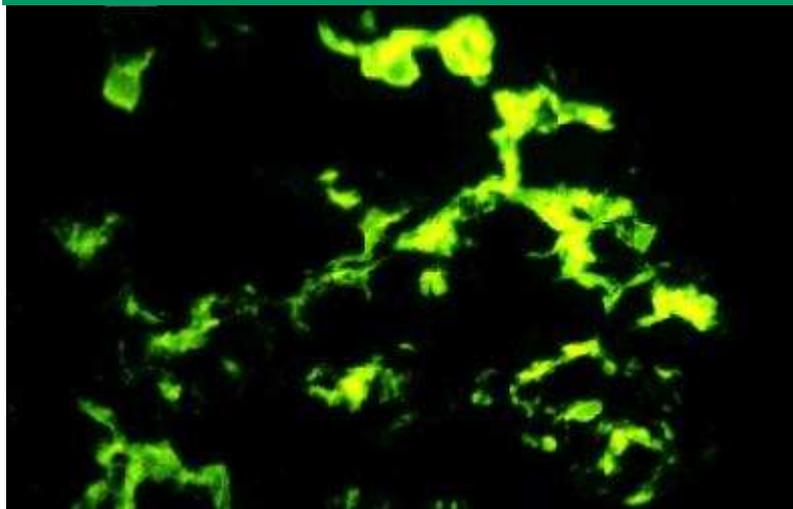
Leukocytoclastic vasculitis involving the dermal papillae capillaries and venules (arrow), a finding that probably reflects an Arthus type III immune complex reaction. *Courtesy of Cynthia Magro, MD.*

#### Leukocytoclastic vasculitis



Skin biopsy from a patient with leukocytoclastic vasculitis showing striking mural fibrin deposition in a postcapillary venule and a concomitant angiocentric mixed neutrophilic and lymphocytic infiltrate. This pattern can be seen in a variety of disorders including hypersensitivity vasculitis, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, Behcet's disease, and relapsing polychondritis. *Courtesy of Cynthia Magro, MD.*

### Mesangial IgA deposits



Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura. Note that the capillary walls are not outlined, since the deposits are primarily limited to the mesangium. *Courtesy of Helmut Remke, MD.*

### Frequencies of clinical features of children with Henoch Schonlein purpura at presentation and during their disease

Clinical features	Taiwan* (%)	Italy* (%)	United States $\Delta$ (%)
Purpura	100	100	100
Arthralgia/arthritis	43	74	82
Abdominal pain	58	51	63
Gastrointestinal bleeding	18	18	33
Intussusception	0.4	0.6	
Renal involvement	21	54	40
Edema		52	
Encephalopathy	1	3	2
Orchitis		13	
Recurrence		33	33

\* Chang, WL. *Acta Paediatr* 2004; 93:1427. Chang, WL. *Pediatr Nephrol* 2005; 20:1269.  
 $\bullet$  Trapani, S. *Semin Arthritis Rheum* 2005; 35:143.  
 $\Delta$  Saulsbury, FT. *Medicine (Baltimore)* 1999; 78:395.

### Petechiae in Henoch-Schönlein purpura

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Clusters of palpable, pruritic petechiae on the thigh of a patient with Henoch-Schönlein purpura. These lesions could be mistaken for thrombocytopenic petechiae.

### Rash HSP A

### Skin manifestations of Henoch-Schönlein purpura

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This picture shows the classic skin manifestations of Henoch-Schönlein purpura, with clusters of typical ecchymoses, petechiae, and palpable lesions on the thigh and legs in a typical distribution (gravity/pressure-dependent areas). *Courtesy of Susan Kim, MD.*

**Skin manifestations of Henoch-Schönlein purpura**



*Courtesy of Susan Kim, MD*

**Acute hemorrhagic edema of infancy**



*Reproduced with permission from Lawrence Zemel, MD. Connecticut Children's Medical Center. Copyright © Lawrence Zemel, MD.*

## Syndrome néphritique aigu

Quelle que soit l'évolution, le type histologique, le pronostic, les néphropathies glomérulaires ont un tableau clinique assez stéréotypé appelé syndrome néphritique aigu.

### 1 Syndrome néphritique aigu

Il associe :

- **une protéinurie non sélective**, inférieure à 50 mg/kg/j, parfois plus abondante, entraînant alors l'apparition d'un syndrome néphrotique ;
- **une hématurie** souvent macroscopique donnant aux urines une couleur "bouillon sale", ou microscopique objectivée à la bandelette ou l'examen du sédiment urinaire. Il existe des cylindres hématiques traduisant l'origine glomérulaire de l'hématurie ;
- **une oligurie avec oedèmes**, les oedèmes sont en général modérés, il s'agit parfois d'une simple prise de poids ;
- **une hypertension artérielle**. Elle peut révéler la maladie par des manifestations bruyantes à type de convulsions. La sévérité de l'hypertension n'est pas corrélée avec la sévérité de l'atteinte rénale ;
- **une insuffisance rénale inconstante**, de degré variable, elle est objectivée par la baisse de la filtration glomérulaire.

Devant ce syndrome néphritique, il faut rechercher une infection, O.R.L., cutanée, profonde (cathéter, valve), chercher des signes de maladie générale (purpura rhumatoïde, lupus, P.A.N.) faire un dosage de la fraction C3 du complément. Au terme de ce bilan, le syndrome néphritique peut être soit apparemment isolé, soit secondaire à une maladie générale.

### 2 Modalités évolutives du syndrome néphritique apparemment isolé

Trois possibilités évolutives :

#### 2.1 Formes à début aigu curable

La plus fréquente. Le tableau correspond à celui de la glomérulonéphrite aiguë post-streptococcique ; d'autres germes peuvent cependant être en cause. L'hypertension artérielle, l'oligo-anurie, l'insuffisance rénale, sont transitoires. S'il existait un syndrome néphrotique, celui-ci disparaît en moins de 15 jours. La fraction C3 du complément abaissée au début de la maladie se normalise en 8 semaines. C'est un critère biologique de surveillance. Le pronostic est excellent, la biopsie est inutile, elle objectiverait une prolifération endocapillaire pure.

#### 2.2 Formes à début aigu d'évolution chronique

Il existe trois possibilités évolutives distinctes :

- L'hypertension artérielle, le syndrome néphrotique, l'insuffisance modérée, persistent plus de quatre semaines.
- Le complément C3 reste bas après 8 semaines.
- L'hématurie et/ou la protéinurie sont toujours persistantes un an après le début.

Ces trois possibilités doivent faire envisager une ponction biopsie rénale. Le pronostic en effet est plus réservé et fonction de l'histologie, soit glomérulonéphrite endo et extracapillaire de type I et II, soit glomérulonéphrite membranoproliférative, soit néphropathie glomérulaire à dépôt mésengiaux d'IgA (maladie de BERGER).

### **2.3 Formes à début aigu avec insuffisance rénale rapidement progressive**

- **L'insuffisance rénale et l'oligo-anurie sont sévères**, elles persistent plus de 5 jours.
- **Le syndrome néphrotique** est intense ou alors apparaît secondairement.

Dans ces deux cas le pronostic est mauvais et impose rapidement une ponction biopsie rénale qui objectivera une glomérulonéphrite endo et extracapillaire type III (glomérulonéphrite maligne). L'évolution vers l'insuffisance rénale terminale est le fait de la majorité des cas.

### **3 Syndrome néphritique secondaire à une maladie générale**

Chez l'enfant, il s'agit essentiellement d'un purpura rhumatoïde, rarement d'un lupus, d'une périartérite noueuse.

## **4 Traitement**

### **4.1 Syndrome néphritique à début aigu curable**

Le traitement est essentiellement symptomatique : lutte contre la rétention hydrosodée par régime sans sel et éventuellement diurétique. Lutte contre l'hypertension.

### **4.2 Traitement anti-infectieux**

Lorsqu'une infection causale a été diagnostiquée, celle-ci doit être traitée (évacuation du foyer dentaire par exemple). Un traitement antibiotique de 10 jours est suffisant dans la glomérulonéphrite aiguë post-streptococcique (Pénicilline orale).

**4.3 Le traitement des autres formes étiologiques** du syndrome néphritique reste encore hypothétique : il fait appel aux immunosuppresseurs, avec corticoïdes et aux échanges plasmatiques.

## Syndromes néphrotiques de l'enfant

### 1 Introduction

Les syndromes néphrotiques constituent un groupement de signes et de symptômes qui expriment toujours une maladie des glomérules rénaux mais dont la nature et la cause sont variables.

La définition est essentiellement biologique :

- protéinurie importante  $> 50 \text{ mg/kg/j}$  ou  $40 \text{ mg/m}^2/\text{h}$
- hypoprotéinémie  $< 60 \text{ g/l}$
- hypoalbuminémie  $< 30 \text{ g/l}$

### 2 Physiopathologie

La fuite massive des protéines dans les urines entraîne une hypoprotéinémie qui aura pour conséquences :

- une diminution de la pression oncotique du plasma responsable d'une hypovolémie, des oedèmes et d'un hyperaldostéronisme secondaire,
- une augmentation de la synthèse hépatique des protéines et des lipoprotéines,
- et dans les formes prolongées, des complications de la fuite protéique et des substances liées à ces protéines (dénutrition, sensibilité aux infections, anémie,...)

### 3 Etude symptomatique

#### 3.1 Les éléments du syndrome néphrotique

##### 3.1.1 Les éléments cliniques

Le début est le plus souvent brusque avec :

- *Symptomes oedémateux*

- des oedèmes périphériques
- possibilités d'épanchement pleural, ascite, hydrocèle rentrant dans le cadre d'un anasarque.
- parfois le syndrome oedémateux est absent et la découverte se fait lors d'un examen systématique.

- *Tension artérielle*

- Le plus souvent normale, voire abaissée, en rapport avec une hypovolémie importante. Parfois HTA.

##### 3.1.2 Les éléments biologiques

###### 3.1.2.1 Protéinurie

Est quantitativement importante, obligatoirement supérieure à  $50 \text{ mg/kg/24h}$ . Elle peut atteindre des taux très élevés de l'ordre de 10 ou même  $20 \text{ g/24H}$ . ou  $40 \text{ mg/m}^2/\text{h}$ . L'immuno-électrophorèse montre que cette protéinurie est faite surtout d'albumine et de sidérophylène.

- si ces deux éléments sont seuls présents, la protéinurie est dite "sélective".
- si ces deux éléments sont associés à des globulines de poids moléculaire plus élevé, la

protéinurie est dite "non sélective" et fait craindre des lésions d'hyalinose segmentaire et focale.

### 3.1.2.2 Hématurie

Il existe une hématurie microscopique dans 15 à 20% des cas. L'hématurie macroscopique est très rare, elle fait craindre une thrombose des veines rénales.

### 3.1.2.3 Syndrome humoral

La protéinurie massive entraîne :

- une hypoprotidémie <50g/l
- une hypoalbuminémie <30g/l
- à l'électrophorèse des protéides :

- hypogammaglobulinémie
- hypo ou alfa globulinémie

- augmentation du taux de cholestérol (VLDL, LDL et HDL) et des triglycérides, parfois de façon considérable.

### 3.1.2.4 Troubles ioniques

- natrémie normale ou diminuée :

- du fait de l'hyperlipidémie.
- du fait de l'inflation hydrique avec hémodilution

- calcium ionisé normal mais calcium total abaissé.

### 3.1.2.5 Fonction rénale

Le plus souvent normale, sauf en cas d'hypovolémie majeure où il y a **possibilité d'insuffisance rénale fonctionnelle**.

### 3.1.2.6 Facteurs de coagulation

- diminution des facteurs IX, XII et d'antithrombine III
- augmentation des facteurs, V, VII, VIII, von Willebrand, X et du fibrinogène
- baisse des protéines C et S.

## 3.1.3 Classification du syndrome néphrotique

- **La néphrose lipidique ou syndrome néphrotique pur et primitif** se définit par : absence d'hématurie, absence d'hypertension artérielle et absence d'insuffisance rénale (sauf insuffisance rénale fonctionnelle transitoire). La protéinurie est sélective.

- **Le syndrome néphrotique est impur** si l'un ou plusieurs des éléments ci-dessus sont présents (hématurie, hypertension et insuffisance rénale). La protéinurie est alors non sélective.

## 3.2 Les complications

### 3.2.1 Les thromboses vasculaires

- Thromboses veineuses :

- veines périphériques
- veines rénales.

- Parfois thromboses artérielles favorisées par la diminution de l'antithrombine III, l'hyperfibrinémie et le déficit fonctionnel en protéines C et S.

### 3.2.2 Collapsus cardio-vasculaire

Au début des poussées, surtout lorsque la débacle urinaire obtenue par les diurétiques est trop brutale. Ce collapsus est dû à une hypovolémie très marquée.

### 3.2.3 Infections

- cutanées, pulmonaires, péritonéales, ,
- le plus souvent à pneumocoque et à streptocoque mais aussi virales :
  - favorisées par l'hypo-gamma-globulinémie.
  - aggravées par les traitements immunosuppresseurs.

### 3.2.4 Syndromes carenciels

- dénutrition par fuite protidique,
- ostéoporose,
- anémie hypochrome (fuite de la transferrine),
- hypothyroïdie par fuite des protéines porteuses,

Ces complications apparaissent lors de syndromes néphrotiques importants ou prolongés et entraînent une cassure de la croissance staturopondérale

## 4 Formes anatomo-cliniques et étiologiques

### 4.1 La néphrose lipoïdique

Environ 80 % des cas de néphrose.

#### 4.1.1 Histopathologie

3 aspects possibles :

- "**lésions glomérulaires minimales**" le plus souvent (plus de 3/4 des cas) :

- en microscope optique, glomérules pratiquement normaux,
- en microscope électronique, fusion des pieds de podocytes,
- en immunofluorescence, pas de dépôts ou petits dépôts d'IgM.

- lésions de "**hyalinose segmentaire et focale**"

- dépôts d'aspect hyalin sous l'endothélium des parois capillaires, dans certaines anses seulement et dans certains glomérules seulement.
- l'immunofluorescence montre surtout des dépôts d'IgM et de complément.

- Plus rarement, **prolifération mésangiale modérée isolée**.

#### 4.1.2 Circonstances étiologiques

- Tous les âges sont concernés, mais le pic de fréquence se situe entre 3 et 8 ans.
- Le garçon est atteint plus fréquemment que la fille.
- Il y a souvent un petit syndrome infectieux dans les jours qui précèdent l'écllosion de la maladie.
- Il existe parfois un contexte allergique, personnel ou familial.

#### 4.1.3 Symptomatologie

- La symptomatologie clinique est souvent évidente, avec un syndrome oedémateux rapidement constitué.
- La symptomatologie biologique est complète et pure.

#### 4.1.4 Evolution et traitement

L'évolution dépend de la réponse à la corticothérapie. Dans la majorité des cas, la néphrose est **corticosensible**. Les rechutes sont fréquentes soit après arrêt du traitement soit lors de la baisse de la corticothérapie, définissant l'état de **corticodépendance**.

L'évolution à long terme est favorable, même si la maladie évolue sur de nombreuses années, de 5 à 15 ans.

Tant que la néphrose est corticosensible, le risque d'insuffisance rénale est presque nul. (10% des enfants sont corticorésistants)

##### 4.1.4.1 Traitement symptomatique

- Régime alimentaire riche en protéines, bien que ceci n'ait pas d'effet sur le niveau d'albuminémie.
- Restriction sodée pour limiter l'importance des oedèmes
- Diurétiques si oedèmes importants : avec prudence !, et associés à une perfusion d'albumine pour une meilleure efficacité (mettre directement le Furosemide dans le flacon d'albumine).
- Pas d'immobilisation et anticoagulant si hypoalbuminémie inférieure à 16g/l.
- Supplémentation en vitamine D et en calcium.
- Antibiothérapie si infection.

##### 4.1.4.2 Traitement étiologique

- **Corticothérapie** : C'est le traitement de fond. Il doit être institué d'emblée.

- PREDNISONNE 60 mg/m<sup>2</sup>/j sans dépasser 80 mg/j pendant 4 semaines ; en une à deux prises.  
Si le syndrome néphrotique est inchangé ou qu'il persiste une protéinurie :
- METHYLPREDNISOLONE 1g/1.73m<sup>2</sup> : 3 injections à 48h d'intervalle.  
Le patient est dit corticosensible si la protéinurie disparaît. Puis :
- PREDNISONNE 60mg/m<sup>2</sup> un jour sur deux pendant 8 semaines puis diminution de 15mg/m<sup>2</sup> tous les quinze jours. (Traitement de 4 mois et demi).
  - Si rechutes espacées ( 75% des cas), reprise du même schéma.
  - Si corticodépendance, le traitement de base est la corticothérapie discontinuée prolongée.
- LEVAMISOLE : L'adjonction de LEVAMISOLE peut espacer la fréquence des rechutes.  
Effet secondaire: neutropénie.

##### - Immunosuppresseurs

- Si la maladie n'est pas maîtrisée par la corticothérapie.
- S'il existe plus de deux rechutes par an, on peut utiliser :
  - **Les agents alkylants par exemple l'ENDOXAN (cyclophosphamide)**. On observe des effets secondaires, principalement une insuffisance gonadique.
  - **Ciclosporine** A.  
Elle diminue la production de lymphokine par les lymphocytes T activés. Elle permet le maintien en rémission de 75 à 90% des cas. Mais en général les enfants corticodépendants sont également ciclosporine-dépendants.

#### **4.1.5 Ponction biopsie rénale**

- Si syndrome néphrotique avant l'âge d'un an.
- Si syndrome néphrotique corticorésistant.
- Si mise sous immuno suppresseurs.

#### **4.2 Autres syndromes néphrotiques**

Ces syndromes néphrotiques justifient la biopsie rénale.

##### **4.2.1 Les syndromes néphrotiques secondaires**

Il s'agit de syndromes néphrotiques impurs avec hématurie, HTA et insuffisance rénale. On les rencontre au cours de maladies générales (LEAD), glomérulonéphrites chroniques, purpura rhumatoïde,...

##### **4.2.2 Les syndromes néphrotiques infantiles**

Un syndrome néphrotique est dit infantile s'il apparaît dans la première année de vie, et il est qualifié de congénital s'il est présent dès la naissance. Dans ces deux cas, il y a fréquemment une notion familiale et le pronostic est nettement péjoratif car la corticorésistance est fréquente.

La plupart des formes histologiques peuvent être rencontrées, mais il y a deux maladies précises et particulières à cet âge de la vie.

###### **4.2.2.1 Le syndrome néphrotique congénital de type finlandais**

C'est une maladie familiale récessive autosomique, surtout fréquente en Finlande mais non exceptionnelle ailleurs.

Elle comporte des lésions presque spécifiques de dilatation microkystique des tubules rénaux. Elle existe dès la vie foetale et s'exprime, dès ce moment, par une hypotrophie foetale, une hypertrophie du placenta et une augmentation de l'alpha- foeto-protéine du liquide amniotique.

L'évolution est très grave et insensible à tous les traitements. Elle évolue vers l'insuffisance rénale avant 3 ans, ayant préalablement déterminé des troubles digestifs importants, des complications nutritionnelles et infectieuses.

C'est une indication de transplantation rénale.

###### **4.2.2.2 La sclérose mésangiale diffuse**

- Caractère familial possible mais non constant.
- Lésions de rétraction fibreuse du flocculus sans prolifération cellulaire.
- Débute soit dès la naissance, soit au cours des premiers mois.
- Note hématurique fréquente.
- Evolution grave vers l'insuffisance rénale terminale avant 3 ans.

## **Syndrome hémolytique et urémique**

Le syndrome hémolytique et urémique est la cause la plus fréquente des insuffisances rénales aiguës du nourrisson.

Après des prodromes, le plus souvent à type de diarrhée et vomissements, s'installe brutalement le tableau clinique caractéristique associant : une anémie hémolytique avec hématies fragmentées (schizocytes), une insuffisance rénale aiguë d'intensité variable, une thrombopénie.

Des convulsions et une hypertension artérielle se rencontrent dans 20 % des cas et aggravent le pronostic.

L'évolution se fait dans 3/4 des cas vers la guérison. Des séquelles sont possibles, surtout chez le grand enfant, à type d'hypertension artérielle résiduelle et d'insuffisance rénale chronique.

Le traitement reste essentiellement symptomatique : lutte précoce contre l'insuffisance rénale aiguë (dialyse péritonéale aiguë) ; correction de l'hypertension artérielle ; correction prudente de l'anémie.

## **Evaluation of proteinuria in children**

**INTRODUCTION** — Proteinuria as a marker of renal disease has been well established. The dilemma that faces the primary care physician is to differentiate the child with transient or other benign forms of proteinuria from the child with proteinuria from renal disease.

An overview of the evaluation of proteinuria in children will be presented here. Some related issues, including the mechanisms of proteinuria, are discussed in more detail elsewhere. (See "Evaluation of isolated proteinuria in adults").

### **PATHOPHYSIOLOGY AND CLASSIFICATION**

**Normal protein excretion** — Urinary protein excretion in the normal child is less than 100 mg/m<sup>2</sup> per day or a total of 150 mg per day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m<sup>2</sup>, because of reduced reabsorption of filtered proteins.

Approximately one-half of normal protein excretion consists of proteins secreted by tubular epithelium, mostly Tamm-Horsfall protein (uromodulin). The other half consists of plasma proteins including albumin, which accounts for approximately 40 percent of the total urinary protein, and low molecular weight proteins, such as beta-2 microglobulin and amino acids.

The normally low rate of urinary protein excretion is due to two factors:

Restriction of the filtration of proteins across the glomerular capillary wall

Reabsorption of freely filtered low molecular weight (LMW) proteins (less than 25,000 Daltons) by the proximal tubule

**Abnormal protein excretion** — Urinary protein excretion in excess of 100 mg/m<sup>2</sup> per day or 4 mg/m<sup>2</sup> per hour is considered abnormal in children. Nephrotic range proteinuria (heavy proteinuria) is defined as  $\geq 1000$  mg/m<sup>2</sup> per day or 40 mg/m<sup>2</sup> per hour.

There are three main mechanisms of increased protein excretion: glomerular, tubular, and overflow proteinuria. (See "Evaluation of isolated proteinuria in adults")

**Glomerular proteinuria** — Glomerular proteinuria is due to increased filtration of macromolecules (particularly albumin) across the glomerular capillary wall. This may arise because of anatomical or functional lesions.

Glomerular proteinurias are a common cause of proteinuria in children. They may result from glomerular disease (most often minimal change disease) or from nonpathologic conditions such as fever, intensive exercise, and orthostatic (or postural) proteinuria, in which protein excretion is increased only in the upright position.

**Tubular proteinuria** — Tubular proteinuria, which is less frequent, results from increased excretion of low molecular weight proteins such as beta-2-microglobulin, alpha-1-microglobulin, and retinol-binding protein. These molecules are normally filtered across the glomerulus and then largely reabsorbed in the proximal tubule. Interference with proximal tubular reabsorption, due to a variety of tubulointerstitial diseases, can lead to increased excretion of these smaller proteins.

Tubular proteinuria often is associated with other defects in proximal tubular function, including glycosuria, proximal renal tubular acidosis with bicarbonate wasting, and phosphaturia. In Fanconi's syndrome, all four of these proximal tubular defects occur.

As will be described below, only albumin is detected by the urine dipstick, while tubular proteinuria is not detected by screening dipstick urinalysis.

Overflow proteinuria — Overflow proteinuria results from increased excretion of low molecular weight proteins due to marked overproduction of a particular protein to a level that exceeds tubular reabsorptive capacity. Overflow proteinuria is not observed in children; it is primarily observed in adults with a plasma cell dyscrasia (eg, multiple myeloma) who overproduce immunoglobulin light chains.

As with tubular proteinuria, overflow proteinuria with low molecular proteins will not be detected by screening dipstick urinalysis.

MEASUREMENT OF URINARY PROTEIN — There are several tests available for the measurement of urinary protein. The most common test, the urine dipstick, and other tests such as the sulfosalicylic acid test that detects all proteins, measure only the urine protein concentration and cannot be used to quantify protein excretion. A dilute urine, for example, will underestimate the degree of proteinuria, while a highly concentrated urine may have a protein concentration greater than 100 mg/dL but not be indicative of increased protein excretion.

Urine dipstick — The urinary dipstick measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample.

Negative

Trace — between 15 and 30 mg/dL

1+ — between 30 and 100 mg/dL

2+ — between 100 and 300 mg/dL

3+ — between 300 and 1000 mg/dL

4+ — >1000 mg/dL

Dipstick testing will not detect low molecular weight proteins. False-positive results may be obtained in samples that are very alkaline or contaminated by antiseptic agents (such as chlorhexidine or benzalkonium chloride) or iodinated radiocontrast agents [1]. Thus, the urine should not be tested for protein with the dipstick for at least 24 hours after a contrast study.

Sulfosalicylic acid test — In contrast to the urine dipstick, sulfosalicylic acid (SSA) detects all proteins in the urine including the low molecular weight proteins that are not detected by the dipstick [2]. The SSA test is performed by mixing one part urine supernatant (eg, 2.5 mL) with three parts 3 percent sulfosalicylic acid, followed by assessment of the degree of turbidity. This test is infrequently necessary in children.

Quantitative assessment — Children with persistent dipstick-positive proteinuria must undergo a quantitative measurement of protein excretion, most commonly on a timed 24-hour urine collection. In children (except neonates), levels of urinary protein excretion higher than 100 mg/m<sup>2</sup> per day (or 4 mg/m<sup>2</sup> per hour) are abnormal. Proteinuria of greater than 40 mg/m<sup>2</sup> per hour is considered heavy or in the nephrotic range.

In very young children, it may be difficult to obtain accurately timed urine collections. An alternative method of quantitative assessment is measurement of the total protein/creatinine ratio (mg/mg) on a spot urine sample, preferably the first morning specimen (show calculator). The normal value for this ratio is <0.2 mg protein/mg creatinine (<20 mg protein/mmol creatinine) in children greater than two years of age and <0.5 mg protein/mg creatinine (<50 mg protein/mmol creatinine) in infants and toddlers from 6 to 24 months [3,4].

Qualitative assessment — A qualitative analysis of urinary proteins may be necessary to differentiate glomerular from tubular proteinuria. A selective measurement, by immunonephelometry of marker proteins that include beta-2 microglobulin, alpha-1-microglobulin, lysozyme and retinol-binding protein can distinguish glomerular from tubular proteinuria. In tubular proteinuria, these levels will be 10 to 100 times higher than normal.

APPROACH TO THE CHILD WITH PROTEINURIA — A positive dipstick for protein on a random urinalysis is common in children. General screening of normal school-age children and adolescents with a urine dipstick will be positive (defined as  $\geq 1+$ ) in 5 to 10 percent. However, only 0.1 percent of children have persistent proteinuria [5]. It is this small subset of children who are at the highest risk for renal disease.

Proteinuria in children presents in three ways: transient or intermittent; orthostatic; and persistent (show table 1). Transient and orthostatic proteinuria are benign conditions that require no further evaluation:

Transient proteinuria is the most common cause. It can be induced by a variety of factors including fever, exercise, stress, seizures, and hypovolemia.

Orthostatic proteinuria is defined as increased protein excretion in the upright position which returns to normal when the patient is recumbent. Long-term studies have documented the benign nature of this condition, with recorded normal renal function up to 50 years later [6]. As will be described below, the diagnosis is established by a negative dipstick on the first morning voided specimen. (See "Orthostatic or postural proteinuria").

Persistent proteinuria should be more fully evaluated for underlying renal disease.

History and physical examination — The evaluation begins with a thorough history and physical examination to determine the type of proteinuria. A urine sample collected during a febrile illness or after intensive physical exercise or a seizure suggests the possible presence of transient proteinuria. Other findings suggest underlying renal disease and persistent proteinuria; these include a change in urine volume or color, evidence of edema or increased blood pressure, recent streptococcal infection, a positive family history for renal disease, and hearing loss, which is most suggestive of Alport disease. (See "Genetics, pathogenesis, and pathology of hereditary nephritis (Alport syndrome)").

Asymptomatic child — The diagnostic evaluation of the child with dipstick-positive proteinuria depends in part upon the presence or absence of symptoms. The following approach is consistent with the recommendations of the 2000 Pediatric Nephrology panel established at the National Kidney Foundation conference on Proteinuria, Albuminuria, Risk, Assessment, Detection and Elimination (PARADE) (show algorithm 1) [2].

In the asymptomatic child with an incidentally discovered positive dipstick for proteinuria, the first step is to repeat the test since, as mentioned above, the great majority of such episodes are transient and do not reflect any renal disease [5]. The simplest approach is to measure the Pr/Cr ratio on a first morning void obtained at home, and to send for urinalysis a second specimen obtained in the office. The parents should be instructed to have the child void before going to bed and to remain recumbent until the first morning sample is obtained. (See "Measurement of urinary protein" above).

The following findings may be obtained:

A normal Pr/Cr ratio on the first morning void and a normal urinalysis indicate transient proteinuria.

A normal Pr/Cr ratio on the first morning void and dipstick-positive proteinuria on the second upright specimen indicate orthostatic proteinuria. (See "Orthostatic or postural proteinuria").

If the proteinuria is transient or orthostatic, the patient should have a repeat urinalysis on a first morning void in one year.

An elevated Pr/Cr ratio on the first morning void and a positive dipstick on the second specimen indicate persistent proteinuria that requires further evaluation, beginning with examination of the urine sediment, looking for other signs of glomerular and/or parenchymal disease such as hematuria, red cell casts, pyuria, and/or lipiduria. Red cell casts are pathognomonic for the presence of glomerulonephritis. Based upon the particular findings, certain patterns on the urinalysis are suggestive of glomerulonephritis, nephrotic syndrome, or other renal parenchymal disorders. (See "Differential diagnosis of glomerular disease").

The urinalysis may also be suggestive of a urinary tract infection with pyuria, bacteriuria, and positive nitrites or leukocyte esterase along with mild proteinuria. Proteinuria in such children typically resolves with successful treatment of the infection. If the proteinuria persists after eradication of the infection, further work-up is indicated.

Among children with persistent proteinuria, a complete history and physical examination should be reviewed, including measurement of the blood pressure. Initial laboratory evaluation includes renal function tests (blood urea nitrogen and creatinine), serum electrolytes, cholesterol, albumin, and total protein. Other tests such as renal ultrasound, serum complement levels (C3 and C4), ANA, streptozyme testing, hepatitis B and C serology, and HIV testing should be considered if appropriate. A voiding cystourethrogram should be considered if there is an abnormal ultrasound with scarring or a history of febrile urinary tract infections. (See "Presentation, diagnosis, and clinical course of vesicoureteral reflux").

If this initial evaluation is normal, the urine dipstick should be repeated on at least two additional specimens. If these subsequent tests are negative for protein, the diagnosis is transient proteinuria.

If the proteinuria persists or if any of the studies are abnormal, the patient should be referred to a pediatric nephrologist. At this point, urinary protein excretion should be quantified by a timed collection, if obtainable.

Indications for renal biopsy — The role of renal biopsy in a child with isolated asymptomatic persistent proteinuria is controversial [7]. Many nephrologists recommend close monitoring for those children with urinary protein excretion below 500 mg/m<sup>2</sup> per day before considering a biopsy [8]. Monitoring should include assessment of blood pressure, protein excretion, and renal function. If any of these parameters shows evidence of progressive disease, a renal biopsy should be performed to establish a diagnosis.

There are limited data on the results of renal biopsy in such children.

In a retrospective review of 53 Japanese children with persistent isolated proteinuria, a significant glomerular disease was present in 25 (47 percent): 15 had focal segmental glomerulosclerosis (FSGS); four had IgA nephropathy, and three each had membranous nephropathy and diffuse mesangial proliferative glomerulonephritis without IgA deposition [8].

In a report of 461 Korean children with an abnormal urinalysis detected by school screening, only nine patients had isolated persistent proteinuria with protein excretion  $\geq 2$  g in a 24-hour collection [9]. Renal biopsy demonstrated changes consistent with minimal change nephrotic syndrome in seven patients, and one case each of mesangial proliferative glomerulonephritis and membranous glomerulopathy.

Symptomatic child — Clinical manifestations in the symptomatic child with proteinuria may be general and nonspecific (eg, fever, malaise, weight loss), non-urinary specific (rash, purpura, arthritis), or urinary specific (eg, edema, hypertension, renal insufficiency). The underlying disorder may be primarily renal in origin or

secondary to a systemic process. Diagnostic categories include infections, rheumatologic and immunologic disorders, and primary and secondary glomerular and interstitial diseases of the kidney.

The diagnosis may be evident and straightforward from the history and physical examination, or it may be more complicated, with a need for early referral to a nephrologist. The practitioner must ensure that children with significant disease are clearly identified.

Children with heavy proteinuria and periorbital or peripheral edema must be evaluated promptly for nephrotic syndrome. The major manifestations of nephrotic syndrome are heavy proteinuria (protein excretion >1000 mg/m<sup>2</sup> per day or spot urine Pr/Cr ratio >1.0), edema, serum albumin <2.5 g/dL, and hypercholesterolemia. Almost all such children have idiopathic nephrotic syndrome, and management decisions should be made in consultation with a pediatric nephrologist. (See "Treatment of idiopathic nephrotic syndrome in children")

Non-nephrotic children with persistent proteinuria who present with hypertension, an abnormal urinalysis, or an elevated plasma creatinine concentration should be referred to a pediatric nephrologist for further evaluation and possible renal biopsy. (See "Differential diagnosis of glomerular disease").

In patients with an abnormal ultrasound or history of febrile urinary tract infections, a voiding cystourethrogram should be considered if there is an abnormal ultrasound with scarring or a history of febrile urinary tract infections. (See "Presentation, diagnosis, and clinical course of vesicoureteral reflux").

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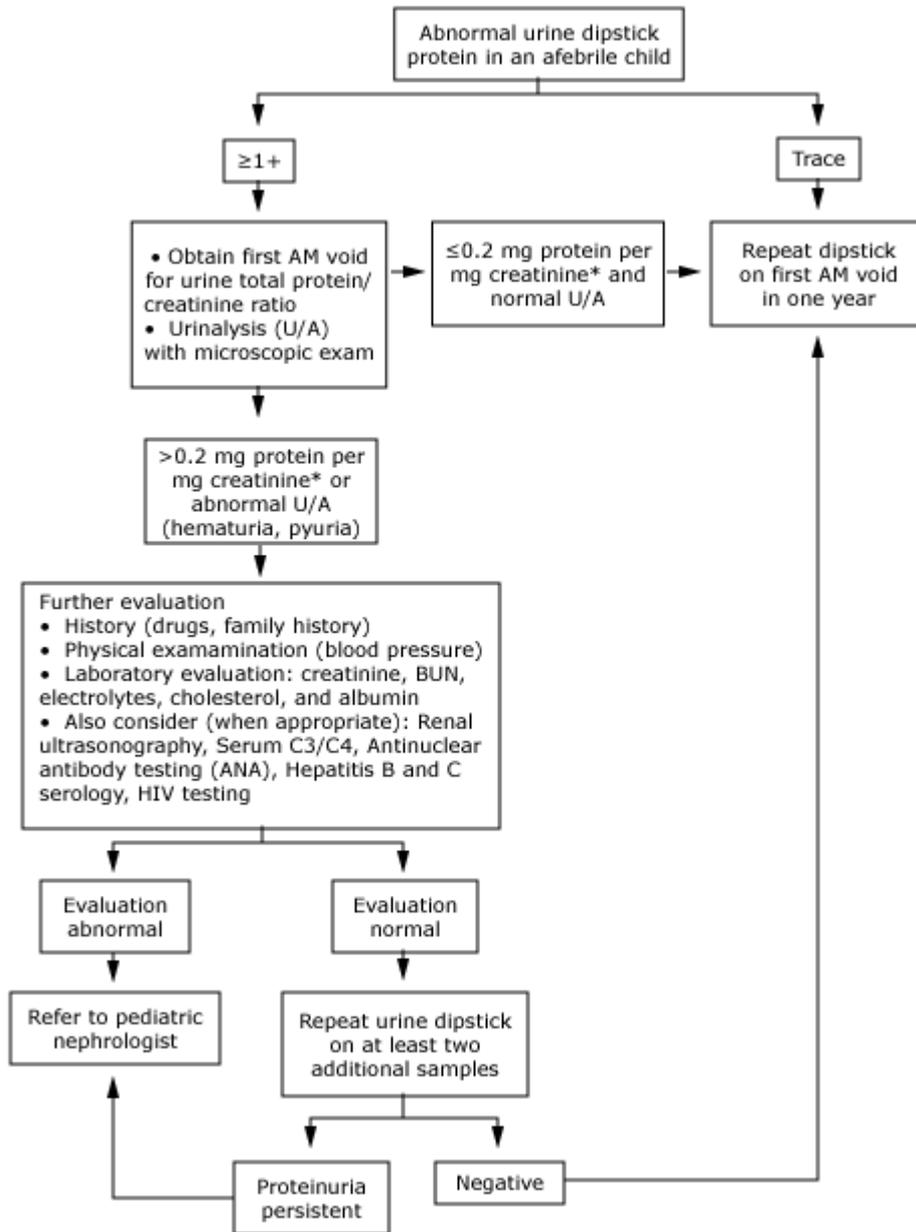
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GRAPHICS

Causes of proteinuria in children

Transient proteinuria
Associated with fever, exercise, seizures and/or hypovolemia
Orthostatic proteinuria
Persistent proteinuria
Glomerular proteinuria
Primary
Minimal change disease
Congenital nephrotic syndrome
"Finnish-type"
Mesangial sclerosis
Focal segmental glomerular sclerosis
IgA nephropathy (Berger's disease)
Membranoproliferative glomerulonephritis
Membranous nephropathy
Alport syndrome
Secondary
Acute post-streptococcal glomerulonephritis
Diabetes mellitus
Systemic lupus erythematosus
Henoch-Schönlein purpura
Tubular proteinuria
Primary
Cystinosis
Dent's syndrome
Wilson's disease
Lowe's syndrome
Polycystic kidney disease
Mitochondrial disorders
Secondary
Heavy metal poisoning
Acute tubular necrosis
Tubulointerstitial nephritis
Secondary to obstructive uropathy

**Algorithm for evaluation of asymptomatic proteinuria in children**



\* For children between 6 and 24 months, the threshold value is 0.5 mg protein to mg creatinine.

Adapted with permission from: Hogg, RJ, Portman, RJ, Milliner, D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). *Pediatrics* 2000; 105:1242.

## **Congenital and infantile nephrotic syndrome**

**INTRODUCTION** — The term congenital nephrotic syndrome refers to disease, which is present at birth or within the three first months of life. Later onset, between three months and one year of age, is called infantile nephrotic syndrome. Most of these children have a genetic basis for the renal disease and a poor outcome. The precise diagnosis of the glomerular lesion is based on clinical, laboratory and histological criteria.

The causes of congenital and infantile nephrotic syndrome will be discussed here.

**ETIOLOGY** — In a review of 89 Central European and Turkish children (from 80 families) who presented with nephrotic syndrome in the first year of life, two-thirds overall and as many as 85 percent of cases that occurred during the first three months of life could be explained by mutations in the following four genes [1] NPHS1, which encodes nephrin (a key component of the podocyte slit diaphragm) and is responsible for the Finnish-type congenital nephrotic syndrome. (See "CNS of Finnish type" below) NPHS2, which encodes podocin (a protein that interacts with nephrin at the slit diaphragm) and is responsible for familial focal glomerulosclerosis. (See "CNS and NPHS2 mutations" below). WT1, which encodes the transcription tumor suppressor (a protein involved in kidney and gonad development) and is responsible for the Denys-Drash syndrome. (See "Diffuse mesangial sclerosis with Drash syndrome" below). LAMB2, which encodes laminin beta 2 (a component of the glomerular basement membrane) and is responsible for the Pierson syndrome. (See "Pierson syndrome" below).

NPHS2 and NPHS1 were the most common, accounting for approximately 95 percent of cases [1] . None of 28 patients with a mutation who were treated with glucocorticoids responded.

In addition to the above defects, mutations in the PLCE1 gene, which encodes phospholipase C epsilon, are responsible for the early-onset of isolated diffuse mesangial sclerosis [2] . (See "Diffuse mesangial sclerosis" below).

Nongenetic causes are often secondary and possibly curable disorders. They include infections, such as congenital nephrotic syndrome induced by syphilis or toxoplasmosis (show table 1), and toxins such as mercury exposure. (See "Infectious causes" below and see "Other causes" below).

**CNS OF FINNISH TYPE** — CNF is most frequent in Finland, with initial studies suggesting an incidence of 1.2 per 10,000 births [3,4] . With prenatal screening, the incidence has fallen to 0.9 per 10,000 births [5] . CNF has also been described in various ethnic groups throughout the world [6-8] .

CNF is inherited as an autosomal recessive trait, with both sexes being involved equally. There are no manifestations of the disease in heterozygous individuals.

**Pathology** — Light microscopic studies of renal biopsy specimens obtained early in the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli [6,9] . No immune deposits are detected by immunofluorescence studies. Over time, there is an increase in mesangial matrix accompanied by progressive glomerulosclerosis.

Tubulointerstitial changes are also prominent in CNF. Irregular microcystic dilatation of proximal tubules is the most striking feature; however, this change is not specific and is not seen in all patients [10]. Later in the course, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli.

**Pathogenesis** — It had been proposed that proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter. The abnormal gene was subsequently localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [11-13].

The defective gene in CNF has been cloned and is named NPHS1 [14,15]. The gene encodes for a transmembrane protein, named nephrin, which is a member of the immunoglobulin family of cell adhesion molecules and is phosphorylated by Src family kinases [16]. Nephrin is specifically located at the slit diaphragm of the glomerular podocytes; this could explain the absence of slit diaphragms and foot processes in patients with CNF who have a mutant nephrin protein [17,18] and in mice with nephrin gene disruption [19].

In the original report, four different mutations in this gene were found to segregate with the disorder in affected Finnish families [14]. However, the two most common mutations, Fin-major (nt121delCT) and Fin-minor (R1109X), account for nearly 90 percent of all affected Finnish patients and is associated with severe early-onset of disease [14,20,21].

In another study, 32 novel mutations in the nephrin gene were discovered in patients elsewhere in Europe and North America, but no abnormalities were found in seven affected individuals (including the 5' flanking region) [12]. These patients may have mutations elsewhere in the promoter or in intron areas, or in a gene encoding another protein that interacts with nephrin [22]. (See "Pathogenesis and diagnosis of focal glomerulosclerosis").

A case report of two siblings with a milder form of CNF (ie, alternating periods of proteinuria and remission) showed that the two children were compound heterozygotes for two novel, nonconserved missense mutations [23]. Additional studies from renal biopsy samples demonstrated expression of nephrin but with impaired function.

**Clinical features** — Most infants with the CNF are born prematurely (35 to 38 weeks), with a low birth weight for gestational age. The placenta is enlarged, being more than 25 percent of the total birth weight. Fetal distress is common and the cranial sutures are widely separated due to delayed ossification. Infants often have a small nose and low ears. Flexion deformities of the hips, knees, and elbows are thought to be secondary to the large placenta.

Edema is present at birth or appears during the first week of life in one-half of cases. Severe nephrotic syndrome with marked ascites is always present by three months. The proteinuria is highly selective early in the course of the disease and hematuria is uncommon, reflecting the lack of inflammation in the glomeruli. The urinary protein losses are accompanied by profound hypoalbuminemia and severe hypogammaglobulinemia due in part to loss of selectivity as the disease progresses. As a result of these changes, nutritional status and statural growth are poor, and affected infants are highly susceptible to bacterial infections (peritonitis, respiratory infections) and to thromboembolic complications due to the severity

of the nephrotic syndrome. Hypothyroidism because of urinary losses of thyroxine-binding proteins is also common. (See "Renal vein thrombosis and hypercoagulability in nephrotic syndrome").

The blood urea nitrogen and creatinine concentrations are initially normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation.

End-stage renal failure usually occurs between three and eight years of age. Several studies, however, have reported that some NPHS1 mutations are associated with end-stage renal failure occurring after the age of 20 years [20,24,25] . Prolonged survival is possible with aggressive supportive treatment, including dialysis and renal transplantation.

Treatment — The nephrotic syndrome in CNF is always resistant to glucocorticoids and immunosuppressive drugs, since this is not an immunologic disease. Furthermore these drugs may be harmful due to the already high susceptibility to infection. A retrospective study of 21 infants with CNF, for example, found that 63 verified and 62 suspected septic episodes occurred over a mean follow-up period of one year [26] .

Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin and thyroxine substitution, and prevention of infections and thrombotic complications. The diet is provided by tube feeding or by parenteral alimentation.

However, the rate of intercurrent complications remains high and growth and development are usually retarded. As a result, some patients may require bilateral nephrectomy to prevent continued massive protein losses before the development of renal failure.

A possible medical alternative to nephrectomy has been described in three children. The combination of an angiotensin converting enzyme inhibitor and indomethacin therapy, both of which should lower intraglomerular pressure, led to a marked fall in protein excretion and striking improvement in nutritional status and growth [27,28] .

If nephrectomy is performed, dialysis is provided until the patient reaches a weight of 8 to 9 kg. At this stage, renal transplantation can be considered [29,30] .

Nephrotic syndrome can develop in the transplanted kidney. In one case series of 65 patients who received 77 kidney transplants, 23 episodes of recurrent nephrotic syndrome occurred in 13 patients with 19 grafts [31] . All 13 affected patients had the Fin-major/Fin-major genotype, which is associated with the absence of nephrin. Eight (of 11 patients tested) had circulating anti-nephrin antibodies. Recurrence of disease is associated with graft loss. In this series, the addition of plasmapheresis to oral cyclophosphamide and increased doses of methylprednisolone appeared to improve the remission and graft survival rates of patients with recurrent disease.

Antenatal diagnosis — The CNF becomes manifest during early fetal life, beginning at the gestation age of 15 to 16 weeks. The initial symptom is fetal proteinuria, which leads to a more than 10-fold increase in the amniotic fluid alpha-fetoprotein (AFP) concentration. A parallel, but less important increase in the maternal plasma AFP level is observed. These

changes are not specific, but they may permit the antenatal diagnosis of CNF in high risk families in which termination of the pregnancy might be considered [32] .

However, false positive results do occur, often leading to abortion of healthy fetuses. In one study of 21 pregnancies that had been terminated because of increased AFP levels in amniotic fluid, only 12 fetuses were homozygous for nephrin gene mutations as determined by DNA sequencing [33] . The remaining nine were heterozygous carriers and would therefore not have developed CNF. The kidneys of both groups had a similar reduction in podocyte foot processes and slit pores.

Genetic linkage and haplotype analyses may diminish the risk of false positive results in informative families [34] . The four major haplotypes, which cover 90 percent of the CNF alleles in Finland, have been identified, resulting in a test with up to 95 percent accuracy. Commercial tests are also available to detect NPHS1 mutations.

**CNS AND NPHS2 MUTATIONS** — NPHS2 encodes an integral membrane protein, podocin, which is found exclusively in glomerular podocytes and is the causative gene for an autosomal recessive form of familial FGS. A few patients with the typical clinical picture of congenital nephrotic syndrome were found to lack NPHS1 mutations: One study found homozygous NPHS2 mutations in two of five such patients [24] . These findings were confirmed in a second report that described 11 patients with two recessive NPHS2 mutations who presented initially with congenital nephrotic syndrome [25] . Two additional cases with similar findings in terms of mutations in NPHS2, but not NPHS1, were also reported in a study of 13 unrelated patients from Japan [35] .

Some patients also have both NPHS1 and NPHS2 mutations, resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other) [24,25,36] . These findings demonstrate the genetic heterogeneity of congenital nephrotic syndrome and the absence of clear genotype/phenotype correlations.

Although affected individuals typically present in early childhood, some have milder disease and present in adolescence or young adulthood. Issues related to treatment of FGS associated with NPHS2 mutations are discussed separately. (See "Pathogenesis and diagnosis of focal glomerulosclerosis", section on NPHS2 gene, and see "Treatment of idiopathic nephrotic syndrome in children", section on NPHS2 mutations).

**DIFFUSE MESANGIAL SCLEROSIS** — Diffuse mesangial sclerosis is a second hereditary cause of infantile nephrotic syndrome associated with glomerular injury and rapid progression to end-stage renal failure. The same glomerular lesions are observed in the Denys-Drash syndrome, which is characterized by the combination of nephropathy, male pseudohermaphroditism, and Wilms' tumor.

Diffuse mesangial sclerosis is seen exclusively in infancy [6,37-41] and appears to be transmitted in some families as an autosomal recessive trait [42] . The defective gene has not been identified.

**Pathology** — The glomerular lesions are characterized in the early stages by a fibrillar increase in mesangial matrix without mesangial cell proliferation [40-42] . The capillary walls are lined by hypertrophied podocytes. The fully developed lesion consists of the combination of thickening of the glomerular basement membranes and massive enlargement

of mesangial areas, leading to reduction of the capillary lumens. The mesangial sclerosis eventually contracts the glomerular tuft into a sclerotic mass within a dilated urinary space. There is usually a corticomedullary gradient of involvement, with the deepest glomeruli being less affected. Tubules are severely damaged, especially in the deeper cortex where they are markedly dilated and often contain hyaline casts.

Electron microscopy reveals hypertrophic mesangial cells surrounded by an abundant mesangial matrix, which often contains collagen fibrils. The podocytes are hypertrophied and contain many vacuoles. There is also irregular effacement of foot processes with focal detachment of the epithelial cell from the glomerular basement membrane.

Immunofluorescence shows mesangial deposits of IgM, C3, and C1q in the least affected glomeruli, while deposits of IgM and C3 outline the periphery of the sclerosed glomeruli. These immune deposits are probably nonspecific, occurring in areas of previous injury.

The same glomerular lesion is observed in the Denys-Drash syndrome. As a result, all patients with diffuse mesangial sclerosis should be screened for the Denys-Drash syndrome. This consists of karyotyping in phenotypic females, looking for male pseudohermaphroditism with a 46 XY genotype, and ultrasonography should be performed in all patients, looking for Wilms' tumor and abnormal gonadal development. Some investigators also suggest that an assessment for mutations in the Wilms' tumor predisposing gene, WT1, should be performed to help identify individuals at risk for the tumor [43,44] . As an example, among 10 patients presenting with isolated diffuse mesangial sclerosis, four had mutations in the WT1 gene [44] . (See "Diffuse mesangial sclerosis with Drash syndrome" below).

**Pathogenesis** — Abnormalities in the PLCE1 gene, which encodes phospholipase C epsilon, appear to cause isolated diffuse mesangial sclerosis. In one study of 12 children from 6 families with the disease, homozygous truncating gene mutations in PLCE1 were found in eight children [2] . By comparison, missense mutations found in two siblings were only associated with focal segmental changes.

Phospholipase C epsilon is a member of the phospholipase family of enzymes that catalyzes the hydrolysis of polyphosphoinositides resulting in generation of second messengers (eg, inositol-1,4,5-triphosphate), which are involved in cell growth and differentiation. A pathogenetic role for PLCE1 in glomerular development was supported by findings of disruption of the glomerular filtration barrier and edema in a PLCE1 knockout zebrafish model.

How a PLCE1 gene defect results in changes in the glomerular nephrotic syndrome is unknown. One possible explanation is that phospholipase C epsilon interacts with GTPase-activating protein, which is known to interact with the slit diaphragm protein, nephrin. Perturbations of this normal interaction would have a downstream effect including the subsequent interaction of GTPase-activating protein with nephrin.

**Clinical and laboratory features** — As opposed to the CNF, children with diffuse mesangial sclerosis appear normal at birth, with a normal birth weight and without placental enlargement. The nephrotic syndrome may be present at birth or even suspected in utero by the finding of an elevated plasma alpha-fetoprotein level in the mother or the discovery of large hyperechogenic kidneys [45] . More commonly, however, proteinuria with a bland

urine sediment develops postnatally, increasing progressively during the first or the second year of life. Various types of extrarenal signs have been reported in isolated patients including nystagmus, cataract, mental retardation, microcephaly, severe myopia, and muscular dystrophy.

All children progress to end-stage renal failure, frequently in association with hypertension. This usually occurs before age three, within a few months after the discovery of renal symptoms [41] .

Treatment — Diffuse mesangial sclerosis is reportedly resistant to corticosteroids and immunosuppressive drugs. In the previously mentioned report, however, there was a clinical response to immunosuppressive therapy in two of the eight children with diffuse mesangial sclerosis due to a genetic mutation in PLCE1 [2] . In one child, remission was achieved with steroids, and the second patient responded to cyclosporine therapy after failing initial steroid therapy. These cases are the first reported cases of successful remission in patients with congenital nephrotic syndrome due to genetic defect.

The degree of proteinuria is typically less severe than in the CNF and specific supplemental therapy is usually not required.

Treatment is supportive and consists of maintenance of electrolyte and water balance and adequate nutrition, prevention and treatment of infectious complications, and management of renal failure. Bilateral nephrectomy has been considered at the time of transplantation because of the theoretical risk of developing a Wilms' tumor. This issue remains unresolved, although some investigators have not found Wilms' tumor in the kidneys from 14 children with renal failure [41] . Recurrent disease does not develop in the transplant.

The combination of an angiotensin converting enzyme inhibitor and indomethacin therapy was used to treat one child with diffuse mesangial sclerosis [28] . The child had a sustained clinical response, normal growth pattern, and suffered no adverse effects.

**DIFFUSE MESANGIAL SCLEROSIS WITH DRASH SYNDROME** — Denys and Drash first reported the triad of progressive renal disease, male pseudohermaphroditism, and Wilms' tumor [46,47] . All of the patients were infants with heavy proteinuria progressing rapidly to renal failure. Incomplete forms of the syndrome were described and the glomerulopathy was identified as diffuse mesangial sclerosis [48] .

Epidemiology and genetics — A number of cases of Denys-Drash syndrome have been reported [46-50] . The Denys-Drash syndrome is usually sporadic, although occurrence in two kindreds has been reported. However, constitutional mutations occur in the Wilms' tumor predisposing gene, WT1 [51] .

Wilms' tumor is an embryonic kidney tumor thought to arise from aberrant mesenchymal stem cell differentiation secondary to the loss of a tumor suppressor gene or genes [52,53] . The WT1 gene lies at chromosomal position 11p13; it appears to encode a zinc finger protein, which is probably a transcription factor [54-57] . WT1 is also expressed in the gonads, suggesting that the genital abnormalities in the Denys-Drash syndrome may result from pleiotropic effects of mutations in the WT1 gene itself. This hypothesis was first

confirmed in a report, which identified constitutional heterozygous mutations within the WT1 gene in some individuals with the Denys-Drash syndrome [58] .

Subsequently, mutations of WT1 have been found in most patients with this syndrome. Most abnormalities are missense changes either in exon 9, which encodes for zinc finger 3 (with a mutational hot spot at an arginine residue thought to interact with the consensus DNA sequence), or in exon 8, which encodes for zinc finger 2 [59] .

Clinical presentation — Diffuse mesangial sclerosis is a constant feature of the Denys-Drash syndrome. It is associated with the two other components of the triad in the complete form, but with only one of the two in the incomplete forms.

The clinical course of the nephropathy is not different from that described above in isolated diffuse mesangial sclerosis. However, Wilms' tumor may be the first clinical manifestation of the syndrome. Thus, careful renal ultrasonography should be performed, looking for nephroblastoma, in any patient found to have diffuse mesangial sclerosis. The tumor may be unilateral or bilateral and is associated in a few cases with nodules of nephroblastomatosis [42,51] .

Male pseudohermaphroditism, characterized by ambiguous genitalia or female phenotype with dysgenetic testis or streak gonads, is observed in all 46 XY patients. In contrast, all 46 XX children appear to have a normal female phenotype, with normal ovaries, when the information was available. The finding of a normal male phenotype seems to exclude the diagnosis of Denys-Drash syndrome. (See "Evaluation of the infant with ambiguous genitalia").

**IDIOPATHIC NEPHROTIC SYNDROME** — Idiopathic nephrosis rarely occurs at birth, more commonly presenting during the first year of life. All the morphological variants of idiopathic nephrotic syndrome seen in older children can occur at this time including minimal change disease, diffuse mesangial proliferation, and focal and segmental glomerular sclerosis.

Establishing the diagnosis of one of these disorders may be important clinically, since steroid-responsiveness with a favorable course can be seen [8,60] . However, most affected infants are resistant to therapy and many progress to end-stage renal disease.

In some cases, particularly those with familial disease, NPHS2 mutations have been detected [21] . NPHS2 encodes for an integral membrane protein, podocin, which is found exclusively in glomerular podocytes. In several case series, NPHS2 mutations have also been detected in infants who present with congenital nephrotic syndrome [24,25,35] .

In addition, there are individuals with both NPHS1 and NPHS2 mutations resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other).

Other genetic defects associated with infantile nephrotic syndrome include mutations for alpha-actinin-4 gene and mutation at the locus of chromosome 2p. The latter appears to be responsible for some forms of steroid-sensitive idiopathic nephrosis, which is inherited in an autosomal recessive fashion [61] . Some affected families, however, do not display linkage to this locus, suggesting additional genetic heterogeneity.

These findings demonstrate the genetic heterogeneity of congenital and infantile nephrotic syndrome and the absence of specific genotype/phenotype correlations.

**MISCELLANEOUS** — A number of other disorders are infrequent causes of congenital or infantile nephrotic syndrome.

**Pierson syndrome** — Pierson syndrome, (also referred to as microcoria-congenital nephrosis syndrome, OMIM #6090409) is an autosomal recessive syndrome with congenital nephrotic syndrome with histologic lesions of diffuse mesangial sclerosis and ocular malformations (microcoria, abnormal lens with cataracts, and retinal abnormalities) [62,63]. This autosomal recessive disorder is due to mutations in the LAMB2 gene, which encodes laminin beta 2 [62,63]. Laminin beta 2 is abundantly expressed in the glomerular basement membrane where it plays a role in anchoring and in the development of podocyte foot processes [64]. LAMB2 knockout mice exhibit congenital nephrotic syndrome in association with anomalies of the retina and neuromuscular junction. LAMB2 mutations have also been found in patients with congenital nephrotic syndrome and either no or less severe ocular abnormalities [65].

**Galloway syndrome** — The Galloway syndrome is characterized by microcephaly, mental retardation, hiatus hernia, and the nephrotic syndrome [66]. It appears to be transmitted as an autosomal recessive trait. The nephrotic syndrome presents early with a mean age of onset of three months and is usually severe and resistant to steroid therapy. Renal biopsy reveals minimal changes or focal and segmental glomerulosclerosis. The underlying diagnosis is unknown.

**Infectious causes** Congenital syphilis — Congenital syphilis can cause membranous nephropathy [67,68]. Histological examination often shows a mixed pattern with membranous nephropathy and mesangial proliferation. Penicillin treatment leads to the resolution of the syphilis and the renal abnormalities. Congenital toxoplasmosis — The nephrotic syndrome may be induced by congenital toxoplasmosis [69]. Proteinuria may be present at birth or may develop during the first three months, in association with ocular or neurologic symptoms. Histological examination often shows mesangial proliferation with or without focal glomerulosclerosis. Treatment of toxoplasmosis or steroid therapy usually leads to remission of the proteinuria. **Other organisms** — Congenital or infantile nephrotic syndrome has been reported in association with cytomegalovirus, rubeola virus, and human immunodeficiency virus.

**Other causes** Nail-patella syndrome. (See "Nail-patella syndrome") Mercury exposure Neonatal nephrotic syndrome due to membranous nephropathy has been diagnosed antenatally in infants with mothers who have mutations in the metalloproteinase endopeptidase gene, which encodes the podocyte protein neutral endopeptidase (NEP) [70]. During pregnancy, the presence of fetal NEP protein induces a maternal alloimmune response. Maternal antibody to NEP fetal protein results in fetal podocyte injury, which may lead to chronic renal failure. The mothers' IgG response to the expression of fetal NEP determined the severity of the neonatal disease.

**DIAGNOSIS** — Because most cases of congenital and infantile nephrotic syndrome are caused by genetic mutations and fail to respond to immunosuppressive therapy, genetic screening should be performed before starting treatment. In addition, extrarenal

manifestations can be helpful in the diagnosis. As an example, genital abnormalities in an affected male infant suggests a WT1 mutation and the diagnosis of Denys Drash syndrome.

**SUMMARY** — Nephrotic syndrome that presents at birth or within the three first months of life is defined as congenital nephrotic syndrome. Later onset, between three months and one year of age, is called infantile nephrotic syndrome. Most of children with congenital or nephrotic syndrome have a genetic basis for the renal disease and a poor outcome.

Mutations of the following genes are responsible for the majority of cases of congenital and infantile nephrotic syndrome. NPHS1, which encodes nephrin (a key component of the podocyte slit diaphragm) and is responsible for the Finnish-type congenital nephrotic syndrome. (See "CNS of Finnish type" above) NPHS2, which encodes podocin (a protein that interacts with nephrin at the slit diaphragm) and is responsible for familial focal glomerulosclerosis. (See "CNS and NPHS2 mutations" above). WT1, which encodes the transcription tumor suppressor (a protein involved in kidney and gonad development) and is responsible for the Denys-Drash syndrome. (See "Diffuse mesangial sclerosis with Drash syndrome" above. LAMB2, which encodes laminin beta 2 (a component of the glomerular basement membrane) and is responsible for the Pierson syndrome. (See "Pierson syndrome" above). PLCE1 gene, which encodes phospholipase C epsilon, is responsible for the early-onset of isolated diffuse mesangial sclerosis. (See "Diffuse mesangial sclerosis" above).

Other etiologies of congenital or infantile nephrotic syndrome include secondary causes such as infections (eg, syphilis or toxoplasmosis) (show table 1), and toxins such as mercury exposure. (See "Infectious causes" above and see "Other causes" above).

Because most cases of congenital and infantile nephrotic syndrome are caused by genetic mutations and fail to respond to immunosuppressive therapy, we suggest genetic screening performed before starting treatment (Grade 2B).

#### Major causes of congenital nephrotic syndrome

- Congenital nephrotic syndrome of Finnish type
- Diffuse mesangial sclerosis
- Diffuse mesangial sclerosis with Drash syndrome
- Idiopathic nephrotic syndrome
- Other
  - Congenital syphilis
  - Congenital toxoplasmosis
  - Certain viral infections
  - Galloway syndrome

## **Endocrine dysfunction in the nephrotic syndrome**

**INTRODUCTION** — The nephrotic syndrome is characterized by a marked increase in the glomerular permeability to macromolecules. The associated urinary losses of albumin and hormone binding-proteins are responsible for many of the metabolic derangements and endocrine abnormalities in these patients [1] .

This topic review will emphasize the alterations in thyroid, vitamin D, and calcium metabolism. The effects on lipid metabolism are discussed elsewhere. (See "Hyperlipidemia in nephrotic syndrome").

**THYROID FUNCTION TESTS** — Thyroid function tests reveal variable results in the nephrotic syndrome, primarily depending upon the level of glomerular filtration. In addition, other factors frequently present in the nephrotic syndrome, such as hypoalbuminemia, increased serum free fatty acid concentrations, and the administration of furosemide, can also affect thyroid function tests (show table 1) [2-4] . (See "Laboratory assessment of thyroid function" for a review of the interpretation of the different tests used to assess thyroid function).

**Relatively normal glomerular filtration rate** — Urinary losses of thyroxine (T4)-binding globulin (TBG) and other thyroid hormone binding proteins (transthyretin and albumin) and the T4 bound to them result in a low total T4 concentrations in approximately 50 percent of nephrotic patients with a relatively normal glomerular filtration rate (GFR) [5-7] . Serum triiodothyronine (T3) concentrations may also be low, due also to decreased binding. There is often a good correlation between the serum T4 and T3 and the serum albumin concentration [7] . Serum reverse T3 (rT3) concentrations are also low.

Despite these changes, nephrotic patients are usually clinically euthyroid [7] : The physiologically important serum free T4 and T3 concentrations, as are serum thyrotropin (TSH) concentrations. The serum T3/T4 ratio is typically normal, suggesting no impairment in the conversion of T4 to T3 and therefore a normal rate of production of T3.

(See "Laboratory assessment of thyroid function"). As a result, thyroid hormone replacement is not typically required in these patients [7] . However, occasional patients with nephrotic syndrome who have limited thyroid reserve or are taking fixed doses of T4 may become hypothyroid due to loss of T4 in the urine [8,9] .

**Renal failure** — When renal failure complicates the nephrotic syndrome, the thyroid function test abnormalities are often more severe than when either renal failure or the nephrotic syndrome is present alone. If hypothyroidism is suspected clinically in such a patient, serum TSH should be measured. (See "Thyroid function in chronic kidney disease" and see "Thyroid function in nonthyroidal illness").

**Effect of glucocorticoids** — Glucocorticoids, given to treat the nephrotic syndrome, can cause a small reduction in TSH secretion and inhibit the peripheral conversion of T4 to T3. The net effect may be persistently low serum T3 and basal serum TSH concentrations, and a rise in serum rT3 concentrations [10] . Thus, the serum free T4

concentrations may be the best marker of thyroid status. Patients with low serum free T4 concentrations probably should be treated as if they were hypothyroid [11] .

**VITAMIN D AND CALCIUM METABOLISM**— The nephrotic syndrome is associated with urinary loss of vitamin D-binding protein (VDBP), a 59-kDa protein that is filtered more easily by nephrotic glomeruli [12] . In serum, calcidiol (25-hydroxyvitamin D), the precursor of the most active metabolite calcitriol, is primarily bound to VDBP and is therefore also excreted in the urine [13,14] . (See "Metabolism of vitamin D"). The net effect is a reduction in serum calcidiol concentrations, while those of calcitriol are normal or reduced [13,15,16] . However, the physiologically important serum free calcitriol concentration is usually normal, suggesting that reduced total concentrations are due to loss of hormone bound to VDBP [16] .

The physiologic consequences of these changes in vitamin D metabolism on calcium homeostasis are uncertain. Hypocalcemia is a common finding in the nephrotic syndrome, due primarily to hypoalbuminemia-induced reduction in calcium binding to albumin. In general, the serum total calcium concentration will fall approximately 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL (10 g/L) reduction in serum albumin concentration. A low serum total calcium concentration induced by hypoalbuminemia does not affect the physiologically important free (or ionized) calcium concentration. The measured serum calcium concentration can be corrected for the presence of hypoalbuminemia from the following equation:

$$\text{Corrected [Ca]} = \text{Measured total [Ca]} + 0.8 \times (4.5 - [\text{alb}])$$

where the serum calcium and albumin concentrations are measured in units of mg/dL and g/dL, respectively. Thus, if the measured values are 7.6 mg/dL and 2.5 g/dL:

$$\text{Corrected [Ca]} = 7.6 + 0.8 \times 2 = 9.2 \text{ mg/dL}$$

A subset of patients has been reported with hypocalcemia out of proportion to hypoalbuminemia, due to low serum calcitriol concentrations and perhaps increased fecal calcium losses. These patients have a decline in ionized calcium concentrations [17,18] and a secondary elevation in serum parathyroid hormone (PTH) concentrations [19] . The hyperparathyroidism can then lead to bone disease characterized by mixed osteomalacia and osteitis fibrosa [16] . (See "Bone biopsy and the diagnosis of renal osteodystrophy" for a review of the histologic changes that may be seen).

The frequency with which true hypocalcemia and bone disease occurs in the nephrotic syndrome is unclear, as many investigators have found relatively normal calcium and bone metabolism. One report, for example, evaluated six adults with the nephrotic syndrome and normal renal function [20] . Although serum calcidiol concentrations were reduced, the serum ionized calcium, calcitriol, and PTH concentrations were normal and there was no histologic evidence of bone disease. Other investigators have also noted normal intestinal calcium absorption and bone histology [21,22] .

In summary, only a subset of patients with the nephrotic syndrome develop clinically important abnormalities in vitamin D, calcium, and bone metabolism. Suggested

predisposing factors include increasing age, prolonged duration of disease, renal insufficiency, marked proteinuria, and glucocorticoid therapy [10] . Another possibility which has been demonstrated in experimental animals is impaired production of calcitriol due to tubular damage induced by heavy proteinuria [23] .

Treatment — Vitamin D replacement therapy is not routinely recommended in patients with the nephrotic syndrome. It may, however, be beneficial in patients with unremitting or relapsing nephrotic syndrome who have persistent reductions in serum ionized calcium concentrations and/or of abnormal bone histology.

The optimal evaluation of calcium and vitamin D metabolism in patients with the nephrotic syndrome is uncertain. We measure serum ionized calcium if the patient has symptoms of hypocalcemia or a low corrected serum calcium concentration from the above formula; measurements of serum PTH also may be useful.

If vitamin D is given, oral therapy is probably sufficient. Studies in experimental animals with the nephrotic syndrome have found that calcidiol absorption is normal [24] . Similar findings have been noted in humans. In one study, for example, oral administration of calcidiol to nephrotic patients resulted in sustained normalization of the serum calcidiol concentrations and, if renal function was normal, calcitriol; these changes were accompanied by correction of the low serum ionized calcium concentrations and of secondary hyperparathyroidism [25] .

Patients with the nephrotic syndrome who develop chronic renal failure will often be at an increased risk for vitamin D-related bone disease due to the associated reduction in calcitriol synthesis. This is discussed separately. (See "Overview of the management of chronic kidney disease in adults" and see "Overview of the management of chronic kidney disease in children").

The effects of the chronic administration of glucocorticoids on bone mineral density in children with the nephrotic syndrome are discussed in detail separately. (See "Treatment of idiopathic nephrotic syndrome in children").

**GLUCOCORTICOID METABOLISM** — Cortisol-binding globulin also is lost in the urine of nephrotic patients, and serum cortisol concentrations may be reduced. As with T4, however, the percentage of unbound cortisol is increased, serum free cortisol concentrations are normal, and symptomatic hypocortisolism does not occur [26] .

**ANEMIA** — Despite normal renal function, anemia may develop in patients with nephrotic syndrome due to both decreased erythropoietin synthesis and loss of the protein in the urine [4] . Such patients appear to respond to the administration of erythropoietin. (See "Erythropoietin for the anemia of chronic kidney disease among predialysis and peritoneal dialysis patients" and see "Erythropoietin for the anemia of chronic kidney disease in hemodialysis patients").

## **Treatment of idiopathic nephrotic syndrome in children**

**INTRODUCTION** — The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier. It is classically characterized by four clinical features, but the first two are used diagnostically because the last two may not be seen in all patients: Nephrotic range proteinuria — Urine protein excretion >50 mg/kg per day Hypoalbuminemia — Serum albumin <3 g/dL (30 g/L) Edema Hyperlipidemia

Idiopathic nephrotic syndrome is the most common form of nephrotic syndrome in children, representing more than 90 percent of cases before 10 years of age and 50 percent after 10 years of age. Idiopathic nephrotic syndrome is characterized by diffuse foot process effacement on electron microscopy and minimal changes (called minimal change disease [MCD]), focal segmental glomerulosclerosis (FSGS), or mesangial proliferation on light microscopy. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on Idiopathic nephrotic syndrome).

The treatment of idiopathic nephrotic syndrome is reviewed here. The etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children are discussed separately. In addition, specific diseases that cause idiopathic nephrotic syndrome are discussed in greater detail separately. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", see "Diagnosis and causes of minimal change disease in adults", see "Pathogenesis and diagnosis of focal glomerulosclerosis" and see "Minimal change variants: Mesangial proliferation; IgM nephropathy; C1q nephropathy").

**BACKGROUND** — Idiopathic nephrotic syndrome is characterized by diffuse foot process effacement on electron microscopy and minimal changes (called minimal change disease [MCD]), focal segmental glomerulosclerosis (FSGS), or mesangial proliferation on light microscopy.

Prior to 1940, the mortality rate in children with nephrotic syndrome was 40 percent, primarily due to infection, but has been significantly reduced with the introduction of steroid treatment and antibiotics. (See "Complications of idiopathic nephrotic syndrome in children", section on Infection).

Patients with histological findings of MCD are generally responsive to steroid therapy. Because clinical findings are highly predictable in differentiating MCD from other forms of nephrotic syndrome, steroid therapy is initiated in patients who are likely to have MCD based upon clinical criteria without histological confirmation by renal biopsy. One third of patients with FSGS will also initially respond to steroid therapy. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", sections on Idiopathic nephrotic syndrome and Initial therapy versus renal biopsy).

Clinical experience has demonstrated that the response to steroid therapy rather than the histologic features seen on renal biopsy is better at predicting long-term prognosis. Patients who respond to steroids have an excellent prognosis and rarely develop end

stage renal failure. As a result, patients with nephrotic syndrome can be defined by their response to steroid therapy as follows: Steroid-sensitive nephrotic syndrome — More than 90 percent of patients who respond to steroid therapy have MCD, and FSGS is seen in the remaining patients [1] . Almost all patients with steroid-sensitive nephrotic syndrome have an excellent outcome with few patients developing end stage renal failure or renal insufficiency. (See "Steroid-sensitive nephrotic syndrome" below). Steroid-resistant nephrotic syndrome — One-fourth of patients who fail to respond to steroids will have MCD [1] . Patients who fail an initial course of steroid should undergo renal biopsy to determine the underlying diagnosis to guide further therapeutic choices. (See "Steroid-resistant nephrotic syndrome" below).

INITIAL PHARMACOLOGIC THERAPY — Empiric steroid therapy can be initiated in patients with a high probability of having minimal change (MCD) without confirmation of the diagnosis by renal biopsy because more than 90 percent of patients with MCD will respond to corticosteroid therapy within eight weeks [1,2] . Initial steroid therapy is given to patients who fulfill all of the following criteria. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on Initial therapy versus renal biopsy). Age older than 1 year and younger than 10 years of age None of the following findings: hypertension, gross hematuria, and a marked elevation in serum creatinine Normal complement levels No extra-renal symptoms such as malar rash or purpura

Although steroid therapy is often started immediately following the diagnosis of nephrotic syndrome, it should be stressed that spontaneous remission occurs in 5 percent of cases within one or two weeks. Therefore, the initiation of steroid therapy may be delayed for a few days or a week [3] .

Steroid response — Idiopathic nephrosis is steroid-responsive in most children [1] . Approximately 30 percent of treated patients will not have a relapse and are therefore cured after the initial course of therapy [2] . Ten to 20 percent will relapse several months after steroid treatment is discontinued, but will have less than four steroid-responsive episodes before permanent remission occurs. However, 30 to 40 percent of patients will have frequent relapses, defined as four or more relapses per year, and some patients will relapse while on steroid therapy (referred to as steroid dependent).

Patients who are frequent relapsers or steroid dependent often require multiple and/or prolonged courses of steroid therapy and are at risk for steroid toxicity. A longer duration of the initial course of steroids, which includes periods of daily and alternate day steroids, appears to reduce the risk of relapse and decreases the cumulative dose of steroids [4-7] .

This is illustrated by a meta-analysis that included 12 trials [5] . The following findings were noted: In a pooled analysis from six trials, treatment with prednisone for three to seven months reduced the risk of relapse at 12 to 24 months post-therapy versus that observed with a two-month regimen (RR of 0.70 95% CI 0.58 to 0.84). There was no difference in cumulative steroid dose. In a pooled analysis of four trials of 382 children, the risk of relapse was lower with six versus three months of therapy (RR of 0.57, 95% CI 0.45 to 0.71). There was no difference in cumulative steroid dose. A reduced risk of relapse was associated with both an increase in the duration and an increase in the dose of steroid therapy.

Similar findings were seen in a randomized controlled trial from the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) that compared a standard initial treatment of prednisone, 60 mg/m<sup>2</sup> per day for four more weeks, to a longer initial regimen of six weeks of continuous prednisone 60 mg/m<sup>2</sup> followed by six weeks of alternate day prednisone of 40 mg/m<sup>2</sup> [6] . The subsequent relapse rate within 12 months after discontinuation of continuous therapy was lower with the prolonged course of therapy compared to the standard treatment (36 versus 61 percent).

In addition, slow tapering to avoid adrenal suppression may be important to maintain long-term remission, since a study in children found that moderate to severe post-prednisone adrenal suppression was associated with an increased risk of relapse [8] .

Based upon the currently available data, we initially treat children with idiopathic nephrotic syndrome who are likely to have minimal change disease with oral prednisone at a dose of 60 mg/m<sup>2</sup> per day (maximum of 60 mg/day). When proteinuria disappears, prednisone is continued at the same dose for 30 days and the patient is then switched to alternate day therapy (at the same daily dose) for two months. Thereafter, the alternate day dose is decreased every two weeks by 15 mg/m<sup>2</sup>. The net effect is that the total duration of initial therapy is 4.5 months.

Further study is required to determine the optimal regimen of steroid therapy in children with nephrotic syndrome balancing the known side effects of steroids with the desire to decrease the rate of subsequent relapses in children with nephrotic syndrome.

Increasing initial immunosuppression by adding cyclosporine to steroid therapy had been proposed as a way to reduce the relapse rate. However, the addition of cyclosporine does not alter the two-year relapse rate and the combination of cyclosporine and prednisone compared to prednisone alone results in a greater number of side effects [9,10] . As a result, steroids alone are used as the initial therapy for childhood nephrotic syndrome.

Time to response — In a report from the International Society of Kidney Disease in Children (ISKDC), approximately 90 percent of patients who will respond to steroids do so within four weeks after starting steroids, with the remaining 10 percent going into remission after two to four more weeks of a daily steroid therapy [1] (show figure 1).

In our practice, among patients who are not in remission after four weeks of daily steroid therapy, we administer three pulses of methylprednisolone (1000 mg/1.73 m<sup>2</sup>) every other day. Patients who have persistence of proteinuria one week after this treatment are considered steroid resistant. A renal biopsy is performed in these patients with steroid resistant nephrotic syndrome, as there is increased likelihood that they have another glomerular disease [1] . No additional steroid therapy is administered until a histologic diagnosis is made, which aids in making therapeutic choices. (See "Steroid-resistant nephrotic syndrome" below).

Other options in those who are not in remission after four weeks of daily steroid therapy include the following: Biopsy patients without administering the three pulses of methylprednisolone, as there is an increased likelihood that they have another

glomerular disease that may not be responsive to additional steroid therapy. (See "Steroid-resistant nephrotic syndrome" below). Continue daily steroid therapy for another four weeks because an additional 10 percent of steroid responsive patients will respond after four weeks of therapy [1] . However, prolongation of daily steroid treatment beyond an initial four to five weeks to a maximum of eight weeks increases the risk of side effects from steroid therapy. Patients who fail to respond to a maximum eight weeks of daily steroid therapy are considered steroid resistant and require a renal biopsy to determine the underlying glomerular disease [1] . (See "Steroid-resistant nephrotic syndrome" below).

Outcome based upon steroid response — A report from the ISKDC evaluated the outcome of 389 children with minimal change disease who were followed for a mean of 9.4 years based upon their response to initial steroid therapy [2] . The following results were noted: Ninety-two percent of patients responded to steroids. Of this group of 334 patients, 41 percent did not relapse within six months after the initial course of steroid therapy, 28 percent relapsed frequently (defined as two or more relapses within six months after initial steroid therapy), 20 percent had a single relapse within the six month time period, and 3 percent failed to respond to subsequent courses of steroid therapy. Prognosis was best in the steroid-responsive patients who did not relapse in the first six months. Approximately 75 percent either continued in remission during follow-up or relapsed rarely. Only 4 percent became frequent relapsers. Patients with persistent proteinuria after eight weeks of steroid therapy (steroid-resistant) had a 21 percent risk of progression to end-stage renal disease (ESRD). This risk rose to 35 percent among the 60 percent of initial steroid-resistant patients who had persistent proteinuria six months after the initial course of steroid therapy. Overall, 95 percent of children did well, 4 to 5 percent died from complications (eg, peritonitis) or progressed to ESRD.

**STEROID-SENSITIVE NEPHROTIC SYNDROME** — As discussed above, almost all patients will initially respond to steroid therapy. After the initial response, management is focused on early detection of relapse and initiation of therapy to minimize the complications of nephrotic syndrome.

The 40 to 50 percent of steroid-sensitive patients who become frequent relapsers and/or steroid-dependent often present therapeutic challenges to the clinician as they are frequently treated with repeated and/or prolonged courses of prednisone and, as a result, suffer many of the adverse effects of steroid therapy. (See "Frequent relapsing/steroid dependent nephrotic syndrome" below).

**Monitoring** — Once a patient responds to steroid therapy, monitoring for proteinuria is required to detect relapses early and initiate therapy to prevent significant fluid accumulation (edema) and minimize the complications associated with childhood idiopathic nephrotic syndrome. (See "Complications of idiopathic nephrotic syndrome in children").

Patients and their parents are taught to frequently measure body weight and monitor urine protein levels by urine dipstick [11] . Increased urinary protein concentration typically provides the first indication of a relapse. When this occurs, the family should call their health care provider for instructions regarding management.

Initial relapse — With the first few relapses, steroid therapy is typically administered at a dose of 60 mg/m<sup>2</sup> per day (maximum of 60 mg/day). The length of steroid therapy varies among pediatric nephrologists. In our practice, daily prednisone is given until proteinuria has disappeared for four to five days. Alternate day therapy is then begun and the dose tapered to 15 to 20 mg/m<sup>2</sup> every other day according to the patient's steroid threshold.

Frequent relapsing/steroid dependent nephrotic syndrome — Two different steroid regimens have been used to treat patients with frequent relapses and/or are steroid dependent: The International Study of Kidney Disease in Children (ISKDC) recommends a prednisone dose of 60 mg/m<sup>2</sup> per day (maximum of 60 mg/day) be initiated when a patient has relapsed and is continued for three days after the urine has become protein free; thereafter, alternate day prednisone, 40 mg/m<sup>2</sup>, is given for four weeks [12] . Another approach recommends treatment of relapses with daily prednisone, 40 to 60 mg/m<sup>2</sup>, until proteinuria has disappeared for four to five days. Alternate day therapy is then begun and the dose tapered to 15 to 20 mg/m<sup>2</sup> every other day according to the patient's steroid threshold (ie, the dose at which the relapse has occurred). This regimen is continued for 12 to 18 months [13] .

The first regimen allows better definition in terms of relapses, but is associated with more relapses because of the shorter duration of therapy resulting in larger cumulative steroid dose. We recommend the second approach, which is associated with fewer steroid side effects, as the duration of high-dose therapy is shorter.

Although it is important to appreciate, especially when considering other therapeutic agents that almost all frequent relapsers have a progressive decrease in the number of relapses over time and ultimately go into permanent remission [14] , steroid-sparing agents (eg, alkylating agents) should be considered in children who have significant steroid toxicity. (See "Alkylating agents" below See "Alkylating agents" below and see "Other therapies" below).

Steroid side effects — Complications secondary to prolonged steroid therapy are well known and are seen in children with nephrotic syndrome, especially those with frequent relapses or steroid dependency. The side effects associated with steroid use in children with nephrotic syndrome are summarized here. Major side effects of steroids are discussed in greater detail separately. (See "Major side effects of systemic glucocorticoids"). Statural growth impairment can be seen with prolonged daily steroid therapy [15] . Alternate day therapy can preserve growth [16] and catch-up growth often occurs when steroid therapy is discontinued [17] . Cataracts [18,19] . Excessive weight gain, which can persist into adulthood [20] . Although, osteoporosis has been reported in adults who had steroid-sensitive nephrotic syndrome as children [20] , a study that compared adolescents and children with steroid-sensitive nephrotic syndrome to control patients by dual energy x-ray absorptiometry (DEXA) found no long-term effects of intermittent high-dose glucocorticoid exposure upon bone mineral content of the spine or body [9] . Suppression of the hypothalamic-pituitary-adrenal axis (HPA). In a case series of patients (mean age of 9.7 years) treated with alternate day steroids, 20 of 32 patients had evidence of HPA suppression, defined as a peak serum cortisol concentration less than 500 nmol/L (18 µg/dL) in response to adrenocorticotrophin stimulation given as a injection of synacthen (0.5 µg) [21] . Although the authors suggest that HPA suppression increased the risk of relapse, the contribution of HPA

suppression is uncertain because the patients in this small study were treated with several different regimens.

In children with significant side effects of steroid therapy, other steroid-sparing agents (eg, alkylating agents) that prolong remissions and reduce the dose of steroids should be considered. (See "Alkylating agents" belowSee "Alkylating agents" below).

Alkylating agents — Alkylating agents, such as cyclophosphamide and chlorambucil, can induce longer lasting remissions than prednisone alone in patients who are frequent relapsers or steroid dependent [22-25] .

This is best illustrated by a meta-analysis of randomized clinical trials that compared the efficacy of alkylating agents to prednisone alone in maintaining remission in children with steroid-sensitive nephrotic syndrome [25] . The following findings were noted: In three trials of 102 patients, oral cyclophosphamide compared to prednisone reduced the risk of relapse at six to twelve months (RR 0.44; 95% CI 0.26 to 0.73). Chlorambucil compared to prednisone reduced the risk for relapse at six months in 41 children (RR 0.19, 95% CI 0.03 to 1.09) and at 12 months in 32 children (RR 0.13, 95% CI 0.03 to 0.57).

Data from the literature demonstrate that cyclophosphamide therapy increased sustained remission in frequently relapsing and/or steroid dependent patients of 67 to 93 percent at one year, 36 to 66 percent at five years, and approximately 25 percent at 10 years [2,22-24,26] .

The response to cyclophosphamide may be related to whether the patient is steroid dependent or not. Only 30 percent of steroid-dependent patients compared to seventy percent of children with frequent relapses had prolonged remissions after an eight-week oral course of cyclophosphamide [27] . In a long-term follow-up (median time, 6 years) report of 93 patients with steroid dependent biopsy-proven minimal change disease, only 35 percent of patients remained in sustained remission after a course of cyclophosphamide [28] . Twenty-eight patients (30 percent) had more than five relapses, 19 (20 percent) had five or less relapses, and 13 were lost to follow-up.

The effect of cyclophosphamide may depend upon the duration of treatment, especially in steroid-dependent children. This was illustrated in a German study in which 18 steroid-dependent children received a 12-week oral course of cyclophosphamide (2 mg/kg per day) [29] . Compared with historical controls treated for eight weeks, more patients treated for 12 weeks were in remission at two years (67 versus 30 percent). However, other studies found no difference in length of remission between an 8 or 12 weeks course of cyclophosphamide [25,30,31] .

It is unclear whether intravenous cyclophosphamide is as effective as oral cyclophosphamide in sustaining remission. One study, for example, reported that intravenous cyclophosphamide was not effective in preventing relapse in steroid-dependent patients [32] . In contrast, a randomized trial of 47 patients found that the risk of relapse at six months was lower with intravenous cyclophosphamide (six monthly doses) than with a 12-week course of oral cyclophosphamide, although the benefit did not persist at two-year follow-up [33] . Further study is required to clarify if there is a role for intravenous cyclophosphamide in children with nephrotic syndrome.

Based upon the above data and the safety data discussed below, we administer a 12-week course of oral cyclophosphamide at a dose of 2 mg/kg per day (cumulative dose 168 mg) to patients with steroid dependency who have evidence of steroid toxicity. The maximum daily dose should not exceed 2.5 mg/kg. (See "Side effects" below).

Similar efficacy can be achieved with chlorambucil [34]. The recommended dose is 0.2 mg/kg for two months. Higher daily doses give similar results but have a greater risk of side effects [35]. As with cyclophosphamide, the likelihood of long-lasting remission is greater in frequent relapsers than in steroid-dependent children.

There are limited data on the use of mechlorethamine (nitrogen mustard) in children with steroid-sensitive nephrotic syndrome. It is useful in some cases, as it induces rapid remission within an average of seven days. The recommended regimen is two courses of four days of intravenous doses of 0.8 mg/kg per day, one month apart. Most children remain in remission without steroid therapy, but the sustained remission rate in steroid-dependent patients is only 15 percent at three years [36]. Vomiting and leukopenia are seen in a third of cases.

Mechlorethamine can be administered to patients in whom steroids are contraindicated (such as those with diabetes) or in whom prompt remission is desirable (as with thromboembolic complications). But in patients with signs of steroid toxicity due to steroid dependency, a 12-week course of oral cyclophosphamide is preferred because of its fewer side effects and ease of administration.

Side effects — Complications associated with the use of alkylating agents include the following [37]: Neutropenia and infection — Bone marrow suppression by alkylating agents requires monitoring complete blood cell counts (CBC). If the white cell count falls below 3000/mm<sup>3</sup>, the drug should be withdrawn until the count rises. Treatment also should be discontinued if infection develops. There are reported cases of significant morbidity and mortality associated with varicella and the administration of cyclophosphamide. If varicella infection occurs, acyclovir should be administered immediately and the alkylating agent discontinued. (See "Complications of idiopathic nephrotic syndrome in children", section on Varicella). Gonadal toxicity — The development of gonadal toxicity resulting in infertility generally requires a total dose greater than 200 to 300 mg/kg for cyclophosphamide, which exceeds the recommended cumulative dose (168 mg/kg for cyclophosphamide) [38,39]. The gonadal toxicity threshold for chlorambucil is 8 to 10 mg/kg. Malignancy — There is a single reported case of malignancy (acute lymphoblastic leukemia) associated with cyclophosphamide administered in a child with nephrotic syndrome using the above recommended regimen [40]. The extensive use of this regimen of cyclophosphamide in children with nephrotic syndrome and only a single reported associated case of malignancy suggest that there is not a clinically significant increased risk of malignancy compared to the general pediatric population with cyclophosphamide at the recommended dosage for treatment of childhood nephrosis. Alopecia and hemorrhagic cystitis rarely occur at the recommended doses used to treat children with nephrotic syndrome. Seizures — Chlorambucil has been associated with an increase risk of seizures in children with nephrotic syndrome [41].

Based upon the above data, a 12-week course of 2 mg/kg per day of cyclophosphamide (cumulative dose of 168 mg/kg) appears to have minimal long-term complications.

**Other therapies** — Other drugs, such as levamisole, cyclosporine, and mycophenolate mofetil, have been tried in frequently relapsing or steroid-dependent children with idiopathic nephrotic syndrome.

**Levamisole** — Levamisole, which stimulates the immune system, has been shown to have a steroid-sparing effect in children with steroid-sensitive nephrotic syndrome [42-45] . The British Association for Paediatric Nephrology performed a multicenter study in which 61 children received either levamisole (2.5 mg/kg on alternate days to a maximum dose of 150 mg) or placebo [46] . Fourteen patients in the levamisole group and four in the control group were still in remission after four months despite prednisone withdrawal. However, most patients relapsed within three months after cessation of treatment.

Regular blood counts should be performed, as the most serious side effect of levamisole is reversible neutropenia, which occurred in 3 of 140 patients.

**Cyclosporine** — Cyclosporine is effective in inducing or maintaining remission in patients with frequently relapsing or steroid-dependent nephrotic syndrome [47-52] . A review of the literature, which included 129 children, reported that cyclosporine either induced remission or maintained remission in 85 percent of patients, thereby allowing withdrawal of prednisone [48] . The recommended dose is 150 mg/m<sup>2</sup> per day in two oral doses. The dose may be adjusted to maintain trough whole blood levels between 100 and 200 ng/mL, but the level should not exceed 200 mg/m<sup>2</sup>.

Cyclosporine-induced remission is not long lasting and most patients relapse within the few months following cessation of treatment [47] . Thus, cyclosporine may have to be administered for long periods of time, exposing patients to its potential nephrotoxicity. As a result, the plasma creatinine concentration should be monitored regularly. However, in our clinical experience, serial renal biopsies can demonstrate histologic lesions of nephrotoxicity without clinical evidence of renal function impairment. Thus, renal biopsy is the best method of detecting cyclosporine nephrotoxicity, which we currently perform in asymptomatic patients after 18 months of therapy [53] . (See "Cyclosporine and tacrolimus nephrotoxicity").

It has been our experience that patients who relapse on cyclosporine or after cyclosporine withdrawal often respond poorly to a second or third course of treatment. Low-dose alternate day prednisone in combination with cyclosporine may be a better approach in these patients.

**Mycophenolate** — Limited data exist suggest that mycophenolate mofetil (MMF) is effective in increasing the duration of remission in children with idiopathic nephrotic syndrome [45,54-57] .

This was best illustrated in a multicenter, prospective, open-label study of 33 patients with frequently relapsing NS [58] . While in remission, patients received MMF at a dose of 600 mg/m<sup>2</sup> twice a day (maximum dose 1 g) for six months and a tapering dose of alternate day prednisone during the first 16 weeks of the study. One patient relapsed

two days into the study. Of the 32 patients who completed the study, 24 remained in remission throughout the six months of MMF therapy. Sixteen patients relapsed when MMF was discontinued and eight remained in remission for 18 to 30 months after discontinuation of MMF.

However, despite these reports suggesting a clinical benefit of MMF, further studies including controlled trials are needed to determine whether mycophenolate has a role in the treatment of children with nephrotic syndrome.

Long-term outcome — There are limited data on adult long-term outcome of patients who were children with steroid-sensitive nephrotic syndrome. At our medical center, 40 percent of the 102 patients born between 1970 and 1975 experienced at least one relapse as an adult [20]. Using multivariate analysis, the number of relapses as a child was the only factor predictive of relapses occurring later in life. Almost half of the adults who relapsed had long-term steroid side effects including osteoporosis and excessive weight gain. One patient developed end-stage renal failure and the remaining patients had normal renal function.

A similar adult relapse rate (33 percent) was reported in 42 patients with steroid-sensitive nephrotic syndrome treated at another single tertiary center [58]. In this study, multivariate analysis demonstrated that only the use of cyclosporine was predictive of relapse in adulthood, suggesting that relapse in adulthood was related to a complicated childhood course of nephrotic syndrome. All 42 patients had normal renal function, final adult height, and body mass index.

These studies suggest the severity of childhood nephrotic syndrome is predictive of relapse in adulthood but, in almost all cases, renal function remains normal in adulthood. Longterm sequelae appear to be related to side effects of steroids.

**STEROID-RESISTANT NEPHROTIC SYNDROME** — Some children fail to respond to initial steroid treatment. A renal biopsy and screening for genetic disorders should be performed in this setting, as the underlying pathology or a detection of a genetic disorder may affect therapeutic choices.

Genetic mutations — Although it is not well understood why some children with nephrotic syndrome are resistant to steroids [59,60], in other patients, genetic mutations cause steroid-resistant nephrotic syndrome (SRNS).

NPHS2 mutations — Mutations in the NPHS2 gene that encodes for podocin, an integral membrane protein found exclusively in glomerular podocytes, are observed in patients with both familial and sporadic SRNS [61,62]. This is illustrated in the following studies: NPHS2 mutation analysis was performed in 338 children from 272 families with SRNS.

- In the 81 families with autosomal recessive SRNS, 43 percent had NPHS2 mutations (homozygous or compound heterozygous). The average age of onset of nephrosis was 58 months.

- In 172 patients with sporadic SRNS, 11 percent had homozygous or compound heterozygous NPHS2 mutations. The average age of onset was 103 months. In a second

study, direct sequencing of the NPHS2 gene was performed in 190 patients from 165 families with SRNS and in 124 patients from 120 families with steroid-sensitive nephrotic syndrome [63] . The following findings were noted:

- In 165 families with SRNS, 43 had homozygous or compound heterozygous NPHS2 mutations (26 percent).

- In 29 patients with NPHS2 genes mutations, neither cyclosporine nor cyclophosphamide induced a complete remission.

- No homozygous or compound heterozygous NPHS2 mutations were noted among the steroid-sensitive patients.

Patients with familial SRNS due to recessive NPHS2 mutations that are nonsense, frameshift, or homozygous for R138Q mutations are more likely to present at an earlier age (mean onset before 2 years of age) than other forms of SRNS including those with other NPHS2 mutations [64] .

Mutations in NPHS2 have been described in approximately 10 to 30 percent of cases of sporadic SRNS in children from Europe and the Middle East [65-69] . These affected children appear to have an early onset of the disease and most patients progress to end-stage renal failure [65,67,70] . Cardiac defects have also been described in these patients [71] .

Based upon these observations, some have suggested that, to avoid unnecessary exposure to steroid therapy, all children with a first episode of the nephrotic syndrome should be screened for NPHS2 mutations [63] . However, given that over 85 percent of children with idiopathic nephrotic syndrome are steroid-sensitive and only approximately 20 percent of steroid-resistant patients have NPHS2 mutations, screening for abnormalities at this genetic locus would identify less than 5 percent of all cases [72] . However, screening a child with a first episode of the nephrotic syndrome with a familial history of SRNS is advisable because they are at increased risk for having a NPHS2 gene mutation.

It should be stressed that not all familial cases of SRNS are associated with NPHS2 mutations, suggesting that yet-to-be-identified genes are responsible in these cases [73] .

Although one might expect that patients with NPHS2 mutations would not develop recurrent disease in the transplant, recurrence has been reported, although rarely. (See "Focal glomerulosclerosis: Recurrence after transplantation", section on Familial FGS).

WT1 mutations — Mutations in WT1, the Wilms' tumor suppressor gene, have been reported in patients who present clinically with sporadic SRNS. In a European study, for example, mutational analysis of the WT1 gene was performed in 115 cases of sporadic SRNS as well as in 100 cases of steroid-sensitive disease [74] . Mutations in WT1 were found in 3 of 60 males (5 percent) and 5 of 55 females (9 percent) with steroid-resistant disease, although no such mutations were found in cases of steroid-sensitive nephrotic syndrome.

Mutations in WT1 are associated with several forms of hereditary nephrotic syndrome including Frasier syndrome, diffuse mesangial sclerosis, and Denys-Drash syndrome. The last disorder consists of the triad of progressive renal disease, male pseudohermaphroditism, and Wilms' tumor. In the previously mentioned European study [74], two of three affected genetic males had urinary and genital malformations and the other genetic male had sexual reversal (female phenotype) and bilateral gonadoblastoma. In contrast, one of five affected females developed a Wilms tumor, and the remaining four had isolated SRNS. (See "Congenital and infantile nephrotic syndrome").

**Screening and treatment** — Because immunosuppressive therapy has not been shown to be effective in treating children with SRNS due to NPHS2 or WTI mutations, identifying these patients can avoid unnecessary exposure to these medications and their side effects. Thus, screening for such mutations should be performed in those with a familial history of SRNS and children with steroid-resistant disease [72-74]. Commercial tests are available to detect NPHS2 mutations. (See "Pathogenesis and diagnosis of focal glomerulosclerosis", section on Familial disease).

**Non-genetic causes** — The optimal approach to steroid-resistant idiopathic nephrotic syndrome not due to a genetic defect is uncertain. Steroid therapy should be withdrawn, as side effects often are pronounced and the treatment is ineffective. The following sections will discuss the various pharmacologic agents used to treat SRNS not associated with a genetic disorder.

**Alkylating agents** — There are no data showing a beneficial effect of alkylating agents in children with SRNS. Partial or complete remissions have been reported in 20 percent of cases following a course of cyclophosphamide, but this is similar to the remission rate of nontreated patients or those who continue to receive steroid therapy alone [2,75-77].

This was illustrated in a randomized trial from the International Study of Kidney Disease in Children (ISKDC) comparing cyclophosphamide plus prednisone to prednisone alone in patients with focal segmental glomerulosclerosis (FSGS) [76]. The same proportion of children in both groups went into remission by six months.

**Cyclosporine** — The efficacy of cyclosporine in SRNS in children has been confirmed in several reports [51,78-83] as illustrated by the following studies: In one study, which was conducted by the French Society of Pediatric Nephrology, 65 children with SRNS were treated with cyclosporine (150 to 200 mg/m<sup>2</sup> per day) in combination with prednisone (30 mg/m<sup>2</sup> per day for one month followed by alternate day prednisone for five months) [78]. Complete remission was observed in 42 percent of the children; 48 percent with MCD and 30 percent with FSGS. One-half of responding patients remitted within the first month of therapy. Eight of the 27 responders became steroid-sensitive when they subsequently relapsed. In 17 patients, remission lasted from five months to three years. None of the responders progressed to end-stage renal disease and only two had persistent nephrotic syndrome. Complications occurred in 12 of the 31 responders and 15 of the 34 nonresponders, respectively. Most patients with a poor outcome had FSGS. In another study, 15 children with SRNS were treated with moderate doses of cyclosporine (mean dose of 6.3 mg/kg per day) plus prednisone [79]. The dose of

cyclosporine was adjusted to maintain a trough whole blood level between 70 to 120 ng/mL. Thirteen patients underwent a remission after a mean duration of treatment of two months. In a randomized trial, cyclosporine alone was compared to supportive therapy [80] . Of the 22 patients treated with cyclosporine, seven underwent complete and six partial remission of proteinuria after six months; in comparison, no untreated patient went into complete remission and partial remission occurred in only 3 of 19. In a retrospective study, 25 children with FSGS treated with cyclosporine (150 mg/m<sup>2</sup> per day) in combination with the initial use of high dose intravenous pulse methylprednisolone (300 to 1000 mg/m<sup>2</sup> per day for 3 to 8 days) and oral prednisone (40 mg/m<sup>2</sup> per day following pulse therapy) were more likely to undergo remission compared to the 27 children with FSGS treated with cyclosporine and only oral prednisone (40 mg/m<sup>2</sup> every other day) with remission rates of 84 versus 64 percent, respectively [84] . All 14 patients with MCNS included in this study underwent remission regardless of which combination regimen was used. In contrast, no patient with genetic disorders responded to any of the combination therapy.

Cyclosporine may protect against progressive renal failure in these patients. One study, for example, found a five-year rate of progression to end-stage renal disease was 24 percent with cyclosporine therapy compared to 78 percent in historical controls in patients with FSGS who failed to respond to cyclophosphamide [82] .

Mycophenolate — A paucity of data exist concerning the use of mycophenolate in patients with SRNS [60] . In a retrospective single-center review, the efficacy of mycophenolate was evaluated in five children with SRNS [60] . Mycophenolate was associated with fewer relapses in three children, and no change in two.

More aggressive regimens — More aggressive regimens have been tried in relatively small numbers of patients with SRNS.

One regimen included vincristine, cyclophosphamide, and prednisolone [85] . Lasting remission was observed in only 7 of 21 patients, starting six months to three years after initiation of treatment.

Another aggressive approach based upon methylprednisolone pulses combines the following drugs [3,86,87] : Pulse methylprednisolone (30 mg/kg given intravenously) administered every other day for two weeks, weekly for eight weeks, every other week for eight weeks, monthly for nine months, and then every other month for six months Oral prednisone (2 mg/kg every other day) If proteinuria has not improved by week 2 of pulse therapy, an alkylating agent is added; either cyclophosphamide (2.0 to 2.5 mg/kg per day) or chlorambucil for 8 to 12 weeks

In one study utilizing this protocol, 21 of 32 children went into remission [87] . The five-year incidence of end-stage renal disease was approximately 5 percent versus 40 percent in historical controls [87] . A poor outcome was associated with segmental sclerosis on renal biopsy prior to pulse therapy [88] . Side effects included nausea during the infusion of pulse methylprednisolone in almost all, impaired growth in four (one of whom caught up with cessation of therapy), small cataracts that did not interfere with vision in five, and infections in two (cellulitis and Herpes zoster). There were no cases of abdominal striae, diabetes mellitus, or aseptic necrosis of bone.

A preliminary multicenter report of 15 children with FSGS was unable to confirm the efficacy of pulse methylprednisolone [89] . A mean of 15 pulses were given and eight patients also received an alkylating agent. At the end of the study, only four patients maintained remission and five had a poor outcome with progression to end-stage renal disease or death.

Further data are required to determine the efficacy and safety of pulse methylprednisolone in children with SRNS.

Angiotensin antagonism— Numerous trials in adults have demonstrated that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) slow the rate of progression of proteinuric chronic renal failure. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease").

Although similar data are lacking in children, use of these drugs is warranted in children with refractory idiopathic nephrotic syndrome and persistent proteinuria based upon the evidence in adults with chronic renal disease and proteinuria.

In one small study, marked benefits with an ACE inhibitor and/or ARB therapy, plus mycophenolate were observed in nine children with steroid-resistant FSGS [90] . At six months, mycophenolate plus angiotensin blockade resulted in a 72 percent decrease in proteinuria from baseline values, a benefit that was maintained for a minimum period of 24 months.

ACE inhibitor and/or ARBs should be terminated if hyperkalemia cannot be controlled or the plasma creatinine concentration increases more than 30 percent above the baseline value.

Our approach We perform genetic screening in children with a familial history of steroid-resistant nephrotic syndrome (SRNS) or those who fail an initial course of steroids [74,76] . In patients with SRNS caused by genetic disorders, we do not administer additional immunosuppressive therapy because it is not effective and has significant adverse effects. Although data are lacking in children, we treat these patients with persistent proteinuria with ACE inhibitors and/or ARBs. (See "Genetic mutations" above and see "Angiotensin antagonism" above) . The optimal approach to SRNS not associated with a genetic disorder is uncertain. We initially use a combination of cyclosporine and prednisone in children with steroid-resistant minimal change disease or FSGS, provided they have normal glomerular filtration rate. In addition, we treat children with refractory nephrotic syndrome and persistent proteinuria with ACE inhibitors and/or ARBs, and symptomatic therapy. (See "Non-genetic causes" above and see "Angiotensin antagonism" above and see "Symptomatic treatment" above).

**SYMPTOMATIC TREATMENT**— Symptomatic treatment is used in conjunction with pharmacologic therapy. It is important in the early course of therapy as response to steroid therapy may take several weeks. Symptomatic treatment also becomes the mainstay of therapy in children who fail to respond to steroids, especially those with genetic mutations that cause their nephrotic syndrome. (See "Steroid-resistant nephrotic syndrome" above).

Edema

Salt restriction — Edema is treated by salt restriction because renal retention of sodium is one of two principal mechanisms that leads to edema in the nephrotic syndrome. In an already edematous patient, salt restriction alone will not significantly improve edema but can reduce further accumulation of fluid. (See "Mechanism and treatment of edema in nephrotic syndrome", section on Mechanisms of primary renal sodium retention).

Optimally, a child with nephrotic syndrome is restricted to a diet of two to three mEq of sodium/kg per day, the amount of sodium required for a growing child. A 10 kg child therefore would receive between 20 to 30 mEq of sodium per day or 460 to 690 mg of sodium per day. This strategy is continued up to a maximum sodium intake of 2000 mg/day in older children.

Diuretics — Although diuretics are commonly used in adults with nephrotic syndrome, their role in often severely hypoalbuminemic children is less clear. Affected children may be intravascularly volume depleted and aggressive diuresis may lead to further volume depletion, thereby possibly precipitating acute renal failure and increasing the risk of thrombosis in this already susceptible group of patients [11,91] . Rarely, diuretics can contribute to severe volume depletion that results in hypovolemic shock [92] . (See "Complications of idiopathic nephrotic syndrome in children").

Diuretics should only be given in cases of severe edema and only if there is not significant intravascular volume depletion. Patients with anasarca may be treated with furosemide (1 to 2 mg/kg per dose) in combination with salt-poor albumin (0.5 to 1 g/kg infused over four hours). Albumin raises the intravascular oncotic pressure and thereby protects the intravascular compartment against volume contraction. Albumin infusion also increases protein-binding of furosemide, which improves the rate of delivery to the kidney resulting in increased renal salt excretion.(See "Mechanism and treatment of edema in nephrotic syndrome", section on Treatment).

In a retrospective study, albumin and furosemide therapy in children with nephrotic syndrome effectively removed fluid with a mean loss of 0.4 kg (1.2 percent of body weight) per infusion [93] . However, the effect is transient and can be associated with complications resulting from increased vascular volume including hypertension and respiratory distress. As a result, aggressive diuresis with albumin and furosemide therapy should be reserved for patients with anasarca who have respiratory compromised due to ascites and/or pleural effusions, severe scrotal edema sufficient to threaten perforation, peritonitis, or severe tissue breakdown [11,14] . Other measures, such as salt and fluid restriction, are needed to prevent reaccumulation of fluid. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on Anasarca).

Furosemide may be given intravenously or orally without albumin, although it is somewhat less effective, it can be useful when given alone. Ongoing oral use of furosemide can still cause hypovolemia and hypokalemia and close monitoring of the patient is required.

Other diuretics used in childhood nephrosis include: Spironolactone (5 to 10 mg/kg per dose) — Although spironolactone interferes with the sodium retention of the cortical collecting tubule, the theoretical site of enhanced sodium reabsorption in nephrotic

syndrome, its weak potency limits its usefulness. However, in combination with loop diuretics such as furosemide, its potassium sparing effect may decrease the risk of hypokalemia. Thiazide diuretic — Thiazide diuretics, such as metolazone (2 mg/kg per dose) in combination with furosemide appear to enhance the natriuretic and diuretic effects of furosemide alone [94] . However, this combination of diuretics is associated with hypokalemia. Amiloride — Amiloride is a potassium-sparing diuretic that decreases sodium channel activity of the cortical collecting tubule. Like spironolactone, it can be used in combination with furosemide to decrease the risk of hypokalemia.

Because of the potential for serious complications, diuretic management should be supervised by a nephrologist who has expertise in treating children with nephrotic syndrome.

Fluid restriction — Although there is debate on the role of fluid restriction, initial restriction of fluid intake to an equivalent volume of the patient's insensible losses plus his/her urine output will result in stabilizing the patient's weight without further accumulation of edema. (See "Maintenance fluid therapy in children", section on Sensible and insensible water loss).

Hypercoagulability — Nephrotic patients with severe hypoalbuminemia are at risk for thromboembolic complications. Preventative measures include mobilization, avoidance of hemoconcentration resulting from hypovolemia, and early treatment of sepsis or volume depletion. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on Thrombosis).

Most clinicians do not give prophylactic warfarin therapy initially. However, a few will initially treat high-risk patients with albumin concentration of less than 2 g/dL (20 g/L), a fibrinogen level of more than 6 g/L, or an antithrombin III level less than 70 percent of normal. Alternatively, high risk patients can be treated with low-dose aspirin or dipyridamole, although there are no controlled trials that demonstrate their efficacy in thrombus prevention in children with nephrotic syndrome.

Heparin is given if thrombi do occur. However, the dose necessary to obtain a therapeutic effect is often greater than normal because of decreased antithrombin III, a cofactor required for heparin activity.

In patients with thromboembolic complications, we will start treatment with warfarin if the patient remains nephrotic placing them at continued risk for thrombosis.

## Infection

Bacterial — Nephrotic children are at increased risk of developing infection (eg, peritonitis, pneumonia, and sepsis) due to encapsulated bacteria, in part due to reduced serum concentrations of immunoglobulin, decreased cellular immunity, and the administration of immunosuppressive therapy. The most common agent is streptococcus pneumoniae followed by Escherichia coli. (See "Complications of idiopathic nephrotic syndrome in children", section on Bacterial infection).

Prophylactic antimicrobials are not recommended, but infections that do occur should be promptly treated. Although antibody response can be blunted, all children with

nephrotic syndrome should receive 23-valent polysaccharide vaccine (PPV23) pneumococcal vaccine (if not already immunized). It is ideally administered when the child is in remission and off of daily corticosteroid therapy. (See "Pneumococcal (*Streptococcus pneumoniae*) polysaccharide vaccines in children", section on Indications).

Varicella — Children with nephrotic syndrome who require immunosuppressive therapy are at increased risk for developing varicella. Varicella vaccination has been shown to be effective in children with nephrotic syndrome and should be given to all patients with negative varicella titers [95] . It is ideally administered as a two-dose regimen when the child is in remission and off of daily corticosteroid therapy.

In cases of exposure of patients who are receiving immunosuppressive therapy and do not have immunity to varicella, VariZIG, a varicella zoster immune globulin product, can be administered. VariZIG should be administered within 96 hours of the exposure at a recommended dose of 125 units/10 kg body weight, up to a maximum of 625 units (five vials); the minimum dose is 125 units. Patients should be monitored for varicella for 28 days after exposure since VariZIG may prolong the incubation period. Any patient who receives VariZIG should receive varicella vaccine. Vaccine should be given five months after administration of VariZIG.

Acyclovir, a synthetic nucleoside analog which inhibits replication of human herpesviruses, is effective therapy for primary varicella infection. It should be instituted promptly in any patient who is receiving immunosuppressive therapy and exhibits any sign of varicella infection. Acyclovir has also been used prophylactically in children exposed to varicella while receiving immunosuppressive therapy [96] . (See "Treatment and prevention of chickenpox" ).

#### Other dietary measures

Caloric intake — Increased caloric consumption as a result of appetite stimulation of corticosteroid therapy can lead to excessive weight gain. Dietary measures that limit excessive caloric consumption, including a low-fat diet, will help children avoid large weight gains.

Calcium and vitamin D — Abnormalities in bone histology can be seen in patients with nephrotic syndrome, primarily due to two processes: Loss of vitamin D binding protein — In children with nephrotic syndrome, urinary loss of vitamin D binding protein may result in low ionized calcium and 25-OH Vitamin D3 (25-hydroxycholecalciferol) concentrations [97] . Prolonged corticosteroid therapy in children with nephrotic syndrome may lead to abnormalities in bone histology [98] and subsequently osteoporosis [99] . However, one study using dual-energy x-ray absorptiometry did not find any difference in spinal or whole body mineral content of glucocorticoid treated children with NS compared to control patients [9] . (See "Prevention and treatment of glucocorticoid-induced osteoporosis").

Based upon the above, calcium (500 mg/day) and vitamin D (2000 to 4000 units) supplements often are prescribed especially when there are documented low calcium and/or vitamin D concentrations, however there are currently no data that have shown this intervention to be effective.

**Hyperlipidemia** — The lipid abnormalities induced by the nephrotic syndrome reverse with remission.

The optimal treatment of hyperlipidemia in children with persistent nephrosis is unknown. Data from adults with persistent proteinuria demonstrate the following: Dietary modification has been shown to have little benefit. The most successful hypolipidemic agents in adults with persistent nephrosis are the statins. These agents generally produce few side effects and can lower the plasma total and LDL cholesterol concentrations by 20 to 45 percent. There is a smaller reduction in triglyceride levels.

In our practice, we treat children who remain persistently nephrotic and have hyperlipidemia with statin therapy based upon the adult data.

A more complete discussion on the treatment of hyperlipidemia in adults with nephrotic syndrome is found separately. (See "Hyperlipidemia in nephrotic syndrome", section on Treatment).

**Hyponatremia** — Fluid restriction is recommended in children with moderate to severe hyponatremia (plasma sodium concentration less than 125 meq/L), because hyponatremia is believed to be a result of excess water retention due to the hypovolemic stimulation of the release of antidiuretic hormone.

**Hypertension** — Children with nephrotic syndrome and persistent hypertension are more likely to have chronic kidney disease with poor outcome. As a result, in patients with hypertension, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are the preferred antihypertensive agents because of their potential additive antiproteinuric benefit and ability to slow progression of renal impairment. ACE inhibitor and/or ARBs should be terminated if hyperkalemia cannot be controlled or the plasma creatinine concentration increases more than 30 percent above the baseline value. (See "Angiotensin antagonism" above and see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease").

Other antihypertensive agents that have been used in children with nephrotic syndrome include beta-blockers and calcium channel blockers. (See "Treatment of hypertension in children and adolescents", section on Pharmacologic therapy).

**SUMMARY AND RECOMMENDATIONS** In children with nephrotic syndrome who have a high probability of having MCD based upon clinical and laboratory findings, we recommend empiric therapy with oral prednisone, thus avoiding renal biopsy (Grade 1B).

We start with oral prednisone at a dose of 60 mg/m<sup>2</sup> per day (maximum of 60 mg/day). When proteinuria disappears, prednisone is continued at the same daily dose for 30 days and the patient is then switched to alternate day therapy (at the same daily dose) for two months, after which prednisone is tapered every two weeks by 15 mg/m<sup>2</sup>. (See "Initial pharmacologic therapy" above and see "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on Initial therapy versus renal biopsy). Most children with idiopathic nephrotic syndrome will respond to steroid therapy. Approximately 30 percent of children with steroid-responsive nephrotic

syndrome will not have a second relapse, 10 to 20 percent will have less than four relapses, and the remaining will have frequent relapses and/or relapse while on steroid therapy (steroid dependent). (See "Initial pharmacologic therapy" above). Children with steroid-sensitive nephrotic syndrome, who are frequent relapsers and/or are steroid dependent, often develop evidence of steroid toxicity. In these patients, we recommend treatment with cyclophosphamide (Grade 1B). In our practice, we administer a 12-week course of 2 mg/kg per day of oral cyclophosphamide. (See "Alkylating agents" above). Ten percent of children will fail to respond to steroid therapy. These children with steroid-resistant nephrotic syndrome are at increased risk for developing end-stage renal disease. (See "Outcome based upon steroid response" above). Mutations of the NPHS2 gene and WT1 gene account for 20 percent of cases of steroid-resistant nephrotic syndrome. In patients with familial steroid-resistant nephrotic syndrome, the incidence of these mutations is higher. In our practice, we screen for these mutations in children with steroid-resistant nephrotic syndrome or in a child with a family history of steroid-resistant nephrotic syndrome. In patients with steroid-resistant nephrotic syndrome due to NPHS2 and WT1 mutations, we do not recommend immunosuppressive therapy (Grade 1B). (See "Genetic mutations" above). Optimal treatment of steroid-resistant nephrotic syndrome not due to a genetic disorder is unknown. We suggest a combination of cyclosporine and prednisone in children with steroid-resistant minimal change disease or FSGS, provided they have normal glomerular filtration rate (Grade 2C). Alternatively, cyclophosphamide or chlorambucil have also been used. (See "Non-genetic causes" above). In patients with persistent proteinuria, salt and fluid restriction, and diuretics (alone or in combination with salt-pore albumin) are used to control edema. (See "Edema" above). Children with nephrotic syndrome are at increased risk for both bacterial and viral infections. We recommend that these children receive 23-valent polysaccharide vaccine (PPV23) pneumococcal and varicella vaccines (Grade 1B). (See "Infection" above).

#### Cumulative rate of remission in response to steroids in MCD

The rate of response of minimal change disease to corticosteroid therapy is lower in adults compared with children, and more prolonged therapy is required to achieve a remission. Adapted with permission from: Nakayama, M, Katafuchi, R, Yanase, T, et al. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. *Am J Kidney Dis* 2002; 39:503.

## Indications for and complications of renal biopsy

**INTRODUCTION** — A percutaneous renal biopsy may be obtained for a number of reasons, including establishment of the exact diagnosis, as an aid to determine the nature of recommended therapy or to help decide when treatment is futile, and to ascertain the degree of active (ie, potentially reversible) and chronic (ie, irreversible) changes [1,2] . The degree of active or chronic changes help determine prognosis and likelihood of response to treatment. In addition, kidney biopsy can be performed to help assess genetic diseases.

It is important to recognize that prognostication based on renal pathology alone may be affected by the sample size (particularly in lesions that are focal in nature) and may not be very accurate in biopsies with few glomeruli (ie,  $\leq 5$ ). The findings in renal biopsy always need to be interpreted in the context of the clinical and laboratory features. Chronic changes (interstitial fibrosis and tubular atrophy), for example, are a sign of the magnitude and duration of prior injury.

The following topic review provides an overview of issues relating to percutaneous renal biopsy. Nonpercutaneous renal biopsy techniques are also discussed in the last section.

**OVERVIEW** — The routine evaluation of a percutaneous renal biopsy involves examination of the tissue under light, immunofluorescence (and immunoperoxidase in some laboratories [3] ), and electron microscopy. Each component of the evaluation can provide important diagnostic information. (See appropriate topic reviews for discussions concerning pathologic findings in individual disorders). The routine immunofluorescence examination of biopsy specimens should include (at a minimum) evaluation of IgG, IgM, IgA, C3, C1q, albumin, fibrin, and kappa and lambda immunoglobulin light chains. Special studies, including evaluation of serum Amyloid A deposits, IgG subclasses (IgG1-4), and collagen chains (alpha 3.4 and 5) may be helpful in some cases where available. (See "Thin basement membrane nephropathy (benign familial hematuria)" and see "Genetics, pathogenesis, and pathology of hereditary nephritis (Alport syndrome)").

Justification for the routine application of electron microscopy comes largely from studies in the 1960s and 1970s, which showed that this technique provided substantive diagnostic information beyond that obtained from light microscopy in nearly 50 percent of cases. However, most of these studies were performed at a time when immunofluorescence microscopy was not widely available.

To assess the present utility of electron microscopy, a study of 288 native renal biopsies performed over a six-month period in 1996 examined the diagnostic findings provided by light, immunofluorescence, and electron microscopy [4] . When viewed in combination with the results from light and immunofluorescence microscopy, electron microscopy provided: Required diagnostic information in 50 cases (21 percent) Important confirmatory data in 48 (21 percent) Additional unrelated findings in 8 (3 percent)

These findings are consistent with the results from earlier studies and support the continued use of routine electron microscopy. Diagnoses that commonly require electron microscopy included minimal change disease, focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, thin basement membrane disease and Alport syndrome, postinfectious glomerulonephritis, HIV-associated nephropathy, amyloidosis, immunoglobulin deposition diseases, and fibrillary (immunotactoid) glomerulopathy. (See "Indications" below).

**INDICATIONS** — The indications for performing a renal biopsy varies among nephrologists, determined in part by the presenting signs and symptoms [1,2,5-7] . The overall rate of native kidney renal biopsy (in number of procedures per million population [pmp]) varies from over 250 pmp in Australia to less than 75 pmp in the USA [8] . The renal biopsy rate is higher in adults than in children.

These differences in renal biopsy rate are not driven by any differences in the spectrum of renal pathology, but rather by opinions regarding the value of the procedure in diagnosis, prognosis, and therapy. In many academic medical centers, biopsies of the transplanted kidney exceed those performed to diagnose disease in the native kidney. (See "Differential diagnosis of glomerular disease" for a review of the causes of each of the following clinical patterns). The results of the renal biopsy impact patient care in up to 60 percent of cases [5,9-11] . However, the utility of the biopsy may differ considerably based on the indication.

**Isolated glomerular hematuria** — In patients with asymptomatic microscopic hematuria (ie, persistent microscopic hematuria with dysmorphic red blood cells, negative "dipstick" for proteinuria, normal serum creatinine concentration, and normal blood pressure), the renal biopsy may not alter therapy, as such patients generally have a good prognosis. When biopsies are performed, they typically demonstrate either a normal kidney biopsy or one of three disorders: IgA nephropathy, hereditary nephritis (Alport syndrome), or thin basement membrane disease. Most patients with IgA nephropathy and thin basement membrane disease without proteinuria have a good long-term prognosis and, other than angiotensin converting enzyme inhibitors, there is no clear effective therapy for any of these conditions. (See "Urinalysis in the diagnosis of renal disease" and see "Glomerular hematuria: IgA; Alport; thin basement membrane nephropathy").

As a result, a renal biopsy is not routinely performed to establish a specific diagnosis, at least in the United States, unless there is evidence of progressive disease, such as increasing proteinuria or a rising serum creatinine concentration [6] . In a prospective study of 276 native renal biopsies, for example, biopsy for isolated hematuria changed a management decision in only one of 36 patients [5] . However, a specific diagnosis may be desired by some patients for genetic counseling purposes, such as in Alport syndrome.

However, careful follow-up is warranted if a biopsy is not performed, since disease progression can occur. This is particularly true with IgA nephropathy since the majority of patients who are first seen with isolated hematuria have progressive disease (eg, development of proteinuria, hypertension, or renal insufficiency) over many years [12] . (See "Treatment and prognosis of IgA nephropathy").

Renal biopsies are not indicated in patients with persistent nonglomerular hematuria; such patients need a thorough urologic evaluation. (See "Evaluation of hematuria in adults").

Isolated nonnephrotic proteinuria — A renal biopsy generally is not performed in a patient who presents with low-grade proteinuria (less than 500 to 1000 mg/day), absence of glomerular hematuria, usually normal renal function, and an absence of clinical or serologic evidence of a systemic disease that can cause glomerulonephritis (eg, systemic lupus erythematosus, vasculitis, or a paraproteinemia). (See "Evaluation of isolated proteinuria in adults"). Some of these patients will have mild primary focal glomerulosclerosis, IgA nephropathy, or membranous nephropathy [13] ; however, immunosuppressive therapy would not be indicated in this setting, since the prognosis with nonnephrotic proteinuria is often excellent. Other patients will have secondary focal glomerulosclerosis as a response to ischemic injury (as in nephrosclerosis) or to nephron loss (as in reflux nephropathy). (See "Secondary factors and progression of chronic kidney disease").

Many nephrologists routinely perform a renal biopsy in patients with somewhat higher degrees of nonnephrotic proteinuria (1 to 2 g/day), except in the setting where this may be explained by conditions, such as longstanding diabetes mellitus or hypertension. If such a patient is reluctant to undergo biopsy, indications for further encouragement of the patient to consent to the procedure include increasing proteinuria or serum creatinine concentrations, or the new onset of hypertension.

Nephrotic syndrome — A renal biopsy typically is not indicated for the nephrotic syndrome that seems, from the history and presence of extrarenal involvement, to be due to primary or secondary amyloidosis or diabetes mellitus. In contrast, a biopsy is usually performed in patients with lupus nephritis to determine the type of disease that is present. (See "Overview of diabetic nephropathy" for a discussion of the settings in which it might be suspected that nondiabetic renal disease is present).

In the absence of a systemic disease, it is quite likely that one of the three major causes of the idiopathic nephrotic syndrome is present: membranous nephropathy, minimal change disease, or focal glomerulosclerosis (accounting for over 80 percent of cases in adults and children). Renal biopsies in children under the age of six years with nephrotic syndrome may not be necessary, as over 90 percent will have minimal change disease. The necessity of renal biopsy for nephrotic syndrome in older children, adolescents, and adults has been controversial, but we now have a better appreciation of the different therapies in these disorders. In one report, for example, renal biopsy for nephrotic syndrome in adults influenced the management decision in 86 percent of cases [5] .

We usually perform a biopsy in this setting both to determine treatment and to occasionally make an unexpected diagnosis, such as primary amyloidosis, fibrillary (immunotactoid) glomerulonephritis, or membranous nephropathy with signs of underlying lupus that may occur in the absence of the typical serologic changes. Occasionally, even rarer diseases, such as Fabry's disease, collagenofibrotic glomerulopathy, and lecithin-cholesterol acyl-transferase deficiency, which have characteristic pathological findings, may be discovered. The management differs for

pediatric patients presenting with typical nephrotic syndrome. (See "Causes and diagnosis of membranous nephropathy" and see "Treatment of idiopathic nephrotic syndrome in children").

Acute nephritic syndrome — The acute nephritic syndrome — hematuria, cellular casts, proteinuria, and frequently hypertension and renal insufficiency — is often caused by a systemic disease that requires a renal biopsy to establish the diagnosis and guide treatment. However, there are situations in which the initiation of therapy is required while awaiting the renal biopsy. Examples include microscopic polyangiitis, Wegener's granulomatosis, or anti-GBM disease. These are disorders that are associated with rapidly progressive glomerulonephritis and, in the appropriate clinical setting, are suggested serologically by the presence of circulating antineutrophil cytoplasmic antibodies (ANCA) or anti-GBM antibodies. (See "Overview of the classification and treatment of rapidly progressive (crescentic) glomerulonephritis" and other topic reviews)

The reason for a biopsy is variable in lupus nephritis. Patients with acute renal insufficiency and an active sediment may have any number of lesions and require a renal biopsy to establish a diagnosis, determine prognosis, and guide therapy. Another indication for renal biopsy is an intermediate clinical presentation — mild proteinuria and hematuria, or nephrotic syndrome with a bland sediment. In this setting, the diagnosis may be focal or diffuse proliferative disease or membranous lupus, each of which may require different forms of therapy. A repeat biopsy may also be performed for late progression of the disease to distinguish between active lupus (which may require immunosuppressive therapy) and scarring of previous inflammatory injury (which may warrant antihypertensive therapy with an angiotensin converting enzyme inhibitor). (See "Overview of the therapy and prognosis of lupus nephritis" and see "Therapy of diffuse or severe focal proliferative or severe membranous lupus nephritis").

Unexplained acute renal failure — The most common causes of acute renal failure — prerenal disease, acute tubular necrosis, and urinary tract obstruction — can be diagnosed without renal biopsy. Biopsy is indicated in those settings in which the diagnosis is uncertain, as may sometimes be the case with acute interstitial nephritis secondary to drugs [6] . By comparison, patients with small kidneys or slowly progressive chronic renal failure over a period of years are generally not biopsied since there is little likelihood of finding a treatable disease.

PREBIOPSY EVALUATION — Prior to a percutaneous renal biopsy, a history, physical examination, and selected laboratory tests should be performed [14] . The skin overlying the biopsy site should be free of signs of infection, and the blood pressure should be well-controlled. The patient should also be able to follow simple directions.

Recommended laboratory tests include a complete biochemical profile, complete blood count, platelet count, prothrombin time, partial thromboplastin time, and bleeding time, if available. A bleeding diathesis, if discovered, should be appropriately evaluated and treated prior to undertaking a renal biopsy.

The value of routine measurement of the bleeding time continues to be debated [15-18] . A position paper from the college of American Pathologists and American Society of Clinical Pathologists reported that the bleeding time lacked clinical benefit to predict surgical bleeding [18] .

However, extrapolation of this information to a closed procedure, such as the percutaneous renal biopsy, is unclear. Nonetheless, the authors acknowledge a correlation between the bleeding time and clinical bleeding in patients with chronic kidney disease [17] ; thus, the bleeding time may be of value in this population. This is significant, since over 50 percent of patients undergoing biopsy in one study had evidence of chronic kidney disease [19] . Although there are no randomized prospective studies evaluating the use of the bleeding time in the setting of a percutaneous renal biopsy, retrospective studies have demonstrated a bleeding complication rate that is three to five times higher in those patients with elevated bleeding times [20,21] . Other series report no increased risk [16,22] . However, these studies did not examine whether the predictive value of bleeding time differed based on level of kidney function. (See "Preoperative assessment of hemostasis", section on Bleeding time). Other tests to determine platelet function may prove to be useful but have not been tested in this setting. (See "Platelet function testing").

A renal ultrasound should precede the biopsy to assess the size of and/or presence of any anatomic abnormalities that may preclude the performance of a percutaneous biopsy (for example, solitary kidney, polycystic kidney, malpositioned or horseshoe kidney, small echogenic kidneys, or hydronephrosis). The renal ultrasound is often performed at the time of the biopsy (unless it is done under CT guidance or as an open procedure by a surgeon).

Since bleeding is the principal complication of renal biopsy, the evaluation should focus upon any evidence for a bleeding diathesis and the recent use of aspirin or nonsteroidal antiinflammatory drugs. To help ensure normal coagulation, patients should refrain from taking anti-platelet or antithrombotic agents (eg, aspirin, GP IIb/IIIa inhibitors, persantine, and nonsteroidal antiinflammatory drugs) for at least one to two weeks prior to a scheduled elective biopsy and remain off of them for one to two weeks after the biopsy. Patients on heparin should have this stopped the day prior to the procedure. The approach to patients on long-term anticoagulation is discussed below.

The incidence of clinically significant bleeding is minimized if these coagulation tests are normal and in the absence of significant anemia [20] . If a diagnosis is urgent in patients with uremia, a renal biopsy may be performed as an open procedure or after the bleeding diathesis is corrected using a variety of possible measures, such as administration of desmopressin (dDAVP). When the bleeding time is elevated and not related to medications known to impair platelet function, we give dDAVP 0.3 mcg/kg intravenously and repeat the bleeding time in one half hour. If the bleeding time normalizes, we proceed with a percutaneous renal biopsy. If the bleeding time remains elevated, we refer the patient for a nonpercutaneous renal biopsy. (See "Nonpercutaneous renal biopsy techniques" below).

**RELATIVE CONTRAINDICATIONS** — Percutaneous renal biopsy for the detection of primary renal disease is generally not pursued in the following settings: Small

hyperechoic kidneys (less than 9 cm), which are generally indicative of chronic irreversible disease  
Solitary native kidney  
Multiple, bilateral cysts or a renal tumor  
Uncorrectable bleeding diathesis  
Severe hypertension, which cannot be controlled with antihypertensive medications  
Hydronephrosis  
Active renal or perirenal infection  
Anatomic abnormalities of the kidney which may increase risk (see above)  
Skin infection over the biopsy site  
An uncooperative patient

While some contraindications may be considered relative in nature, absolute contraindications for the performance of a percutaneous native kidney renal biopsy were defined in a position paper by the Health and Public Policy Committee of the American College of Physicians in 1988 [23]. These include uncontrolled severe hypertension, uncontrollable bleeding diathesis, uncooperative patient, and a solitary native kidney. The absolute contraindication of biopsying a solitary kidney has been challenged due to the improved safety associated with newer imaging and biopsy techniques. (See "Solitary native kidney" below).

Patients on chronic anticoagulation — There are a number of issues that must be considered in patients on chronic anticoagulation in whom a renal biopsy is being considered. These include: Whether the renal biopsy is essential for diagnosis, prognosis, and/or management  
The indications for chronic anticoagulation and risk of thrombosis if anticoagulation is temporarily stopped (eg, venous versus arterial thrombosis, mechanical heart valve).  
The risk for bleeding after the renal biopsy.  
Factors other than anticoagulation that increase the risk of bleeding post-biopsy include the level of kidney function (and associated platelet dysfunction), anemia, and blood pressure [24]. (See "Bleeding" below).

Thus, the management of patients chronically anticoagulated with warfarin must be individualized, often in consultation with hematology and cardiology, as appropriate. A full discussion of the relevant issues is presented separately. (See "Management of anticoagulation before and after elective surgery").

The following is a general guide concerning the management of such patients: Stop warfarin to allow the INR to drift below 1.5, or reverse it with vitamin K if the biopsy must be performed urgently. Whether heparin is required prior to the biopsy once the INR falls below 2.0, and after the biopsy until oral anticoagulation is restarted, depends upon the perceived risk of thrombosis or embolism (eg, type of event, and frequency and remoteness of prior events). (See "Management of anticoagulation before and after elective surgery", section on Thrombotic risk). For patients who require intravenous heparin, it should be stopped for at least six hours prebiopsy to allow the PTT to normalize, and if possible, should not be resumed for at least 12 to 24 hours. In our opinion, withholding heparin for a more prolonged period of up to one week is preferred, unless the thrombotic risk outweighs the bleeding risk. Although most clinically significant bleeding is recognized in the first 12 to 24 hours post-biopsy, bleeding may occur up to several days after the procedure [19]. Patients on heparin should be closely monitored for signs of bleeding (vital signs, serial hematocrit). Most clinicians would resume oral anticoagulation approximately seven days post-biopsy if there is no evidence of clinically significant bleeding as determined in part by serial monitoring of hemoglobin or hematocrit. For all patients, but particularly those with an increased risk of bleeding, we suggest controlling blood pressure before and after the biopsy to a goal of less than 140/90 mmHg.

An open or, if available, transjugular renal biopsy can be considered if the percutaneous approach is not feasible. (See "Open renal biopsy" below and see "Transjugular renal biopsy" below).

**Solitary native kidney** — A solitary native kidney has been considered an absolute contraindication to percutaneous biopsy, because of the concern that marked bleeding may lead to nephrectomy and loss of all of the patient's functioning renal mass. A surgically performed, open renal biopsy has been the procedure of choice in this setting.

Percutaneous renal biopsy of a solitary kidney has been performed successfully in a few selected cases, and it has been suggested that the risk of surgery and nephrectomy with percutaneous biopsy is, as noted below, so low that it may be less than the risk of general anesthesia [1,25,26] . However, the experience with this practice is too limited to recommend it safely for widespread practice. Thus, we recommend the use of nonpercutaneous techniques in patients with solitary kidneys who require biopsy. (See "Nonpercutaneous renal biopsy techniques" below).

**TECHNIQUE** — All patients should provide informed consent for the biopsy. Possible allergy to local anesthetics and iodine containing solutions should be elicited. Just prior to the procedure, peripheral intravenous access is placed and the patient is usually placed prone with a pillow under the abdomen [14] . If the patient is pregnant or very obese, the biopsy can be performed in the seated or lateral decubitus position [28,29] . Some anxious patients may require mild sedation, but when prescribing sedatives, caution should be taken and side effects considered.

Percutaneous renal biopsy is usually performed under ultrasonic guidance with local anesthesia (usually 1 percent lidocaine hydrochloride) [1,14] . Ultrasonography can localize the desired lower pole site (at which the risk of puncturing a major vessel is minimized), determine renal size, and detect the unexpected presence of cysts that might necessitate using the contralateral kidney.

After the lower pole is localized, a skin mark is made to identify where the biopsy needle will be inserted. The site is subsequently prepped and anesthetized. Under ultrasound guidance, a spinal needle is then used to locate the capsule of the lower pole and to provide anesthesia for the biopsy needle tract.

After a small skin incision is made to facilitate passage, real time ultrasonography is most commonly used to guide the biopsy needle directly into the lower pole [14,30] . This somewhat more cumbersome procedure has the advantage of direct visualization of the location of the needle as the core of tissue is obtained.

The use of real-time ultrasound has been compared to the "blind" approach (using ultrasound for localization only). A retrospective study demonstrated a higher diagnostic yield (100 percent versus 84 percent) as well as a lower major hemorrhagic complication rate (0 percent versus 11 percent) in the group using real-time ultrasound [31] . We therefore suggest the use of real-time ultrasonography rather than ultrasonography for localization only.

A CT scan is an alternative when the kidneys cannot be well visualized, as with marked obesity or small echogenic kidneys [14] .

A variety of different biopsy needles are available, including manual needles (TruCut™ disposable, Franklin-Silverman, Vim-Silverman) and automated spring-loaded biopsy needles [1,2,4,30,32-34] . The choice of biopsy needle is largely one of individual preference.

Several studies have compared the safety and adequacy of different needle gauges and types. The larger gauge needles have provided more glomeruli per core and per biopsy [32,35] . In addition, the automated needles have provided more glomeruli per core and per biopsy when compared to the manual needle of the same gauge [36,37] . There is no difference in complication rate between a manual needle and an automatic needle of the same gauge [36] . However, a higher complication rate with a manual 14 gauge compared to smaller automated needles has been reported [32,33,38] .

It is unclear if larger size or manual approach was responsible for the modest increase in risk in these studies. However, a prospective observational study has reported no difference in frequency of complications or number of glomeruli obtained between automated needles of 14 gauge compared to 16 gauge [22] .

Similar findings appear to occur in comparing biopsy needles for percutaneous renal transplant biopsies [27,33,34,39] . In a prospectively randomized study of patients with renal transplants, biopsies were performed with automated needles of varying sizes: 14 gauge, 16 gauge, and 18 gauge. The diagnostic yield was the greatest with the 14 gauge needle. The complication rates were no different between the three groups; however, more pain was associated with the 14 gauge needle [39] .

To optimize safety, adequacy, and patient comfort, we recommend the use of a 14 gauge spring-loaded needle with real time ultrasonic guidance for native kidney biopsies [2,14] . Transplant biopsies require less tissue and there is no movement of the kidney with respiration to help determine when the biopsy needle is in the renal parenchyma. We use a 16 gauge spring-loaded needle with real time ultrasonic guidance in this setting.

Obtaining two cores of renal tissue is generally recommended [1,2,14] . However, the quantity of tissue required varies with the likely diagnosis. As an example, the distinction of focal (arbitrarily defined as fewer than 50 percent of glomeruli affected on light microscopy) from diffuse proliferative lupus nephritis may require up to 100 glomeruli to make the diagnosis with a reasonable degree of statistical certainty [1] ; obtaining this quantity of renal tissue is rare with percutaneous biopsy and sampling error may therefore explain the seeming variability in clinical outcome in patients with focal disease. (See "Overview of the therapy and prognosis of lupus nephritis").

## COMPLICATIONS

**Bleeding** — Bleeding is the primary complication of renal biopsy (show radiograph 1) [1,2] . Postbiopsy bleeding can occur at three sites: (1) into the collecting system, leading to microscopic or gross hematuria and possible ureteral obstruction; (2) underneath the renal capsule, leading to pressure tamponade and pain; or (3) into the

perinephric space, leading to hematoma formation and a possibly large fall in hematocrit. Most clinically significant bleeding is recognized within 12 to 24 hours of the biopsy [19] .

As previously mentioned, the incidence of bleeding can be minimized by documenting that the partial thromboplastin time, prothrombin time, platelet count, and bleeding time are normal [20] . Additional clinical risk factors for bleeding include hypertension, renal insufficiency, and anemia [14,19,24,40] . In one retrospective study of 645 renal biopsies, post-biopsy bleeding occurred in 2 and 12 percent of patients with serum creatinine concentration below or above 2 mg/dL (177 micromol/L), respectively [24] . Post-biopsy bleeding occurred in <5 and >10 percent of patients with systolic blood pressures less than and greater than 160, respectively (similar for diastolic blood pressures less than or greater than 100 mmHg). The lowest frequency of bleeding was reported for blood pressures <120/80.

The approximate incidence of the different bleeding complications is as follows, but is influenced by the expertise of the operator [1,2,14,24,25,41] : Transient microscopic hematuria in almost all patients; this is associated with postbiopsy CT scan evidence of an intrarenal or perinephric hematoma in 60 to 80 percent. Transient gross hematuria in 3 to 12 percent. Decrease in hemoglobin level of 1 g/dL or more in approximately 50 percent. Bleeding severe enough to cause hypotension in 1 to 2 percent, and to require transfusions in up to 6 percent. Surgery is required to control the bleeding in 0.1 to 0.4 percent with a nephrectomy rate of roughly 0.3 percent. The risk of mortality is 0.02 to 0.1 percent [14] , but many highly experienced and manually skilled operators have performed native kidney biopsies over many decades and not encountered a single mortal event. In two large series spanning the years 1952 to 1990, the death rate was reported to be 0.1 percent [26,41] . Another study reviewed biopsy complications from 1988 to 1994 and reported a mortality rate of 0.02 percent, implying that the use of modern techniques may reduce the rate of death [25] . However, another large series using real-time ultrasound and automated needles reported a mortality rate of 0.1 percent, suggesting that significant morbidity may still occur even with modern techniques. This may reflect factors that increase risk of bleeding in many patients undergoing biopsy such as hypertension, anemia, and chronic kidney disease [19] .

Rarely, severe bleeding may occur due to puncture of the renal artery, aorta, or venous collaterals (in patients with renal vein thrombosis).

Other — The incidence of additional complications that may or may not be related to bleeding include: Pain lasting more than 12 hours in 4 percent; this problem may be due to ureteral obstruction from a blood clot in patients with gross hematuria or to stretching of the renal capsule by a subcapsular hematoma. Arteriovenous fistulas form in 4 to 18 percent of cases due to damage to the walls of an adjacent artery and vein (show radiograph 2) [1,42] . Postbiopsy fistulas are usually clinically silent and resolve spontaneously over one to two years. Symptomatic fistulas, causing hematuria, hypotension, or high-output heart failure, are now rare. The diagnosis can be established by color Doppler ultrasonography or arteriography [42] . Either transcatheter arterial embolization or surgical ligation can be used to close a symptomatic fistula [42] . Another rare complication is chronic hypertension due to

the "Page kidney" [43,44] . In this setting, pressure-induced ischemia from a large subcapsular hematoma can lead to persistent activation of the renin-angiotensin system. Perirenal soft tissue infection may occur in 0.2 percent of cases, most often in patients with active parenchymal renal infection [1,41] . Rarely, puncture of the liver, pancreas, or spleen may occur.

**POSTPROCEDURE OBSERVATION AND TIMING OF COMPLICATIONS —**  
Immediately after the procedure, a post-biopsy ultrasound is often obtained to evaluate for the presence of hematoma. However, the utility of this practice is uncertain, since a hematoma is frequently present and not predictive of subsequent blood loss.

The patient should be supine for four to six hours and then should remain at bed rest overnight. To help detect bleeding and other complications, vital signs are closely monitored, and the urinalysis and complete blood count are obtained at various time points postbiopsy. To minimize the risk of bleeding, blood pressure should ideally be well controlled (goal <140/90 mmHg) [24] .

An important question in this era of cost-containment is what is the optimal period of observation after renal biopsy. This is determined primarily by the time course of complications, particularly bleeding.

One report best addressed this issue in 750 native kidney biopsies in adults with a normal bleeding time, no evidence of coagulopathy, and a stable blood pressure [19] . The biopsies were performed with real-time ultrasonic guidance and the last 523 used an automated biopsy needle. The following findings were noted: The overall major complication rate (bleeding severe enough to require a transfusion or invasive procedure, septicemia, acute renal obstruction or failure, or death) was 6.4 percent, while the rate of minor complications was 6.6 percent. Clinical recognition of a major complication occurred within 4, 8, 12, and 24 hours among 38, 67, 89, and 91 percent of patients, respectively. A similar time course was noted with minor events. Observation for eight hours or less would have missed 33 percent of complications.

It was concluded that observation for 24 hours was optimal, with more than 90 percent of major complications being identified within this period. Thus, most patients should be observed overnight with monitoring of vital signs and a repeat hematocrit in the morning [19,20,45] . However, in low risk patients (eg, serum creatinine concentration <2 mg/dL [177 micromol/L], blood pressure <140/90 mmHg, and no evidence of coagulopathy), a shorter observation period has been described [24,46] .

Another study evaluated the predictive value of an initial six-hour hematocrit with respect to the hematocrit at 24 hours in patients undergoing percutaneous renal biopsy of transplant and native kidneys. The authors found that in patients observed in the hospital for 24 hours, a linear correlation of the hematocrit at six hours to the hematocrit at 24 hours existed [47] .

Based on our experience and published literature, we would recommend observing the patients for at least 12 hours and optimally up to 24 hours in the hospital at bedrest after biopsy.

## NONPERCUTANEOUS RENAL BIOPSY TECHNIQUES

Open renal biopsy — An open (surgical) renal biopsy (or a modified open biopsy done under local anesthesia) should be considered in three settings: (1) when there is an uncorrectable bleeding diathesis, in which a transjugular biopsy is another alternative (see "Transjugular renal biopsy" below); (2) when there is a solitary kidney; and (3) after failed attempts at percutaneous biopsy [1,48,49] . A large core or wedge of renal cortex can usually be obtained, the incidence of severe bleeding is very low, and mortality is rare. Other relatively minor postoperative complications can occur, including fever, atelectasis, and ileus. In addition, an open biopsy under general anesthesia is associated with a longer hospital stay and a larger surgical scar.

Open renal biopsy has also been suggested in intensive care unit patients who are being mechanically ventilated. Even in this setting, however, it is possible to perform a percutaneous renal biopsy with portable ultrasonic guidance and the patient prone and being ventilated manually with an ambu bag [50] .

Laparoscopic renal biopsy — Laparoscopic renal biopsy is advocated by some investigators as a viable alternative to open renal biopsy among patients unable or unwilling to undergo percutaneous renal biopsy [51,52] . In one series of 32 patients who underwent laparoscopy for a variety of indications, all biopsies were successful and were associated with minimal complications [51] . An accurate assessment of the role of this technique requires further study, particularly in additional surgical centers.

Transjugular renal biopsy — Another technique is transjugular renal biopsy. This procedure is generally performed by interventional radiologists in the angiography suite, and requires a small amount of intravenous contrast.

The risk of perinephric bleeding is theoretically reduced since the renal capsule is not intentionally penetrated [53-55] . In centers with experience, the complication rate of this technique is similar to the percutaneous approach [56-58] . However, intrarenal bleeding due to arterial trauma may still occur, and some centers have reported high rates of bleeding due to capsular perforation [55,56,58] . Another limitation of the procedure is that obtaining adequate tissue for establishing a diagnosis ranges from only 73 to 97 percent [17] .

The major indication for this modality is an uncorrectable clotting disorder; other indications include the requirement for combined liver or heart and kidney biopsy, morbid obesity, or a single kidney [54-62] . Some have also performed simultaneous transjugular renal biopsy and hemodialysis catheter placement in patients with dialysis-dependent acute renal failure in whom a histologic diagnosis may alter patient management [63] .

Contraindications to a transjugular renal biopsy include bilateral internal jugular vein thrombosis, allergy to contrast media, and the lack of experienced clinicians [60] . The greater cost in time, personnel, and radiologic guidance make this procedure impractical for routine renal biopsy, but may be an option in selected circumstances when the appropriate expertise is available.

## SUMMARY AND RECOMMENDATIONS

A percutaneous renal biopsy may be obtained to obtain a diagnosis, help guide therapy, and ascertain the degree of active and chronic changes. The routine evaluation of a percutaneous renal biopsy involves examination of the tissue under light, immunofluorescence, and electron microscopy. (See "Introduction" above and see "Overview" above). The indications for performing a renal biopsy vary among nephrologists, being determined in part by the presenting signs and symptoms:

- Among patients with the nephrotic syndrome, a biopsy is usually performed in those with lupus nephritis to determine the type of disease that is present. We also usually perform a biopsy in patients with the nephrotic syndrome and no evidence of systemic disease both to determine treatment and to occasionally make an unexpected diagnosis.

- The acute nephritic syndrome is often caused by a systemic disease that requires a renal biopsy to establish the diagnosis and guide treatment. Even in the absence of a systemic disease, the acute nephritic syndrome often requires a biopsy to ascertain a diagnosis and direct treatment.

- Among patients with unexplained acute renal failure, a biopsy is indicated in those settings in which the diagnosis is uncertain.

Among patients with isolated glomerular hematuria, a renal biopsy is NOT routinely performed to establish a specific diagnosis, at least in the United States, unless there is evidence of progressive disease such as increasing proteinuria or a rising serum creatinine concentration.

A renal biopsy is also generally NOT performed in a patient who presents with low-grade proteinuria (less than 500 to 1000 mg/day), the absence of glomerular hematuria, usually normal renal function, and an absence of clinical or serologic evidence of a systemic disease that can cause glomerulonephritis.

(See "Indications" above). Prior to a percutaneous renal biopsy, a history, physical examination, and selected laboratory tests should be performed. Recommended laboratory tests include a complete biochemical profile, complete blood count, platelet count, prothrombin time, partial thromboplastin time, and bleeding time, if available. There are a number of relative contraindications to the performance of a percutaneous renal biopsy. (See "Prebiopsy evaluation" above and see "Relative contraindications" above). Percutaneous renal biopsy is usually performed under ultrasonic guidance with local anesthesia. We suggest the use of real-time ultrasonography rather than the blind approach in which ultrasound is used for localization only (Grade 2C). To optimize safety, adequacy, and patient comfort, we recommend the use of a spring-loaded needle for native kidney biopsies rather than a manual needle (Grade 1B). For native kidney biopsies, we usually use a 14 gauge spring-loaded needle and try to obtain two cores of renal tissue. Bleeding is the primary complication of renal biopsy. (See "Technique" above and see "Complications" above). After a percutaneous renal biopsy, we recommend observing the patients for at least 12 hours (and optimally up to 24 hours) in the hospital at bedrest (Grade 2C). (See "Postprocedure observation and timing of complications" above). Nonpercutaneous renal biopsies are indicated in settings in which a percutaneous renal biopsy cannot be performed. These techniques

include an open, laparoscopic, and transjugular renal biopsy. (See "Nonpercutaneous renal biopsy techniques" above).

#### Renal hematoma

CT scan shows hemorrhage into the left perirenal and pararenal spaces following percutaneous biopsy of the left kidney. The hematoma has displaced the kidney anteriorly. Courtesy of Jonathan Kruskal, MD.

#### Renal AV fistula

Arteriovenous fistula following biopsy of a transplanted kidney. Following injection of contrast material into the right common iliac artery (long arrow), there is prompt filling of the iliac vein (short arrow) with poor perfusion of the transplanted kidney. Courtesy of Jonathan Kruskal, MD.

## Diagnosis of urinary tract obstruction and hydronephrosis

**INTRODUCTION** — Urinary tract obstruction (UTO) is a relatively common problem. The obstruction to urinary flow may be acute or chronic, partial or complete, unilateral or bilateral, and may occur at any site in the urinary tract. The major causes of UTO vary with the age of the patient. Anatomic abnormalities (including urethral valves or stricture, and stenosis at the ureterovesical or ureteropelvic junction) account for the majority of cases in children. In comparison, calculi are most common in young adults, while prostatic hypertrophy or carcinoma, retroperitoneal or pelvic neoplasms, and calculi are the primary causes in older patients [1,2] . (See "Ureteropelvic junction obstruction, congenital megaureter, ureterocele, and ectopic ureter" and see "Clinical presentation, diagnosis, and staging of bladder cancer" and see "Neoplasms of the renal pelvis and ureter").

**SYMPTOMS AND SIGNS** — The clinical manifestations of UTO vary with the site, degree, and rapidity of onset of the obstruction [1] .

**Pain** — Pain is frequently present, due to distention of the bladder, collecting system, or renal capsule. Pain is typically minimal or absent with partial or slowly developing obstruction (as with congenital ureteropelvic junction [UPJ] obstruction or a pelvic tumor). It is not uncommon, for example, to see an adult who is noted to have hydronephrosis due to previously unsuspected UPJ obstruction.

In comparison, relatively severe pain (renal or ureteral colic) may be seen with acute complete obstruction (as with a ureteral calculus) or when acute dilatation occurs after a fluid load that increases the urine output to a level greater than the flow rate through the area of obstruction. An example of the latter problem occurs after beer drinking in a college student with previously asymptomatic and unsuspected UPJ obstruction.

The site of obstruction determines the location of pain. Upper ureteral or renal pelvic lesions lead to flank pain or tenderness, whereas lower ureteral obstruction causes pain that may radiate to the ipsilateral testicle or labia.

**Renal insufficiency** — Patients with complete or severe partial bilateral obstruction also may develop acute or chronic renal failure. In the latter setting, the patient is often asymptomatic and the urinalysis may be relatively normal or reveal only a few white cells or red cells [1] . Thus, UTO should be considered in all patients with otherwise unexplained renal insufficiency. The history may be helpful in some cases, possibly revealing symptoms of prostatic enlargement or prior malignancy or renal calculi.

**Urine output** — The urinary findings are generally nondiagnostic with one possible exception: anuria. Although the urine volume can be reduced in any form of renal disease, anuria is most often seen in two conditions: complete bilateral UTO and shock. (Other less common causes are the hemolytic-uremic syndrome, renal cortical necrosis, bilateral renal arterial obstruction, and crescentic or rapidly progressive glomerulonephritis, particularly anti-GBM antibody disease).

It is important to remember, however, that a normal or even elevated urine output does not exclude partial obstruction. The latter can cause tubular injury that over time impairs both concentrating ability and sodium reabsorption [3,4]. These defects can maintain the urine output and even cause symptoms of nocturia or polyuria, despite the presence of a reduced glomerular filtration rate. (See "Urine output in urinary tract obstruction and postobstructive diuresis").

In contrast to the findings in bilateral disease, the plasma creatinine concentration is usually normal or only slightly elevated in patients with unilateral obstruction due to presence of the normal contralateral kidney. In rare cases, however, unilateral obstruction leads to anuria and acute renal failure; vascular or ureteral spasm, mediated by autonomic activation, is thought to be responsible for the loss of function in the nonobstructed kidney [5].

Hyperkalemic renal tubular acidosis — Type 1 renal tubular acidosis with hyperkalemia is described with urinary tract obstruction [2]. Distal tubular injury in this setting may diminish sodium reabsorption by reducing the activity of the cellular Na-K-ATPase. In turn, impairing sodium reabsorption will tend to induce both metabolic acidosis and hyperkalemia. (See "Pathophysiology of renal tubular acidosis and the effect on potassium balance").

Hypertension — Hypertension is occasionally induced by UTO. The mechanism responsible for the elevation in blood pressure varies with the duration and type of obstruction. What remains unclear, however, is the factors described below result in hypertension in only a minority of obstructed patients. Acute, unilateral obstruction can cause hypertension via activation of the renin-angiotensin system; renal vein renin studies lateralize the increase in renin secretion to the obstructed kidney, a finding similar to that in unilateral renal artery stenosis [6]. Renin secretion is usually normal in patients with bilateral UTO or obstruction of a solitary functioning kidney [7]. In this condition, renal failure leading to volume expansion is typically present; the elevation in blood pressure is probably volume-mediated and resolves with the diuresis following correction of the obstruction. The plasma renin activity is also typically normal in chronic unilateral obstruction and the presence of the contralateral normal kidney prevents both renal failure and fluid retention [7]. Furthermore, relief of the obstruction may not correct the hypertension. These observations suggest that there may be some permanent damage to the kidney and that the elevation in blood pressure is unrelated to the renal disease.

DIAGNOSIS — Early diagnosis of UTO is important, since most cases can be corrected and a delay in therapy can lead to irreversible renal injury. (See "Recovery of renal function after relief of urinary tract obstruction").

Bladder catheterization should be performed initially if there is reason to suspect that bladder neck obstruction leading to acute or chronic urinary retention may be present. Possible clues to this diagnosis include suprapubic pain, a palpable bladder, or an older man with unexplained renal failure. (See "Acute urinary retention").

Radiologic tests are generally used to exclude obstruction at the level of the ureters or above. These procedures are dependent upon their ability to detect dilatation of the collecting system (hydronephrosis). It is important to remember, therefore, that

there are three settings in which obstruction can occur without dilatation [8-10] : Within the first one to three days, when the collecting system is relatively uncompliant and less likely to dilate. In this setting, unilateral obstruction can usually be diagnosed by duplex Doppler ultrasonography, which detects an increased resistive index (a reflection of increased renal vascular resistance) in the affected compared to the contralateral kidney [10] . This test is of no value with bilateral involvement, since it cannot distinguish obstruction from intrinsic renal disease. When the collecting systems are encased by retroperitoneal tumor or fibrosis. In this setting, hydronephrosis may be present in the absence of ureteral dilatation. Retroperitoneal fibrosis can occur in a number of settings including retroperitoneal fibrosis (most commonly idiopathic or associated with beta blocker or methysergide use, malignancy, or a connective tissue disorder) and with the fibrotic reaction that surrounds a renal transplant [11] . Thus, the diagnosis of renal insufficiency due to asymptomatic obstruction in a transplanted kidney may be made on renal biopsy which shows diffuse tubular dilatation, rather than the signs of rejection or cyclosporine nephrotoxicity. When the obstruction is mild, a setting in which there is usually no impairment in renal function.

Renal ultrasonography is the test of choice to exclude UTO, avoiding the potential allergic and toxic complications of radiocontrast media (show radiograph 1). It can, in the majority of affected patients, diagnose hydronephrosis and establish its cause; it can also detect other causes of renal disease such as polycystic kidney disease. CT scanning should be performed if the ultrasound results are equivocal or the kidneys cannot be well visualized, or if the cause of the obstruction cannot be identified.

The combination of a plain film of the abdomen (including tomographic cuts to detect radiopaque calculi), ultrasonography, and, if necessary, CT scanning will be adequate for diagnostic purposes in over 90 percent of cases [8,12] . It should be noted, however, that the false positive rate of ultrasonography may be as high as 25 percent if only minimal criteria (any visualization of the collecting systems) are used to diagnose obstruction [8] .

An intravenous pyelogram (IVP) has a number of advantages in relation to ultrasonography (show radiograph 2A-2B). The false positive rate is very low, it can identify the site of obstruction, and it can detect associated conditions such as papillary necrosis or caliceal blunting from previous infection [8] . Nevertheless, an IVP is more cumbersome to perform and requires the administration of a radiocontrast agent. As a result, it can be used to screen for UTO in the following settings [8] : With staghorn calculi or multiple renal or parapelvic cysts, since hydronephrosis is usually not distinguishable from cysts or stones by ultrasonography or CT scanning. When CT scanning cannot identify the level of obstruction. With suspected acute obstruction due to kidney stones (or less frequently, to other problems, such as a sloughed papilla or blood clot); dilatation of the collecting system may not be seen at this time, but the presence and location of the obstructing stone can be identified.

Antegrade or retrograde pyelography is usually used to relieve, rather than diagnose, UTO. These tests, however, can also be performed for diagnosis when the history is highly suggestive (unexplained acute renal failure in a patient with known pelvic

malignancy), even though hydronephrosis may be absent (due to possible ureteral encasement) on ultrasonography and CT scanning [8] .

**HYDRONEPHROSIS WITHOUT APPARENT OBSTRUCTION OR WITH ASYMPTOMATIC OBSTRUCTION** — In some cases, one of the above radiologic tests demonstrates hydronephrosis without evident obstruction. This is a normal finding in pregnant women. (See "Renal and urinary tract physiology in pregnant women"). Megaureter due to previous marked vesicoureteral reflux or a dilated but nonobstructed extrarenal pelvis are the most common examples of this problem. These patients are often being evaluated for back or flank pain and two questions need to be answered: (1) Is obstruction present?; and (2) Is the obstruction responsible for the pain?

In this setting, three different tests have been used: the diuretic renogram or, less often, IVP and perfusion pressure flow studies [8,13-16] . The former involves the administration of a loop diuretic (such as 0.5 mg/kg of furosemide) prior to a radionuclide renal scan or during an IVP, while the latter involves percutaneous insertion of a catheter into the dilated renal pelvis, followed by fluid perfusion into the pelvis at a rate of 10 mL/min. The marked increase in urine flow should, if obstruction is present, slow the rate of washout of the radioisotope during a renal scan, further increase the size of the collecting system on IVP, or elevate the renal pelvic pressure to above 22 mmHg during a perfusion study. Furthermore, any of these procedures may precipitate pain similar to the patient's initial complaint.

The noninvasive diuretic renogram is generally preferred. However, optimal interpretation of either of these tests is uncertain, because both false positive and false negative tests may be seen [13-15] . Nevertheless, the following general recommendations have been made [14,16] : Surgical correction should be considered in a patient with pain and a positive diuretic renogram. No therapy is necessary in an asymptomatic patient with a positive diuretic renogram but normal renal function. These patients often present as adults and have therefore had the partial obstruction for many years without apparent damage to the kidney. Hydronephrosis may be first noted after a radiologic study is done for some other reason or, as noted above, obstruction may be suspected when pain is induced after a period of high fluid intake leads to a diuresis that exceeds the rate at which urine can flow through the obstructed area. Similarly, the decreased washout observed on the renogram occurs only at a urine flow rate much higher than the patient is likely to achieve on his or her own. Periodic monitoring of renal function and renal parenchymal size (by ultrasonography) is indicated in these patients to exclude progressive renal injury. No therapy is indicated in an asymptomatic patient with a negative renogram. Long-term follow-up has demonstrated stable renal function in most of these patients. A perfusion pressure flow study should be performed in a symptomatic patient with a negative or equivocal diuretic renogram. Some nonrenal cause for the pain is probably present if the perfusion study is negative. On the other hand, a positive study is suggestive of obstruction and the need for surgical correction. A perfusion pressure flow study may also be performed in patients with hydronephrosis and poor renal function. The diuretic renogram may be falsely negative in this setting, because the diuretic may not sufficiently raise the urine flow.

In general, approximately 50 percent of patients with a positive diuretic renogram will eventually require surgery, either for pain or progressive parenchymal loss [16] .

#### Urinary tract obstruction

Renal ultrasonogram showing hydronephrosis due to urinary tract obstruction. The collecting structures (CS) are distended by fluid, rather than being closely bunched together as in the normal kidney. This study was performed in a renal transplant.

#### Normal renal ultrasound

Normal renal ultrasonogram showing the renal outline and the normal width of the renal parenchyma (RP) which is represented by the black area between the renal capsule and, in white, the collecting system (CS). The collecting system structures are closely bunched together.

#### Urinary tract obstruction

Intravenous pyelogram showing massive bilateral hydronephrosis and ureteral dilatation (arrow) due to urinary tract obstruction which, as shown in the next film, is due to ureterovesical obstruction. From Rose, BD, Pathophysiology of Renal Disease, 2d ed, McGraw-Hill, New York, 1987.

#### Urinary tract obstruction

Pelvic view of intravenous pyelogram showing bilateral ureterovesical junction obstruction (arrows) with proximal ureteral dilatation. From Rose, BD, Pathophysiology of Renal Disease, 2d ed, McGraw-Hill, New York, 1987.

## INFECTION URINAIRE DE L'ENFANT

L'infection urinaire (I.U.) est fréquente chez l'enfant. Elle touche plus fréquemment la fille que le garçon (3 pour 1) bien que cette proportion soit inversée chez le nouveau-né. Le diagnostic d'infection urinaire est affirmé par l'examen cyto-bactériologique des urines. L'imagerie joue un rôle essentiel au stade du bilan et en particulier le couple échographie - cystographie. Ce bilan sera différent s'il s'agit d'une infection urinaire haute (= pyélonéphrite) ou d'une infection urinaire basse (= cystite).

Dans 40 % des cas d'infections urinaires, il existe une lésion causale précise, facteur de risque de détérioration rénale et dans ce pourcentage de patients, il s'agit dans un cas sur deux d'un reflux vésico-urétéral.

En matière de reflux vésico-urétéral, il convient de distinguer le bilan initial surtout échographique et cystographique à valeur diagnostique et les bilans ultérieurs à visée pronostique ; l'échographie et la scintigraphie tiennent une place plus importante.

Toute infection urinaire haute ( ou supposée telle) doit être bilantée dès le premier épisode, qu'il s'agisse d'un garçon ou d'une fille. La néphropathie du reflux est d'autant plus sévère qu'il s'agit d'un enfant très jeune en pleine période de croissance rénale.

### 1. CLINIQUE

Le mode de présentation des infections urinaires est variable, surtout en fonction de l'âge de l'enfant.

#### 1.1. Chez le nouveau-né

A l'extrême il peut s'agir d'un syndrome septicémique, mais souvent on est en présence de vomissements ou d'un refus alimentaire. Il faut connaître la possibilité d'un ictère très trompeur.

#### 1.2. Chez le nourrisson

Un épisode fébrile mal expliqué est souvent le signe révélateur. Parfois des troubles digestifs avec en particulier une diarrhée ou une mauvaise croissance staturo-pondérale sont les seuls signes cliniques.

#### 1.3. Chez l'enfant plus grand

L'épisode fébrile isolé sans signe à l'examen est souvent encore le mode de révélation principal. Des signes d'accompagnements peuvent orienter vers une infection urinaire basse (dysurie, pollakiurie, troubles mictionnels, douleurs pelviennes). En revanche, une fièvre

élevée supérieure à 38, des douleurs lombaires ou abdominales, des urines troubles, doivent d'emblée faire penser à une infection urinaire haute (pyélonéphrite). Une hématurie se rencontre plus fréquemment dans les cystites.

*L'examen des bandelettes* réactives accompagne l'examen clinique, il permet de suspecter une infection urinaire s'il y a une réaction pour les leucocytes et les protéines. Cette réaction aux protéines est très forte dans les infections hautes. Celle des nitrites est présente dans les infections urinaires basses au contraire.

## 2. BIOLOGIE

Le diagnostic d'infection urinaire repose en définitive sur l'examen cyto-bactériologique des urines, sa valeur est d'autant plus décisive que le recueil des urines a été fait de façon stérile (ce qui n'est pas toujours facile, en particulier chez le nourrisson) et que l'analyse a été pratiquée rapidement après le prélèvement.

Pour affirmer une infection urinaire il faut :

- *une bactériurie* : égale ou supérieure à 100 000 germes par ml ;
- *une leucocyturie* : supérieure à 10 par ml ;
- *une culture bactérienne mono-germe*.

Le germe le plus souvent rencontré est *Eschérichia Coli*, vient ensuite le *Protéus*. Les infections à pyocyanique ou fongiques (*Candida*) se voient essentiellement en milieu hospitalier. La tuberculose urinaire est très rare à l'heure actuelle chez l'enfant.

Une culture mettant en évidence plusieurs germes évoque d'emblée une contamination des urines au moment du prélèvement ou une analyse trop tardive. Les faux positifs sont ainsi beaucoup plus fréquents que les faux négatifs.

L'examen cyto-bactériologique des urines (CBU) ne permet pas d'affirmer qu'il s'agit d'une infection urinaire haute ou d'une infection urinaire basse, bien que des protéines ou des sédiments en quantité élevée orientent vers une infection urinaire haute. Un bilan sanguin est justifié chez l'enfant très jeune ou quand l'état général est altéré. Une élévation des leucocytes, significative dans le sang, témoigne en principe d'une infection urinaire haute. Il en est de même d'une élévation de la VS, de la CRP.

Au terme de ce bilan clinique et biologique, il est généralement possible d'évoquer une infection urinaire haute (pyélonéphrite) ou une infection urinaire basse (cystite). Ce n'est pas toujours le cas chez l'enfant très jeune et dans ces conditions, il faut considérer jusqu'à preuve du contraire que l'on est en présence d'une infection urinaire haute.

La première urgence après le prélèvement urinaire est la mise en oeuvre du traitement antiseptique urinaire qui pourra être adapté après les résultats de l'antibiogramme. Le bilan étiologique n'est pratiqué qu'ensuite.

Compte tenu de l'importance prise par la diffusion des échographies anténatales, les uropathies avec dilatation des cavités excrétrices sont volontiers bilantées précocement après la naissance avant toute infection urinaire. Dans ces conditions, le bilan d'une infection

urinaire à l'heure actuelle est d'emblée axé sur la recherche d'un possible reflux vésico-urétéral qui bien souvent n'entraîne aucune dilatation pyélo-calicielle ou urétérale visible à l'examen échographique. Les formes les plus sévères sont souvent découvertes en anténatal. La cystographie rétrograde garde une place majeure dans le bilan initial des infections urinaires, car c'est le seul examen permettant avec fiabilité de mettre en évidence un reflux vésico-urétéral.

De part sa fréquence (14 à 35 % des infections urinaires avant la puberté), de part ses conséquences néfastes possibles sur la croissance rénale (néphropathie de reflux), le reflux vésico-urétéral mérite un chapitre particulier.

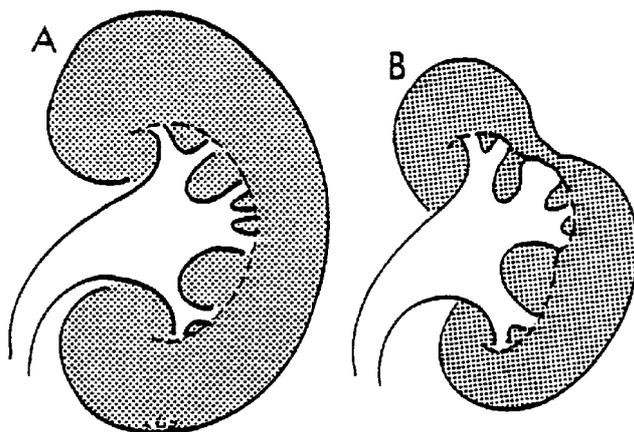
### 3. LE REFLUX VÉSICO-URÉTERAL

#### 3.1. La néphropathie du reflux

Il est généralement admis que l'infection des urines accroît considérablement le risque de détérioration rénale en présence d'un reflux vésico-urétéral et ce d'autant plus que l'enfant est plus jeune.

On considère que 10 % des enfants sains (sans infection urinaire) sont porteurs d'un reflux vésico-urétéral, et cela sans conséquence pour l'avenir.

La notion de néphropathie du reflux a été introduite assez récemment (BAILEY, 1973). Elle se définit macroscopiquement par une cicatrice segmentaire du parenchyme rénal avec atrophie du cortex, amincissement de la papille en regard et élargissement du calice correspondant (schéma 1). Ces lésions prédominent aux pôles rénaux et sont retrouvées électivement dans les zones où un reflux intra-rénal peut être mis en évidence par cystographie.



*Schéma 1 : Néphropathie du reflux. A - normal. B - néphropathie de reflux : encoche corticale en regard de la déformation calicielle.*

Il a été montré que dans le territoire touché, les papilles étaient des papilles dites composées, surtout polaires, avec des tubes collecteurs s'abouchant perpendiculairement à l'interface papillo-caliciel (fornix).

Bien que Hodson ait pu montrer qu'un reflux non infecté, sous haute pression, puisse être responsable de cicatrices pyélonéphritiques (théorie confirmée a priori par l'importance des lésions du parenchyme rénal au cours des reflux de grade élevé in utéro ?), il semble que l'infection urinaire ait un rôle nocif prépondérant pour créer ces cicatrices pyélonéphritiques. Celles-ci apparaissent dans les semaines qui suivent un épisode d'I.U. et sont irréversibles.

Les études histologiques laissent suggérer que d'autres facteurs interviennent aussi dans la survenue des lésions cicatricielles : zone rénale de dysplasie, d'hypoplasie corticale, de sclérose glomérulaire segmentaire et focale. Cela pourrait jouer un rôle important dans les lésions observées au cours de reflux de grade élevé in utéro. L'évolution pour leur propre compte de néphropathies du reflux après traitement correct du reflux et des infections (16 % des cas) souligne la complexité et la multiplicité des facteurs intervenant dans la néphropathie du reflux.

Il est donc essentiel de dépister et de traiter le plus précocement possible une infection urinaire qui peut être liée à un reflux vésico-urétéral.

Certains auteurs (Zerin) préconisent la réalisation systématique d'une cystographie rétrograde chez tous les nouveau-nés ayant présenté un élargissement même modéré ou transitoire des cavités excrétrices rénales in utéro. Il invite aussi à la mise en oeuvre d'un traitement antiseptique de principe lorsqu'un reflux vésico-urétéral est objectivé chez ces enfants quel qu'en soit le grade. Le caractère un peu lourd et irradiant de ce protocole fait qu'il est loin d'être accepté par tous à l'heure actuelle. En effet, on sait que bon nombre de reflux vont disparaître spontanément dans les premières années de vie et que dans bien des cas il n'y aura pas d'infection urinaire associée. De plus, cette étude n'est pas randomisée.

La règle actuelle est de bilancer soigneusement toute infection urinaire haute (ou supposée telle) dès le premier épisode, qu'il s'agisse d'un garçon ou d'une fille.

En cas de néphropathie du reflux, la fréquence de survenue d'une hypertension artérielle est de l'ordre de 20 % et il a été rapporté à la suite d'études internationales que 1,8 % à 15 % des insuffisances rénales chroniques sont en relation avec une pyélonéphrite chronique, conséquence de la néphropathie du reflux (cette proportion peut atteindre 24,7 % dans les insuffisances rénales chroniques survenant avant l'âge de 15 ans).

### **3.2. L'anomalie de la jonction urétéro-vésicale**

La plupart des reflux vésico-urétéraux sont dits primitifs, en relation avec une anomalie du bas uretère dans sa portion intra-pariétale vésicale, trop large, trop courte ou trop perpendiculaire à la paroi. Ce type d'anomalie plus fréquent chez la fille, peut être accentué ou favorisé par une légère ectopie d'implantation de l'uretère dans la vessie (en particulier sur l'uretère du pyélon supérieur d'une duplication complète), par des saculations ou un diverticule à proximité de la jonction urétéro-vésicale (diverticule de HUTCH - Figure 1), ou aussi sur l'uretère du pyélon inférieur en cas de duplication complète avec urétérocèle sur

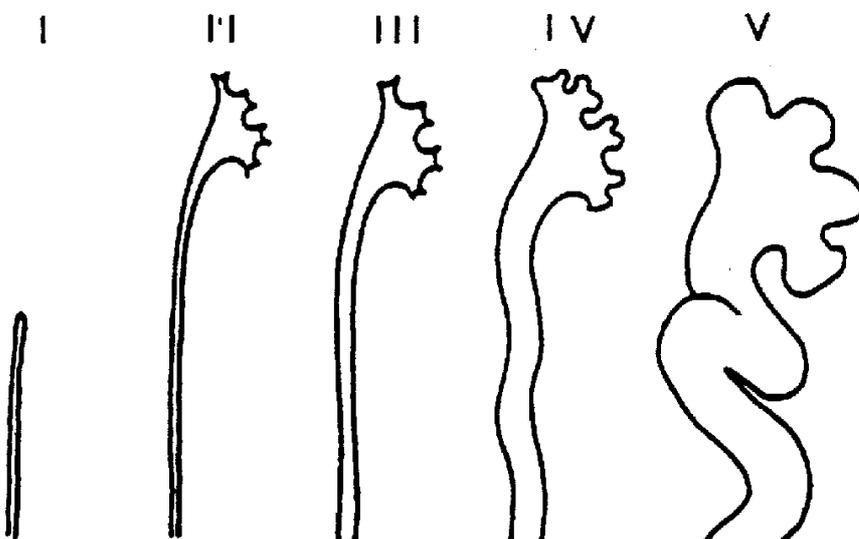
l'uretère du pyélon supérieur. Les reflux dits secondaires sont plus rares et surviennent en cas d'obstacle à l'évacuation vésicale (valve de l'urètre, vessie neurologique... ).



*Figure 1 : Diverticule para-urétéral de HUTCH avec reflux vésico-urétéral gauche de grade II*

Enfin certains reflux, en particulier chez la fille, sont en relation avec une instabilité vésicale qui peut être organique ou fonctionnelle.

La classification internationale du reflux (LEIBOWITZ, 1985) fait état de cinq grades de gravité croissante, à partir des données de la cystographie (schéma 2).



*Schéma 2 : Classification internationale du reflux.*

- **Grade I** : reflux purement urétéral, n'atteignant pas le bassinet ;
- **Grade II** : reflux atteignant les cavités pyélo-calicielles sans les élargir (Figure 5) ;
- **Grade III** : reflux avec élargissement pyélo-caliciel sans déformation significative ou permanente des fornix ;
- **Grade IV** : reflux avec tortuosité de l'uretère et dilatation permanente urétéro-pyélo-calicielle, déformation des fornix, mais avec persistance d'une certaine empreinte papillaire sur les calices ;
- **Grade V** : dilatation majeure de l'ensemble avec uretère tortueux et disparition de l'empreinte papillaire sur les calices (Figure 8).

Cette classification a le mérite d'exister pour fixer les idées entre correspondants, mais elle n'apparaît pas idéale, surtout dans les reflux de faible grade car elle ne tient pas compte d'éléments péjoratifs qui doivent toujours être soulignés : précocité d'apparition du reflux lors du remplissage, renforcement lors de la miction, hypotonie des cavités, présence de saculations ou de diverticules (Figure 1) à proximité de la jonction urétéro-vésicale, reflux intra-parenchymateux rénal (Figure 2) surtout qui peut être présent même avec un reflux de grade II.

De plus, malgré le caractère reconnu fiable de la cystographie, cet examen peut être faussement négatif et certains auteurs préconisent plusieurs remplissages successifs en laissant la sonde en place. D'autre par, un aspect de reflux de grade I peut n'être que transitoire et peut correspondre à un grade II lors d'un examen réalisé quelques jours plus tard. Il est recommandé de réaliser la cystographie à distance de l'infection urinaire (trois semaines) car celle-ci pourrait modifier transitoirement un reflux en l'amplifiant ou en le diminuant.



*Figure 5 : Cystographie à vessie vide, de face. Reflux vésico-urétéral droit de grade II. Bonne visibilité des fonctions urétéro-vésicales.*



*Figure 8 : Cystographie : reflux vésico-urétéral bilatéral de grade V. Uretères tortueux. Disparition de toute empreinte papillo-calicielle.*



*Figure 2 : Reflux vésico-urétéral bilatéral de grade IV avec reflux intraparenchymateux rénal bien visible à gauche.*

Enfin, la cystographie radiologique ne permet pas une étude permanente du remplissage et de la vidange et peut donc méconnaître un reflux fugace.

Rappelons pour finir qu'un reflux n'est pas immuable dans le temps, qu'il peut s'amplifier ou à l'inverse diminuer et disparaître. Ainsi, 80 % des reflux de grade I ou II vont disparaître spontanément. Ce pourcentage tombe à 50 % pour les reflux de grade III et à 30 % pour les reflux de grade IV.

Dans quelques cas, le reflux vésico-urétéral peut être associé ou se compliquer de sténose de la jonction urétéro-vésicale.

## **4. LES MÉTHODES DU BILAN**

### **4.1. L'échographie**

Cette méthode non invasive est réalisée en première intention dès que l'on recherche une pathologie de l'appareil urinaire. Elle permet une étude morphologique des cavités pyélo-calicielles, des reins, (Figure 3) de la vessie et des bas uretères. Elle est largement insuffisante en revanche pour l'étude des uretères lombaires et de l'urètre (malgré un abord possible par voie périnéale).

Il faut toujours commencer par l'étude du pelvis chez le très jeune enfant car la miction peut être très rapide après pose du gel et de la sonde, afin de ne pas méconnaître certaines anomalies du bas appareil urinaire (dilatation des uretères pelviens, urétérocèle...).



*Figure 3 : Duplication rénale, le bassin est barré par une colonne de BERTIN, hypertrophie d'aspect pseudo-tumoral*

L'échographie n'apparaît pas fiable pour la recherche d'un reflux vésico-urétéral, même si des études ont été poussées dans le sens du Doppler couleur et de la cysto-échographie avec des micro-bulles d'air.

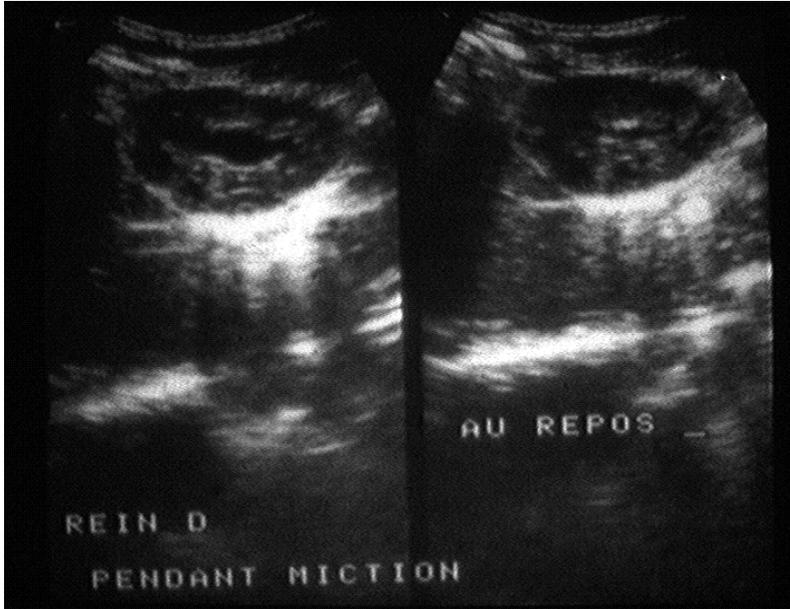
En présence d'un reflux vésico-urétéral, l'échographie peut être strictement normale (c'est assez souvent le cas), même en présence d'un reflux de grade II (voire III). Par ailleurs, il existe un flou dans l'appréciation des limites du normal pour les dimensions du bassin en fonction de l'âge de l'enfant et du degré de dilatation. Un élargissement même discret des tiges caliciformes est en principe anormal chez un enfant à jeun.

Tous les intermédiaires peuvent se voir en cas de reflux entre l'aspect normal et la dilatation urétéro-pyélocaliciforme majeure. Une variation de calibre du bassin en cours de miction est un argument présomptif en faveur du reflux (Figure 9).

L'échographie apprécie de façon imparfaite les cicatrices corticales modérées. En période d'infection urinaire on peut observer un épaississement de la paroi de la vessie très net quand il s'agit d'une cystite.

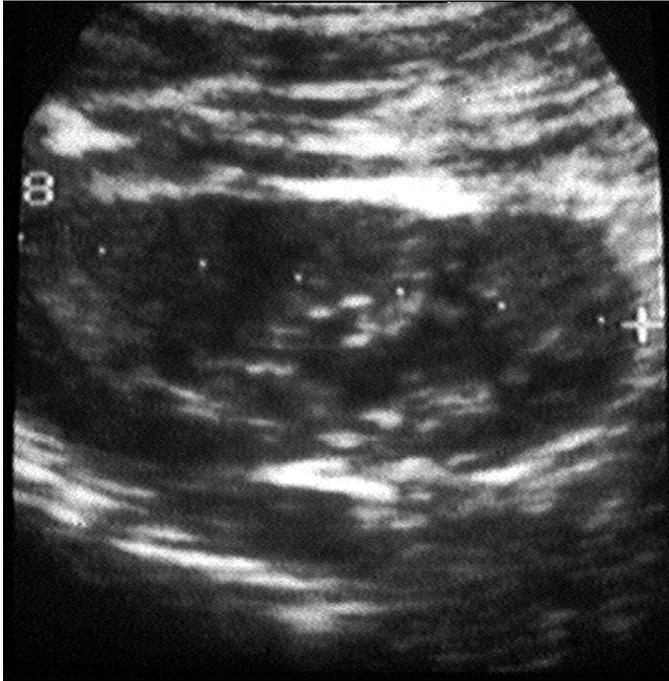
Parfois un discret épaississement de la paroi des cavités pyélo-caliciformes peut être observé dans les infections urinaires hautes avec éventuellement des échos fins dans les urines voire une hyper-échogénicité anormale des pyramides de Malpighi dans des cas très rares.

La néphrite focale bactérienne (Figure 4) correspond à un stade de pré-abcédation local. Elle se traduit par une plage parenchymateuse assez bien délimitée, plutôt hypo-échogène et pouvant prendre un caractère hyper-échogène en cas de saignement dans ce territoire. Il est très rare avec le traitement antibiotique instauré précocement de voir apparaître maintenant des abcès rénaux correspondant à une collection franche .

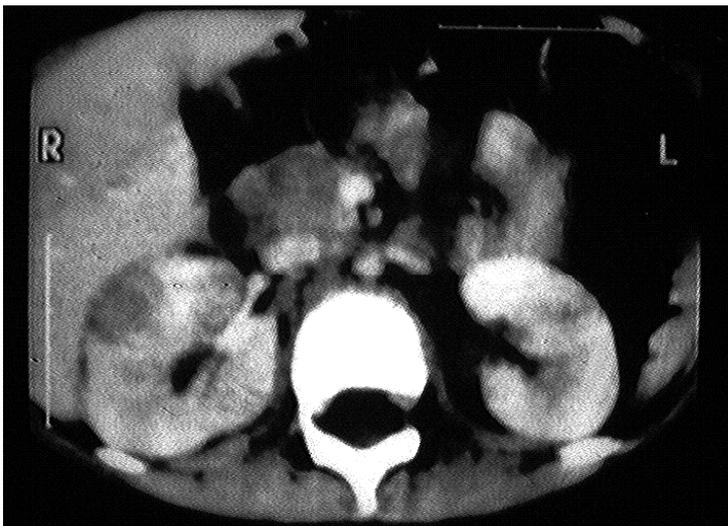


*Figure 9 : Reflux vésico-urétéral suspecté lors de l'échographie au repos et en cours de miction (élargissement transitoire du bassinet).*

*Figure 4 : Néphrite focale bactérienne du rein droit*



*4 a : Echo : lésion rénale périphérique hypo-échogène*



*4 b : TDM : hypodensité droite correspondante par rapport au parenchyme normal prenant le contraste*

#### **4.2. Cystographie**

Avec l'échographie, elles forment le couple essentiel pour l'exploration en pratique courante d'une infection urinaire.

Deux méthodes peuvent être utilisées : la cystographie radiologique et la cystographie isotopique.

- *La cystographie radiologique* : est généralement pratiquée par voie rétrograde avec une sonde mise en place dans la vessie. La voie sus-pubienne en principe est réservée aux patients présentant un obstacle sous vésical, mais certains la pratiquent assez systématiquement chez les très jeunes garçons (moindre risque infectieux ?).

Cette cystographie permet la recherche d'un reflux vésico-urétéral, mais aussi elle permet une excellente étude de l'urètre et du comportement de la vessie au cours du remplissage et de la miction.

A côté de la méthode classique de miction interrompue avec des clichés comportant des incidences de profil et des deux trois quarts, nous préférons (sauf cas très particulier) la cystographie dite "à vessie vide" (DEFFRENNE), des clichés en série sont pris uniquement de face chez la fille (Figure 5) et uniquement sous le même trois quart oblique chez le garçon, sans interrompre la miction. Les clichés en fin de miction (à vessie vide) sont déterminants pour apprécier au mieux les jonctions urétéro-vésicales. Cette méthode est aisée quand on dispose d'une table de fluoroscopie numérisée et de plus elle est peu irradiante.

Dans les cystites avec vessie instable, on observe volontiers un aspect crénelé de la paroi vésicale et un urètre en toupie chez la fille (Figure 6).

Lors des clichés mictionnels chez le garçon, on peut observer des variantes du normal sur l'urètre (Figure 7) : opacification des glandes de Cowper ou d'un petit utricule prostatique, empreinte du muscle nuda au dessus du verum montanum.



Figure 6 : Instabilité vésicale chez une fille. Cystographie : Urètre en toupie.



Figure 7 : Urètre de garçon, variante du normal  
. glandes de Cowper (en arrière de l'urètre bulbaire)  
. utricule prostatique (en arrière de l'urètre prostatique)

- *La cystographie isotopique* : elle permet une étude continue et elle est peu irradiante (jusqu'à 50 fois moins irradiante qu'une cystographie classique non numérisée). Malgré tout, elle renseigne assez mal sur le bas appareil urinaire et sa valeur anatomique est bien inférieure à celle d'une cystographie radiologique.

La tendance actuelle est de conserver la cystographie radiologique lors du bilan initial et de donner une plus large place à la cystographie isotopique pour les explorations de contrôle ultérieurement.

#### 4.3. Urographie intraveineuse

Bien qu'elle offre une excellente analyse des cavités excrétrices rénales et qu'elle permet mieux que l'échographie de déceler des cicatrices corticales (Figure 10) ou une duplication sans dilatation, cet examen ne trouve plus sa place qu'en deuxième intention. Sa valeur pour l'appréciation de la valeur fonctionnelle des reins est limitée.

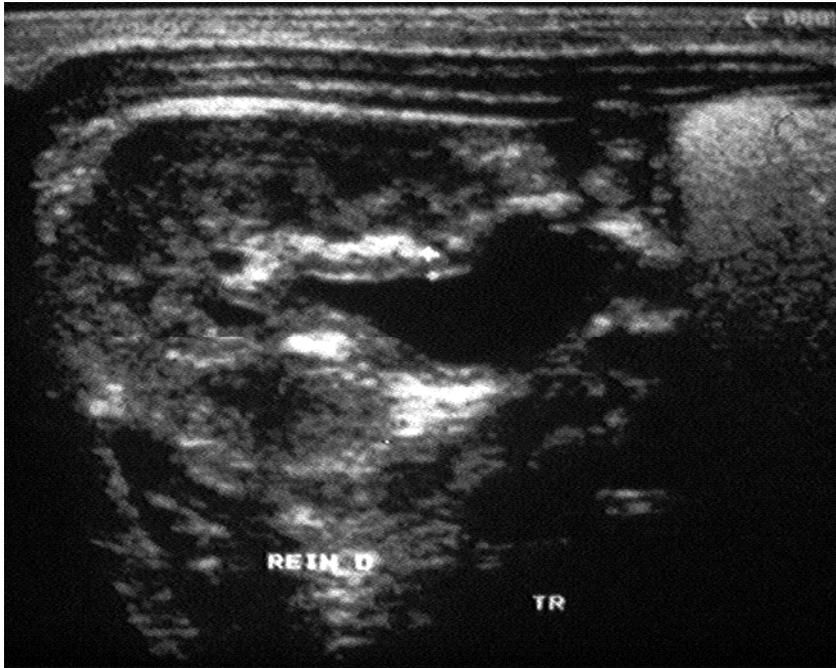
Elle est souvent demandée pour mieux préciser une pathologie urinaire complexe ou importante dépistée par échographie, mais aussi en pré-opératoire quand une indication chirurgicale est retenue.

En présence d'un reflux vésico-urétéral elle est rarement demandée en dessous d'un grade III. Si l'UIV est réalisée précocément après l'infection urinaire, on peut observer une hypotonie des cavités pyélo-urétérales avec un aspect de striation longitudinale (urétérite striée) (Figure 11).



*Figure 10 : Néphropathie du reflux : déformation calicielle en fleur fanée et encoche corticale en regard*

*Figure 11 : Infection urinaire avec pyélite au stade aigu.*



*Figure 11 a : UIV : pyélite striée*



*Figure 11 b : Echo : élargissement de la paroi du bassin*

#### **4.4. Explorations isotopiques rénales**

- *DTPA* : il permet d'étudier l'excrétion rénale et donne un urogramme isotopique de faible irradiation. L'adjonction d'une épreuve au LASILIX autorise une bonne appréciation du caractère organique ou non d'une stase urinaire.
- *DMSA* : il donne une image morphologique et fonctionnelle séparée des deux reins. Son irradiation n'est pas négligeable et se rapproche de celle d'une urographie à minima. Il manque de spécificité pour distinguer une atteinte parenchymateuse aiguë segmentaire d'une zone cicatricielle en présence d'une plage d'hypofixation (le glucoheptonate de technecium fournit des résultats proches avec une moindre irradiation).
- *leucocytes marqués* (au Gallium ou à l'Indium) : méthode utilisable pour mettre en évidence un foyer infectieux en cas de doute.
- *MAG III* : renseigne aussi bien sur des données d'ordre fonctionnel que morphologiques par sa fixation tubulaire et son excrétion urinaire.

D'une façon générale, les explorations isotopiques rénales trouvent surtout des indications dans le bilan pronostique d'une infection urinaire et sont assez peu utilisées en France dans leur bilan initial.

#### **4.5. Tomodensitométrie**

Bien supérieure à l'échographie pour objectiver une atteinte rénale aiguë localisée, elle n'est jamais pratiquée en première intention du fait de sa lourdeur et de son irradiation.

Elle est surtout utile pour préciser ou confirmer une suspicion échographique de néphrite focale bactérienne (Figure 4), voire un abcès ou une collection péri-néphrétique.

#### **4.6. Autres investigations**

Dans le bilan des cystites à répétition, il peut être justifié de réaliser une cystomanométrie voire une étude de la moelle épinière par échographie ou IRM selon l'âge de l'enfant.

## **5. BILAN DES INFECTIONS URINAIRES**

Le bilan initial (diagnostique) diffère avec l'âge de l'enfant, avec la gravité des signes cliniques et la suspicion d'infection urinaire haute ou d'infection urinaire basse.

### **5.1. Infection urinaire haute (pyélonéphrite)**

#### **5.1.1. Infection urinaire haute d'un enfant de moins de un an**

Une hospitalisation est souhaitable pour mettre en oeuvre un traitement efficace le plus vite possible, l'échographie est réalisée d'emblée.

Si un obstacle est suspecté lors de cette échographie, il est réalisé une urographie intra-veineuse (ou une scintigraphie rénale plus ou moins LASILIX) et une cystographie.

Si l'échographie est normale ou presque, ou qu'elle est compatible avec un reflux vésico-urétéral, il est pratiqué une cystographie radiologique après désinfection des urines.

*En cas de reflux vésico-urétéral :*

- de grade I ou II : instauration d'un traitement antiseptique urinaire pendant 6 mois puis contrôle échographique et cystographie radiologique.
- de grade III ou plus : traitement volontiers chirurgical avec cystographie radiologique de contrôle à trois mois.

#### **5.1.2. Infection urinaire haute d'un enfant plus grand**

On réalise une échographie et une cystographie au bout de 3 à 4 semaines lorsque les urines sont désinfectées.

*En cas de reflux :*

- de grade I ou II : traitement médical pendant 6 mois puis contrôle échographique et cystographique (isotopique de préférence).
- de grade III ou plus : faire une urographie intra-veineuse (plus ou moins scintigraphie rénale).

Le traitement peut être endoscopique (Téflon ou analogue), ou chirurgical.

#### **5.1.3. Bilan à distance**

L'étude de la croissance rénale sera faite par :

- échographie (une par an jusqu'à 5 ans)
- scintigraphie rénale

L'étude la fonction rénale sera faite par :

- isotopes
- clearance, tension artérielle

## **5.2. Infection urinaire basse**

### **5.2.1. Cystite isolée**

Pas de bilan s'il n'y a pas de trouble de la miction.

### **5.2.2. Cystites à répétition ou avec troubles de la miction**

telles que énurésie, mictions impérieuses, pollakiurie.

Faire une échographie (étude des reins, de la vessie avec recherche d'un épaissement de sa paroi et d'un résidu) ainsi qu'une cystographie radiologique.

Un reflux vésico-urétéral (non chirurgical) de faible grade est trouvé dans 20 % des cas.

S'il existe une dysurie (jet faible et poussée abdominale) on réalisera une cystomanométrie.

En l'absence de dysurie, un traitement d'épreuve (DITROPAN) est mis en oeuvre. S'il est sans effet, une cystomanométrie s'impose.

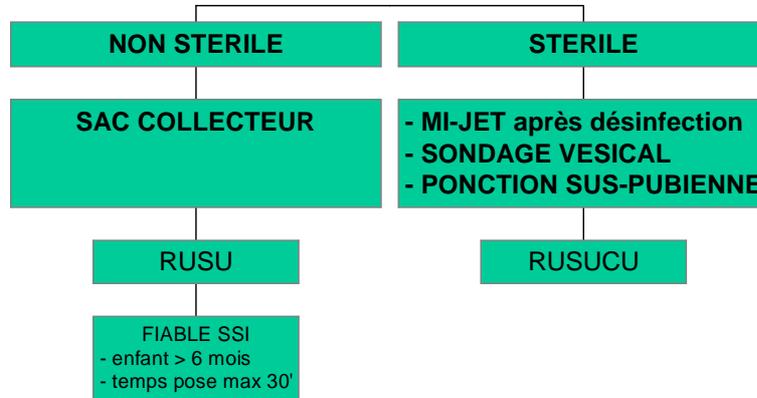
## **6. AU TOTAL**

L'infection urinaire est courante chez l'enfant et elle représente une des indications les plus fréquentes d'examen d'imagerie à cet âge.

Le reflux vésico-urétéral en est la cause la plus classique et il doit être recherché de principe du fait des risques évolutifs d'une néphropathie du reflux dont la menace est d'autant plus importante qu'il s'agit d'un enfant très jeune.

Le bilan initial repose essentiellement sur l'échographie et la cystographie rétrograde.

## Technique de prélèvement



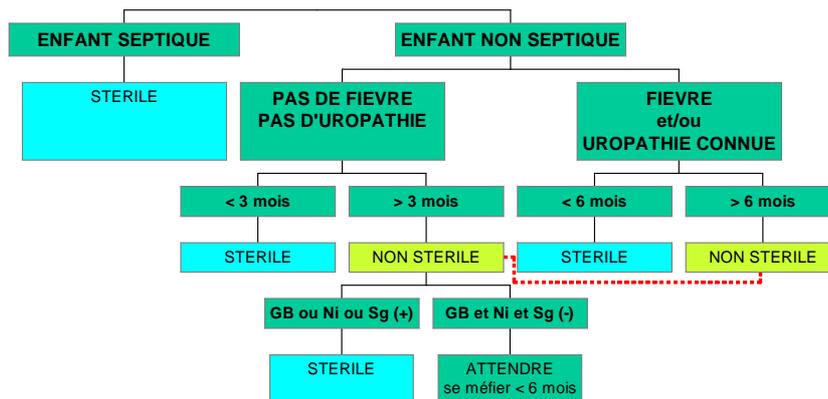
## SAC COLLECTEUR

- **Utile** pour RUSU chez enfant non propre (!  
Ne pas cocher CU !) ssi
  - > 3 mois sans fièvre ni uropathie connue
  - > 6 mois
- **Inutile** chez enfant non propre si
  - < 3 mois, avec ou sans fièvre
  - < 6 mois, avec fièvre ou uropathie connue
  - Enfant septique

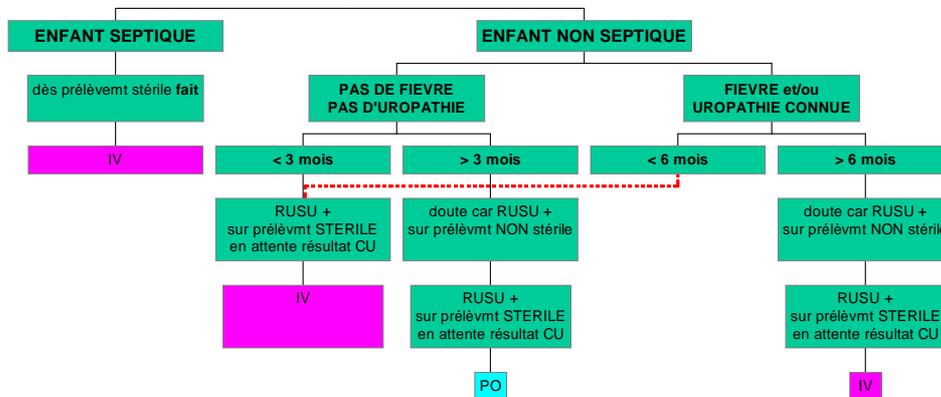
## Prélèvement stérile

- **Urine au mi-jet**
  - Après désinfection par une infirmière
- **Sondage vésical**
  - Chez fille
  - Chez garçon ssi expérimenté, par docteur
- **Ponction sus-pubienne**

## Technique de prélèvement



## Quand et comment traiter?



## Quelle antibiothérapie?

- **PO**
    - TMP-SMX 40/8 mg/Kg en 2x
    - ou amoxy.clav. 40 mg/Kg en 3x
  - **IV**
    - Amoxy-clav. 100 mg/Kg en 4x + 75 mg/Kg d'amoxicilline en charge pour 1ère dose si septique\*
    - Amukin 20 mg/Kg en 15-30', idéalement 30' après fin amoxy.clav.
- \*Choc septique et/ou méningite : Claforan+amukin +ampi (< 1mois)

## Durée antibiothérapie

- PO : 7 jours
- IV : Amoxy-clav. (*adapter selon antibiogramme pour spectre le <*)
  - < 1 mois : 10 j
  - > 1 mois, pas d'uropathie ni IRC :
    - jusqu'à 24h apyrexie
  - > 1 mois, uropathie et/ou IRC :
    - jusqu'à 48h de CRP (-)
  - Quand relais oral : 14 j au total (IV + PO)
  - Abscès rénal : min. jusqu'à 48h CRP (-), durée totale 6 semaines (avis néphropédiatre)

## Amukin : combien de doses?

- < 1 mois
  - 3 doses minimum
  - 5 doses si sepsis ou germe non identifié
- > 1 mois
  - 2 doses
  - 3 doses si post-op uro. si germe tjrs ? (pyo?)
- **Pyocyanique, qq soit l'âge**
  - 10 jours
- Reprise amukin à discuter si **abcès rénal**

## explorations

- **Enfants traités PO**
  - Échographie dans la semaine
- **Enfants traités IV**
  - Échographie dans les 48h (dilatation, obstacle?)
  - Biologie (SC, CRP, urée, créatinine, ions, pH)
  - Hémoculture si < 3 mois et fièvre
  - Ponction lombaire si < 1 mois et fièvre (3m si symptômes)
  - Prévoir DMSA dans la semaine

## Suivi immédiat enfant traité IV

- Contrôle CRP si
  - Persistance de la fièvre > 48h
  - Critère d'arrêt du tt IV (uropathie, IRC)
- Pic amukin (1h après perfusion)
  - Si > 3 doses prévisible
    - Enfant < 1 mois
    - Pyocyannique prouvé ou craint (post-op uro)
  - À répéter tant que pas optimal (> 35 µg/mL)
  - Après la 2<sup>ème</sup> dose

## Suivi immédiat enfant traité IV

- Vallé amukin : < 2 µg/mL
  - Toujours si > 3 doses prévisibles
    - < 1 mois
    - Pyocyanique
  - Avant la 2<sup>ème</sup> dose
  - À répéter tant que l'intervalle doit être modifié
- CU de contrôle ssi
  - Cystographie envisagée pendant hospitalisation
  - Infection à pyocyanique
  - Mauvaise évolution clinique

## Suivi ultérieur enfant traité IV

- Conseils « hygiène »; lever constipation
- Cystographie : **tous**
  - possible dès 48h apyrexie mais non urgente
  - Pendant ⊕ si compliance ?
  - Si prévue après fin traitement
    - Couvrir par prophylaxie « comme si RVU+ »
    - Doubler la dose la veille et le jour de l'examen
    - TMP ou furadantine 1 mg/Kg 1 ou 2 x/j si propre ou pas
    - ou clamoxyl 25 mg/Kg en 2x (< 1 mois)
- Proposer consultation néphro-pédiatre
- DMSA (si +) à 6-9 mois : cicatrice ?

## **Long-term management and prevention of urinary tract infections in children**

**INTRODUCTION** — Urinary tract infections (UTI) are a common and important clinical problem in childhood. Upper urinary tract infections (ie, acute pyelonephritis) may lead to renal scarring, hypertension, and end-stage renal dysfunction. Although children with pyelonephritis tend to present with fever, it is often difficult on clinical grounds to distinguish cystitis from pyelonephritis, particularly in young children (those younger than 2 years) [1] . Thus, we have defined UTI broadly here without attempting to distinguish cystitis from pyelonephritis. Acute cystitis in older children is discussed separately. (See "Acute cystitis in children older than two years and adolescents").

The long-term management and prevention of UTI in children will be reviewed here. The epidemiology, risk factors, clinical features, diagnosis, acute management, and prognosis of UTI in children and UTI in newborns are discussed separately. (See "Epidemiology and risk factors for urinary tract infections in children" and see "Clinical features and diagnosis of urinary tract infections in children" and see "Acute management, imaging, and prognosis of urinary tract infections in children" and see "Urinary tract infections in newborns").

### **LONG-TERM MANAGEMENT**

**Recurrent symptoms** — Approximately 8 to 30 percent of children with UTI experience one or more symptomatic reinfections [2-5] , usually within the first six months after the initial UTI. Breakthrough UTI are most common in girls [6] .

Progression of renal scarring is associated with recurrent episodes of pyelonephritis [7-10] . Prompt diagnosis and treatment of these infections is critically important in reducing renal scarring [2,11,12] .

In a study comparing oral and intravenous therapy, parents of young children with UTI were instructed to immediately seek care if their child had unexplained fever or urinary symptoms [2] . Eight percent of children had recurrence of UTI, but none suffered from additional renal scarring.

Families of young children with UTI should receive instruction about the risk of recurrent UTI and be advised to seek medical attention promptly for fever and/or urinary symptoms [13] . The evaluation of these episodes should include urinalysis, urine culture, or both [1] . (See "Clinical features and diagnosis of urinary tract infections in children", section on Laboratory evaluation).

**Children with VUR** — The long-term management and follow-up of children with vesicoureteral reflux (VUR) is discussed separately. (See "Management of vesicoureteral reflux").

**Children with dysfunctional voiding** — An important task in the management of children with UTI, especially those with recurrent UTI, is to address underlying voiding dysfunction, if present. Treatment of voiding dysfunction decreases UTI recurrence (and is associated with faster resolution of VUR) [14-16] . (See "Management of voiding dysfunction in children").

Treatment of voiding dysfunction should be initiated by the primary care provider. The first steps in the treatment of voiding dysfunction include timed voiding (scheduled voids every

two to three hours) and/or the use of laxatives for children with constipation [17] . In chronically constipated children, treatment with laxatives has been shown to significantly reduce UTI recurrence [18] .

Referral to a urologist for further management (pelvic floor muscle training with biofeedback, anticholinergics) is recommended if the patient's symptoms do not respond to the initial management.

**PREVENTION OF RECURRENT UTI**— To prevent renal scarring, risk factors for subsequent infection must be addressed. The discussion below focuses on prevention of recurrent UTI in children who do not have VUR, urinary obstruction, or dysfunctional elimination. The management of VUR and dysfunctional elimination are discussed elsewhere. (See "Management of vesicoureteral reflux" and see "Children with dysfunctional voiding" above).

**Surveillance cultures** — We do not suggest routine surveillance cultures for asymptomatic children after their first UTI. In a study comparing oral and intravenous antibiotics for UTI in children, routine surveillance of asymptomatic children with monthly urine studies was not associated with a better long-term outcome [2] . In addition, the benefit of treatment in patients who have bacteriuria without symptoms is unproven, and potentially harmful [13,19] . (See "Clinical features and diagnosis of urinary tract infections in children", section on Asymptomatic bacteriuria).

**Prophylaxis** — Children with recurrent febrile UTI may be candidates for low-dose, long-term antimicrobial therapy. Systematic reviews of studies evaluating this issue concluded that the quality and size of the primary studies precluded any conclusions regarding the efficacy of antimicrobials for the prevention of UTI [20-22] .

Two of the systematic reviews found some evidence that long-term antibiotics reduced the risk of recurrent positive urine culture, but not the risk of recurrent symptomatic UTI [21,22] . Although nitrofurantoin was more effective than trimethoprim sulfamethoxazole (TMP-SMX) in preventing recurrence, it was associated with more adverse effects (nausea, vomiting, stomach ache).

We suggest antimicrobial prophylaxis with TMP-SMX or nitrofurantoin for 6 to 12 months in children with recurrent febrile UTI in whom other treatment options have been ineffective. Antimicrobial prophylaxis can be discontinued if no infection occurs during the period of prophylaxis; if infection recurs, resumption of prophylaxis may be warranted [13] .

The use of prophylactic antibiotics in children with VUR is discussed separately. (See "Management of vesicoureteral reflux").

**Cranberry juice** — A systematic review found some evidence that cranberry juice (or cranberry-ligonberry juice) is effective in preventing symptomatic UTI recurrence in healthy women compared to placebo (RR 0.61 95% CI 0.4 to 0.9) [23] . This finding has not been confirmed in children.

Although cranberry juice has not been proven to be beneficial in children with recurrent UTI, it is unlikely that cranberry juice in moderation is harmful.

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "Patient information: Urinary tract infections in children"). We encourage you to print or e-mail this topic, or to refer patients to our public web site [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

**SUMMARY AND RECOMMENDATIONS** Families of young children with urinary tract infection (UTI) should receive instruction about the risk of recurrent UTI and be advised to seek medical attention promptly for fever and/or urinary symptoms. (See "Recurrent symptoms" above and see "Epidemiology and risk factors for urinary tract infections in children", section on Risk factors for renal scarring). The evaluation for episodes of fever and/or urinary symptoms should include urinalysis, urine culture, or both. (See "Clinical features and diagnosis of urinary tract infections in children", section on Laboratory evaluation). The long-term management and follow-up of children with vesicoureteral reflux is discussed separately. (See "Management of vesicoureteral reflux"). The treatment of voiding dysfunction may include timed voiding, the use of laxatives, and/or referral to a urologist. (See "Children with dysfunctional voiding" above). We suggest not obtaining routine surveillance cultures in asymptomatic children after their first UTI (Grade 2C). (See "Surveillance cultures" above). We suggest antimicrobial prophylaxis to prevent recurrent UTI in children in whom other treatment options have been ineffective (Grade 2B). Trimethoprim sulfamethoxazole or nitrofurantoin may be used for prophylaxis. (See "Prophylaxis" above). Prophylactic antibiotics are usually continued for 6 to 12 months. They can be discontinued if no infection occurs during the period of prophylaxis. Resumption of prophylaxis may be warranted if infection recurs. (See "Prophylaxis" above). Regular ingestion of cranberry juice may be helpful in the prevention of recurrent UTI in children, and is unlikely to be harmful. (See "Cranberry juice" above).

## **Prehypertension and borderline hypertension**

**INTRODUCTION** — Long-term follow-up of patients destined to develop essential (primary) hypertension demonstrates that blood pressure (BP) readings gradually increase over time. They may initially be normal, then prehypertensive (or high-normal), and then intermittently elevated; however, the readings may show considerable variability or lability [1]. The term "labile" hypertension should not be used, but "borderline" hypertension may be appropriate for those patients with some values below 140/90 mmHg.

**DEFINITIONS** — The seventh report of the Joint National Committee (JNC 7) proposed a new definition of BP values below 140/90 from that of JNC 6 [2]. Based upon the average of two or more readings at each of two or more visits after an initial screen, the following classification was proposed in JNC 7 [1]: Normal blood pressure — systolic <120 mmHg AND diastolic <80 mmHg Prehypertension — systolic 120 to 139 mmHg OR diastolic 80 to 89 mmHg

Since many studies used the definitions from JNC 6, it is useful to compare the differences. The normal category was called optimal blood pressure in JNC 6 and the prehypertension category combines the normal and high-normal categories in JNC 6 [3]. Thus, in JNC 6, the following categories were defined: Optimal blood pressure — systolic <120 mmHg and diastolic <80 mmHg Normal blood pressure — systolic 120 to 129 mmHg and diastolic 80 to 84 mmHg High-normal blood pressure — systolic 130 to 139 mmHg or diastolic 85 to 89 mmHg

In children, high-normal blood pressure is defined as  $\geq$  90th but less than the 95th percentile for age, sex, and height. (See "Definition and diagnosis of hypertension in children and adolescents").

By comparison, the 2007 guidelines for the management of hypertension from the European Societies of Hypertension and Cardiology defined optimal, normal, and high-normal blood pressure categories similarly as those recommended in JNC 6 [4]. Among other reasons, the task force thought that the normal and high-normal categories were too heterogeneous to justify combining them into one prehypertension category.

**Prevalence** — Data from the 1999 and 2000 National Health and Nutrition Examination Survey (NHANES III) suggested that the prevalence of prehypertension among adults in the United States was approximately 31 percent [5]. The prevalence was markedly higher among men than women (39 and 23 percent, respectively).

**CARDIOVASCULAR RISK** — Multiple epidemiologic studies have demonstrated the increase in cardiovascular risk in patients with prehypertension and borderline hypertension: The Framingham Heart Study examined the risk of cardiovascular disease at 10 year follow-up among subjects with high-normal blood pressure at baseline examination [6]. After adjustment for cardiovascular risk factors and when compared to those with optimal blood pressure, the hazard ratios for a cardiovascular event at 10 years for those with high-normal values (130 to 139/85 to 89 mmHg) were 2.5 and 1.6 for women and men, respectively (show figure 1). An increased hazard ratio was also observed in those with normal values (120 to 129/80 to 84 mmHg) compared with participants with optimal (called normal in JNC 7) blood pressures (<120/<80 mmHg). A subsequent analysis of data from the Framingham Heart

Study demonstrated that relative to blood pressure <120/80 mmHg, prehypertension (120 to 129/80 to 84 mmHg) was associated with an increased risk of myocardial infarction (relative risk 3.5) and coronary artery disease (relative risk 1.7), but not stroke [7] . In the Women's Health Initiative study involving over 60,785 postmenopausal women who were followed for 7.7 years, women with prehypertension, compared to normotensive individuals, had an increased risk of cardiovascular death (HR 1.76, 95% CI 1.40 to 2.2), myocardial infarction (1.93, 95% CI 1.49 to 2.50) and stroke (1.36, 95% CI 1.05 to 1.77) [2] .

Patients with prehypertension appear to have a greater prevalence of traditional cardiovascular risk factors than those with normal blood pressures. Based upon data from the 1999 to 2000 NHANES, the presence of at least one adverse risk factor (above-normal cholesterol levels, overweight/obesity, and diabetes mellitus) was significantly more likely among prehypertensive than normotensive individuals (RR of 1.65) [5] .

However, the increase in cardiovascular risk associated with prehypertension cannot be explained entirely by a higher prevalence of other cardiovascular factors. This was illustrated in a substudy of the Strong Heart Study, in which the risk of incident cardiovascular events at 12 years was higher in patients with prehypertension and diabetes than in those with either risk factor alone [8] .

There also appears to be an association between prehypertension and microalbuminuria, a risk factor for cardiovascular disease and early cardiovascular mortality. Based upon data from NHANES III and using the 1997 JNC 6 definitions, an increased incidence of microalbuminuria was observed among individuals with high-normal blood pressure (now called prehypertension) compared to those with optimal blood pressure (odds ratio of 2.1) [8] . (See "Microalbuminuria and cardiovascular disease").

**PROGRESSION TO SUSTAINED HYPERTENSION** — As a result of the rise in BP with time, the incidence of hypertension increases from approximately 10 percent at age 30 to 30 percent at age 60. A rise in BP with aging is relatively common in normotensive subjects [9] .

**Predictors** — The rate at which new onset hypertension occurs varies importantly with the blood pressure at baseline. The magnitude of this effects is illustrated by the following observations: A report from the Framingham Heart Study examined the incidence of hypertension (defined as blood pressure greater than 140/90 mmHg or use of antihypertensive agent) over a four year period among patients who initially had optimal (less than 120/80 mmHg), normal (120-129/80-84 mmHg) or high-normal (130-139/85-89 mmHg) blood pressures [10] . A progressive increase in the frequency of development of hypertension was observed in these three groups; 5, 18, and 37 percent, respectively, under age 65; and 16, 26, and 50 percent, respectively in older subjects.

A later report from the Framingham Heart Study estimated that individuals age 55 to 65 who do not have hypertension have a lifetime risk of developing hypertension (mostly mild) of approximately 90 percent [11] . The differential incidence of isolated diastolic (IDH, diastolic blood pressure greater than 90) and isolated systolic (ISH, systolic blood pressure greater than 140) was examined in another report from the Framingham Heart Study with a mean follow-up time of 10 years [12] . Patients started on antihypertensive therapy were censored. Among patients who initially had optimal (less than 120/80 mmHg), normal (120-129/80-84 mmHg) or high-normal (130-139/85-89 mmHg) blood pressures, the incidence of new onset IDH was 3, 8 and 10 per 1000 person-years at risk, and the incidence of ISH was 6, 23 and 35 per 1000

person-years at risk. The incidence of SDH was intermediate. (See "Hypertension: Who should be treated?").

Framingham risk score — The identification of prehypertensive patients who are at greatest risk for progression to hypertension may allow for more intensive targeted therapy to prevent or delay the onset of hypertension. Using data from the Framingham Heart Study, a risk calculator has been developed to estimate the risk of developing hypertension [13]. Clinical variables including age, blood pressure, body mass index (all continuous variables), sex, family history of hypertension, and smoking predict the development of hypertension in nondiabetic individuals. The most important predictors were higher blood pressure and older age.

The four-year risk of developing hypertension was classified as low (less than 5 percent) in 34 percent, medium (5 to 10 percent) in 19 percent, and high (more than 10 percent) in 47 percent. The utility of this risk calculator in diabetic patients and in nonwhite cohorts remains to be tested.

Preventive therapy — The TRial of Preventing HYpertension (TROPHY) study examined whether therapy in patients with prehypertension may prevent progression to clinical hypertension [14]. In this four year trial, 806 patients with systolic blood pressures of 130 to 139 mmHg and/or diastolic pressures of 85 to 89 mmHg were randomly assigned to two years of therapy with either placebo or candesartan (16 mg/day). After two years, patients continued therapy with placebo for another two years. Baseline blood pressure, body mass index, and plasma creatinine and lipid concentrations were similar in the two groups.

The main outcome measure was the development of hypertension, defined as average blood pressure  $\geq 140/90$  mmHg at any three clinic visits, any single reading  $\geq 160/100$  mmHg, use of antihypertensive medications, or blood pressure  $\geq 140/90$  mmHg at the four-year visit. The following significant benefits were noted with candesartan therapy, although there were important limitations [15]: A lower rate of hypertension at some point during the two years of active therapy (14 versus 40 percent with placebo). This cannot be considered an effect on the natural history of prehypertension since one would expect lower blood pressures with antihypertensive therapy. At four years, the rate of hypertension was significantly lower in treated patients (53 versus 63 percent). However, this was driven by a lower proportion of patients with blood pressure  $\geq 140/90$  mmHg at any three clinic visits, which included the first two years of active therapy and did not have to be consecutive clinic visits. The proportions of patients with the other components of the primary end point were similar in the two groups. At two years, the systolic and diastolic pressures were, not surprisingly, significantly lower with candesartan therapy compared to placebo. However, within nine months of cessation of candesartan therapy, the pressures rose to values similar to those in the placebo group (show figure 2). The same findings were noted in the much larger Medical Research Council trial of mild hypertension, which demonstrated that after five to six years of active therapy with a thiazide diuretic or beta blocker, cessation of therapy resulted in a rise in blood pressure that, within six months, was not distinguishable from the placebo group that had not been treated from trial onset (show figure 3) [16]. In contrast, patients continued on active therapy maintained the fall in blood pressure. (See "Can therapy be discontinued in well-controlled hypertension?").

In addition, TROPHY did not incorporate lifestyle modifications, which are currently recommended for the treatment of patients with prehypertension.

Similar findings were noted in a double-blind study of normotensive patients at increased risk of familial hypertension who were treated with an angiotensin receptor blocker [17] .

We conclude that the evidence is not convincing that transient antihypertensive therapy changes the course of prehypertension or hypertension. Further study is required to determine the role, if any, of pharmacotherapy in prehypertension among individuals without other indications for such therapy (eg, chronic kidney disease, heart failure).

**Screening** — The optimal interval for screening for hypertension is not known. The 2007 United States Preventive Services Task Force (USPSTF) guidelines recommend screening every two years for persons with systolic and diastolic pressures below 120 mmHg and 80 mmHg, respectively, and yearly for persons with a systolic pressure of 120 to 139 mmHg or a diastolic pressure of 80 to 89 mmHg [18] .

**TREATMENT** — Careful monitoring for signs of end-organ damage or progression to hypertension is an important part of the follow-up of patients with prehypertension or borderline hypertension. Any change in BP classification should be confirmed on at least one subsequent visit.

As recommended in JNC 7, patients with prehypertension who do not have diabetes, chronic kidney disease, end-organ damage, or clinical evidence of cardiovascular disease are generally treated with nonpharmacologic therapies such as weight reduction, sodium restriction, increased physical activity, and avoidance of excess alcohol. (show table 1). (See "Diet in the treatment and prevention of hypertension").

The major indication for antihypertensive drug therapy is progression to overt hypertension (BP  $\geq$  140/ $\geq$  90 mmHg). The threshold is lower in patients with diabetes, chronic kidney disease, or cardiovascular disease in whom the BP goal is less than 130/80 mmHg. (See "Hypertension: Who should be treated?" and see "Choice of therapy in essential hypertension: Recommendations").

Cardiovascular risk increased with high-normal BP

Cumulative incidence of cardiovascular events over time in 6859 men and women in the Framingham Heart Study who were initially free of hypertension or cardiovascular disease. The patients were put into one of three BP categories: optimal blood pressure (BP 120/80), normal BP (120 to 129/80-84), and high-normal BP (130-139/85-89 mmHg). If the systolic and diastolic pressures were discordant, the higher of the two categories was used. High-normal BP, compared to optimal BP, was associated with an adjusted hazard ratio for cardiovascular disease of 1.6 in men and 2.5 in women. Data from Vasan, RS, Larson, MG, Leip, EP, et al, N Engl J Med 2001; 345:1291.

Candesartan in prehypertension in TROPHY

In the TROPHY trial, 806 patients with prehypertension (systolic BP 130-139 mmHg and/or diastolic BP 80-89 mmHg) were randomly assigned to candesartan or placebo for two years; all patients were then continued on placebo therapy for another two years. The systolic pressure was significantly reduced in the candesartan group during the two years of active therapy, but returned to placebo levels within nine months of cessation of candesartan. Although not shown, similar findings were noted with the diastolic pressure. Data from Julius, S, Nesbitt, SD, Egan, BM, et al, N Engl J Med 2006; 354:1685.

#### Discontinuation of antihypertensive therapy

In a trial performed by the Medical Research Council Working Party of Mild Hypertension, 2765 patients were randomly assigned to bendrofluzide, propranolol, or placebo. Both systolic and diastolic pressures fell more with drug therapy than placebo (phase 1). At six years, patients in the drug therapy groups were reassigned to continued therapy or placebo (phase 2). The fall in both systolic and diastolic pressures was maintained in those on continued therapy, while switching to placebo led, within nine to twelve months, to a rise in blood pressure to a level similar to the values in patients treated with placebo from the beginning. Data from Medical Research Council Working Party of Mild Hypertension, Br Med J 1986; 293:988.

#### Lifestyle modifications in the management of hypertension

Modification Recommendation Approximate systolic BP reduction, range\*

Weight reduction Maintain normal body weight (BMI, 18.5 to 24.9 kg/m<sup>2</sup>) 5-20 mmHg per 10-kg weight loss

Adopt DASH eating plan Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat 8 to 14 mmHg

Dietary sodium reduction Reduce dietary sodium intake to no more than 100 meq/day (2.4 g sodium or 6 g sodium chloride) 2 to 8 mmHg

Physical activity Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week) 4 to 9 mmHg

Moderation of alcohol consumption Limit consumption to no more than 2 drinks per day in most men and no more than 1 drink per day in women and lighter-weight persons 2 to 4 mmHg

For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals; they are not all additive.

BMI: body mass index; BP: blood pressure; DASH: Dietary Approaches to Stop Hypertension.

Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JAMA 2003; 289:2560.

## **Hypertension artérielle de l'enfant : abords néphrologique et cardiologique**

L'HTA est rare chez l'enfant, mais elle doit être décelée le plus rapidement possible par la mesure systématique de l'HTA qui fait partie de l'examen de l'enfant comme celui de l'adulte. Quand on a découvert l'HTA, il faut s'acharner à en trouver la cause car l'hypertension de l'enfant est pratiquement toujours secondaire.

### **1 Symptomatologie**

Elle est souvent peu évocatrice :

- céphalées : douleurs abdominales
- insuffisance cardiaque
- signes nerveux : coma, convulsions.

Techniques de mesure (cf examen clinique).

### **2 Etiologie**

#### **2.1 H.T.A transitoire**

**2.1.1 Causes rénales :** Glomérulonéphrites aiguës, syndrome néphrotique.

**2.1.2 Causes nerveuses :** Paralysie respiratoire, tumeurs cérébrales, hématomes sous-duraux, HT intra-crânienne.

**2.1.3 Intoxication :** Saturnisme, hypervitaminose D, corticothérapie.

#### **2.2 H.T.A permanente**

**2.2.1 Causes cardio-vasculaires :** Coarctation de l'aorte : cf cardiopathies par obstacle sans shunt, périartérite noueuse.

#### **2.2.2 Causes rénales :**

- insuffisance rénale globale,
- néphropathie unilatérale :
  - pyélonéphrite unilatérale,
  - anomalie vasculaire rénale,
  - petit rein dysplasique unilatéral.

#### **2.2.3 causes endocriniennes :**

- hyperplasie surrénale congénitale,
- phéochromocytome, sympathoblastome.

**2.2.4 l'HTA essentielle est fréquente :** la plupart des hypertensions artérielles de l'adulte commencent dès l'adolescence.

#### **AU TOTAL :**

les deux causes principales de l'HTA permanente à rechercher chez l'enfant sont :  
la coarctation de l'aorte et les néphropathies unilatérales.

**De manière plus précise :**

**Etiologies :**

→ Primaire ( ou essentielle ) : rare chez l'enfant

→ Secondaire : 90 % :

- rénale ( parenchymateuse ou vasculaire)
- Coarctation de l'aorte
- endocrinienne

Plus l'enfant est jeune et l'HTA sévère, plus la probabilité de trouver une cause sous-jacente est importante !

***Les atteintes rénales :***

Une atteinte rénale quelle qu'elle soit peut entraîner une chute de filtration glomérulaire au niveau d'un certain nombre de néphrons. Celle-ci entraînera une hypersécrétion de rénine, d'angiotensine puis d'aldostérone avec rétention hydrosodée et donc augmentation du volume circulant mais aussi augmentation de la sécrétion d'angiotensine II qui est un des plus puissants vasoconstricteurs de l'organisme.

Quelles sont les atteintes rénales ?

Toute atteinte telle que : → glomérulonéphrite aiguë, chronique : → uropathie,  
→ pyélonéphrite, → chez le nouveau-né, les sténoses de l'artère rénale ( suite à la mise en place de KT ombilical )

***Les atteintes endocriniennes :***

- phéochromocytome et neuroblastome ( ↗ catécholamines circulantes )
- hyperthyroïdie
- hyperplasie congénitale des surrénales
- syndrome de Cushing
- hyperaldostéronisme

***Les atteintes vasculaires :***

- Coarctation de l'aorte
- états à large débit cardiaque :  
persistance du canal artériel, insuff. aortique, fistule artério-Veineuse, Bloc AV complet ;
- anémie, polycythémie.

***Les atteintes neurologiques:***

- hypertension intracrânienne

***Les atteintes métaboliques :***

- diabète
- hypercalcémie

***Les traitements médicamenteux :***

- stéroïdes
- gouttes vasoconstrictrices
- cyclosporine

**Hypertensions essentielles :** Il a été prouvé que l'HTA essentielle de l'adulte est précédée par une augmentation de la Tension Artérielle dans l'enfance. La fréquence chez l'enfant est toujours méconnue, se rencontre en fin d'enfance et en pré-adolescence.

• **Diagnostic :**

**L'anamnèse :**

- antécédents familiaux
- médicaments
- une augmentation de poids rapide ( trouble endocrinien tel qu'un Cushing)
- une diminution de poids ( hyperthyroïdie ou un phéochromocytome)

Chez le nouveau-né, rechercher les anomalies vasculaires, cardiaques et les antécédents de cathétérisme de l'artère ombilicale qui peuvent entraîner des sténoses de l'artère rénale.

\* **Examens complémentaires :**

En première phase exploratoire On réalisera :

- RU SU CU
- ions sanguins
- urée, créatinine
- Ph sanguin
- clearance de la créatinine
- protéinurie de 24H
- écho reins et cœur
- Rx thorax

Deuxième phase

→ En cas d'uropathie : - scintigraphie au DMSA  
- cystographie rétrograde  
- urographie IV ( dans certains cas )

→ En cas de suspicion de phéochromocytome ou neuroblastome :  
- catécholamines urinaires de 24 h : doser : adrénaline, Noradrenaline, Dopamine, HVA et VMA

Si cette diurèse est positive :  
scintigraphie au MIBG à la recherche d'une masse thoracique ou abdominale

→ En cas de suspicion de maladie endocrinienne :  
- stéroïdes urinaires et particulièrement la cortisolurie de 24 heures  
- ARP : ( activité rénine plasmatique )  
- après 15 min. de situation couchée  
- conservation sur glace

N.B. : valeurs sont plus élevées :  
- chez le nouveau  
- après l'administration de drogues telles que vasodilatateurs, diurétiques, bêtabloquants  
- après l'administration d'un régime désodé  
- en position debout.

Troisième phase :

- En cas de suspicion d' une sténose de l'artère rénale

du côté  
générale  
efférente  
traceur

1. Test au captopril : il s'agit d'une scintigraphie avec et sans Captopril,  
( scintigraphie fonctionnelle soit DTPA ou Mag 3 )

En cas de sténose de l'artère rénale : il y a une réduction de la filtration

atteint qui se fera par deux mécanismes : - chute de la pression artérielle

- vasodilatation de l'artère

On enregistrera donc un retard d'accumulation et d'élimination du

Ce test est positif dans 68% des cas.

2. Echo. Doppler et artériographie rénale : ( 95 % de diagnostic + )

→ indispensable au diagnostic

3. Les dosages étagés de rénine sur les veines rénales sont de plus en plus  
abandonnés. Ils

sont positifs dans 74% des cas. Du côté atteint, les dosages de rénine sont  
supérieurs

d'une fois et demi par rapport au côté sain.

• **Bilan de la répercussion sur les organes cibles :**

- ECG – echo cœur

- Fond d'Oeil

- Holter TA : étude du maintien de la TA en fonction du rythme nyctéméral

- Epreuve d'effort : étude de la tolérance et de la variation de la TA avec l'effort

**Thérapeutique :** + voir tableau des doses

**\* Traitement de la crise :**

HTA symptomatique et / ou HTA menaçante : > à P97 +30 mmHg (voir définition)

Il faut atteindre une zone non menaçante en deux heures et une zone d'hypertension limite en 48 heures.

**1. Inhibiteurs calciques :**

Adalat per os. Rydène en IV.

Ils agissent en entraînant une vasodilatation et une diminution des résistances vasculaires périphériques. Le métabolisme est hépatique. La vasodilatation entraîne une augmentation de l'activité rénine plasmatique mais aussi une augmentation de la synthèse des catécholamines urinaires par riposte orthosympathique (→ prélèvements catécholamines et act. Rénine à interpréter avec précaution)

**2. Trandate :**

Alpha-bloquant ( entraîne une vasodilatation par diminution des résistances vasculaires périphériques.) et bêta-bloquant ( effet cardiaque.)

**3. Vasodilatateurs artériels directs:** Lonnoten ( Minoxidil ) et Nepresol ( Hydralazine) per os. Hyperstat (Diazoxide ) en IV

Action directe sur les fibres musculaires lisses de parois artérielles. Ils sont très mal tolérés parce que l'effet vasodilatateur est très puissant mais leur efficacité est importante.

**4. Alpha-bloquants :**

Minipress ( Prazosine) per os

Effet dilatateur périphérique en bloquant les récepteurs alpha périphériques.

**5. Diurétiques :**

Lasix PO ou IV

**6. Inhibiteurs d'enzyme de conversion :**

Captopril per os. Enalapril qui peut s'utiliser en IV et per os.

Ils agissent :

- en diminuant la formation d'angiotensine II à partir de l'angiotensine I
- en bloquant donc l'action vasoconstrictrice de l'angiotensine II, ils diminuent les résistances vasculaires périphériques mais ils augmentent également les taux de bradykinines et les prostaglandines qui sont normalement dégradées par les enzymes de conversion. Les bradykinines et prostaglandines sont des vasodilatateurs naturels.

Au niveau du rein, les inhibiteurs de l'enzyme de conversion lèvent la vasoconstriction de l'artère efférente. Il y a donc une perte de l'autorégulation rénale. Cette baisse de contrepression diminue la filtration glomérulaire et parfois de façon dramatique en cas d'insuffisance rénale et en cas de sténose de l'artère rénale

Les contre-indications absolues sont donc les sténoses bilatérales des artères rénales ou une sténose unilatérale sur rein unique.

Les répercussions au niveau sanguin sont :- une diminution d'angiotensine II - une diminution d'aldostérone

- une augmentation de la rénine , de l'angiotensine I
- une augmentation du potassium

Au niveau urinaire : - une augmentation du sodium éliminé

- une diminution du potassium

Elimination par voie rénale. ( prudence )

#### **Quelques cas particuliers :**

##### **\* En cas d'urgence,**

utiliser d'abord

1° l' Adalat en sublingual, rectal, nasal.

Si inefficace, utiliser ensuite

2° le Rydène en IV

3° ajouter le Trandate

4° ajouter le Captopril

##### **\* En cas de galop et de défaillance du ventricule gauche,** il faut d'abord utiliser le Rydène

IV puis

le Lasix puis le Captopril.

##### **\* En cas de sténose de l'artère rénale,**

faire attention à ne pas diminuer les pressions artérielles

trop rapidement parce qu'on peut entraîner une thrombose qui entraînera une insuffisance rénale.

##### **\* En cas de phéochromocytome,**

les drogues de choix sont donc les médicaments qui bloquent les effets des catécholamines. Le premier choix est le Trandate IV puis per os et si c'est insuffisant,

on adjoindra la Prazosine.

**\* En cas de surcharge en sodium,**

ne faut pas oublier d'utiliser le Lasix.

**\* Traitement au long cours :**

Indications :

**A. Hypertensions artérielles confirmées :** c'est à dire des hypertensions systoliques et/ou diastoliques supérieures au 97<sup>ème</sup> percentile + 10 mmHg.

	Systolique	Diastolique
Nné	> 100	> 70
< 2 ans	> 112	> 74
3 – 5 ans	> 116	> 76
6 – 9 ans	> 122	> 78
10 – 12 ans	> 126	> 82
13 – 15 ans	> 136	> 86
16 – 18 ans	> 142	> 92

**B. Hypertensions artérielles limites :** ( voir bilan de la répercussion )

Si le holter de TA de 24 heures et le test d'effort sont corrects, il n'y a pas d'indication à traiter mais il faut suivre l'enfant par des tensions artérielles répétées 4X / an, des échos et des holters de tension artérielle de 24 heures 1X / an.

Il faut également faire diminuer le poids, admettre la pratique d'un sport non statique, diminuer les rations de sodium à un peu près 3 meq / kg / J et diminuer les ingestats de café, coca, tabac. Chez les filles, encourager une contraception de type progestatif.

Traitements selon l'état d'urgence, l'étiologie, l'âge, l'état cardio-vasculaire, la fonction rénale et le retentissement viscéral.

1 - Inhibiteurs calciques ;

2 - Béta-bloquants ( action sur le cœur, sur le système rénine, une action centrale au niveau des récepteurs centraux aux catéchomlamine et une action périphérique) ;

3 -Diurétiques ( jamais en monothérapie ni au long cours car ils ont des effets secondaires : par exemple le Lasix → hyperlipémie, hypokaliémie, alcalose mais aussi hyperglycémie et hyperuricémie ;

4 - Inhibiteurs de l'enzyme de conversion ( risque d'altération du goût et de la toux ) ;

5 - Agents centraux stimulateurs des récepteurs alpha. Les récepteurs alpha centraux ont un effet

inhibiteur sur les centres vasomoteurs et cardio-accélérateurs. Dans cette classe, il y a deux molécules : la clonidine (Catapressan) et l'alpha-méthyl dopa ( Aldomet).

Quelques cas particuliers :

- \* En cas d'hypertension artérielle sévère, on utilisera des associations de béta-bloquants, d'inhibiteurs d'enzyme de conversion puis diurétiques et inhibiteurs calciques.
- \* En cas d'insuffisance rénale chronique, se méfier des rétentions sodées et des inhibiteurs de l'enzyme de conversion

\* Chez le nouveau-né, il faut être très prudent. Les béta-bloquants sont très inotropes négatifs, les inhibiteurs de l'enzyme de conversion entraînent rapidement une chute de la filtration glomérulaire et les inhibiteurs calciques entraînent des vasodilatations parfois trop importantes.

- **Follow up :**

Tensions artérielles tous les deux mois  
Echo cœur deux fois par an  
Test d'effort une fois par an.

N.B. : L'utilisation de molécules retard telles que : - Isoten ( béta-bloquant cardio sélectif )

- Adalat oros ( (-) calcique)
- Kredex ( alpha et béta-bloquant )

reste du domaine du spécialiste !

**Traitement de la crise : per os**

DROGUE	MODE ACTION	VOIE	POSOLOGIE	DEBUT	DUREE	C.I.	EFFETS SEC.
NIFEDIPINE Adalat°	(-) cal	sublinguale per os rectal nasal	initial 0,25 mg / kg renouvelé 15 – 30 min. puis 0,5 > 1 mg / kg dose	15 – 30 min	3 – 6 H		Céphalées flush TC
CAPTOPRIL Capoten°	(-) enz. Conv.	per os sublinguale	Nné : 0,2 mg / kg max 2 enfant : 1,5 mg / kg max 6	15 à 30 min	6 – 8 H		
MINOXIDIL Lonnoten°	Vasod. direct	per os	0,2 mg / kg	1 à 2 H	> 12 – 24 H		
HYDRALASINE Nepresol°	Vasod. direct	per os	0,5 mg / kg				
PRAZOSINE Minipress°	Alpha-bloquant	per os	0,01 → 0,05 mg / kg/dose puis 0,1 → 0,7 mg / kg / jour	< 1 H	8 – 12 H		Hypotension orthostatique

Traitement de la crise : IV							
DROGUE	MODE ACTION	VOIE	POSOLOGIE	DEBUT	DUREE	C.I.	EFFETS SEC.
NICARDIPINE Rydène°	(-) calc.	• IV	• Charge IV lente 10' 10 – 20 gamma / kg puis perfusion continue 0,5 à 3 gamma / Kg / min	5 à 60 min.	30 min. à 6 H		céphalées flush tachycardie Nausées site injection
LABETALOL Trandate°	Alpha et béta bloquant	IV	Bolus 1 min : 0,3mg / kg renouveler après 10' si néc. : ↗ 0,6 → 1 mg / kg puis perfusion continue 2 – 25 mg / kg / J par paliers (2 – 8 – 12 – 15 – 25)	5 min.	3 – 24 H	Insuff. Card. BAV asthme	bradycardie hypotension hyperK+
DIAZOXIDE	vasodilatateur	IV	IV direct 2,5 mg / kg	< 10	4 – 12		hypotension tachycardie

Hyperstat°			renouvelé ttes les 10 - 15 min. → 5 à 10 mg / kg puis IV lent 20 - 30' : 5 mg / kg	min.	H		nausées vôissements
URAPIDIL Ebrantil°	vasodilatateur	IV	3 mg / kg / H ( 1 → 14 ) puis relais 1mg / kg / H				hypotension tachycardie oedème
FUROSEMIDE Lasix°	diurétique	IV	IV lent 30' 1 - 3 mg / kg ttes les 3 - 4 H → 10 mg / kg	5 min.	2 - 3 H		HypoK+ ototoxicité hyperglycémie
ENALAPRIL Renitec°	(-) enzyme de conversion	IV	5 à 10 gamma / kg / dose		8 H	Sténose art. rénale Insuff. rénale	hypotension

**Traitement au long cours**

• DROGUE	MODE	DOSE INITIALE		LONG COURS	Nbre de prises / 24 H
		mg / kg			
ACEBUTOLOL Sectral°	béta-bloquant	1,5	à 3	5 -	1 (2)
PROPRANOLOL Inderal°	béta-bloquant	1 mg / kg		1 - 5	3X
BISOPROLOL Isoten°	béta-bloquant				
CAPTOPRIL Capoten°	(-) enzyme conversion	Nné	0,01	1 - 3	2 à 3 X
ENALAPRIL Renitec°		Nr	0,1		
		E	0,2		
		Nné	0,05		1X
		Nr	0,05		
		E 2 à 5 mg / prise et non par Kg			
LABETALOL Trandate°	alpha et béta- bloquant	1,5 à 3		5 - 15	2 à 4 X
NIFEDIPINE Adalat°	(-) calc	0,25		0,5 - 3	3X
HYDRALAZINE Nepresol°	vasodil. direct	0,5		1 - 3	2X
FUROSEMIDE Lasix°	diurétique	1		1 - 5	2X
PRAZOSINE Minipress	Alpha-bloquant	0,01		0,1 - 0,7	2X

## Addendum : la décompensation cardiaque chronique

### Etiologies:

Cardiopathie congénitale non corrigée

Hypertension artérielle aiguë

Myocardite virale

Cardiomyopathies dilatées (maladie métabolique, post myocardite, post anthracyclines,...)

Maladie de surcharge (Fer, glycogène)

Troubles du rythme

### Classification

I : pas de diminution des capacités d'effort

II : légère diminution des capacités d'effort, pas de plaintes au repos

III : diminution franche des capacités d'effort, symptômes même lors d'un léger effort, pas de plaintes au repos

IV : symptômes au repos et à l'effort

### Clinique

Dyspnée

Prise de poids exagérée ou du contraire prise de poids insuffisante

Fatigue, gémissement, « mal dans sa peau », hypotonie chez les nourrissons.

Diminution de la capacité à l'effort

Œdèmes

Tachycardie

Crépitations pulmonaire, tachypnée, détresse respir

Hépatomégalie, stase jugulaire

Hypotension artérielle, mauvaise perfusion périphérique (extrémités froides)

### Traitement :

- **Régime hypercalorique (+30% par rapport besoins de base d'un enfant normal):**

3 mois 140ml/kg/j, 115kcal/kg/j +30% (donc 149 kcal/kg/j)

≥6 mois 125ml/kg/j, 95 kcal/kg/j +30% (donc 123 kcal/kg/j)

ne pas limiter les volumes mais plutôt majorer les diurétiques

enrichir les biberons (DM ou huile)

- **Caloreen = glucides exclusivement**

380kcal/100g, en gén cc de 7% càd 7g/100g de lait, parfois difficile à digérer (coliques et diarrhée)

présence d'une mesurette dans la boîte : 7%= 1mes/100ml de lait

Fantomalt = glucides exclusivement

384 kcal/100g, cc idem

pas de mesurette dans la boîte, donner 1.5mes de lait pour avoir une cc de 7%

Duocal = graisses+glucides

Le plus riche : 492kcal/100g, le mieux toléré au niveau dig, mais le plus cher

Pas de mesurette dans la boîte ; Cc : commencer à 7% càd 1.5mes /100ml

Viser 10% qui est le max toléré

Garder le lait et ne pas introduire les repas trop vite avant correction chirurgicale

Ne pas diminuer trop vite le nombre de repas mais evt fractionner et donner un biberon la nuit

Un bébé cardiaque boit lentement avec des pauses, les biberons durent parfois 1h!!! (importance d'expliquer cela aux parents et aux infirmières) → il faut parfois cranter les tétines

- Traiter un RGO si nécessaire

Alimentation éventuellement par sonde naso-gastrique

### **Traitement médicamenteux**

#### → Digitaliques : LANOXIN:

Effet: Inotrope +, ↓ FC (inhibe noeud AV et tissu de conduction)

Contreindication: lésions obstructives, Cardiomyopathie hypertrophique

Conditionnement: Elixir pédiatrique 0,05mg/ml, co de 125 et 250mg

Dosage: en cas de décompensation chronique, pas de nécessité de dose de charge prématuré: 5 gamma/kg/j en 2x

<1mois: 10 gamma/kg/j en 2x (0,1ml/kg/dose 2x/j)

3-6 kg et >1 mois: 20 gamma/kg/j en 2x

6-9 kg: 15 gamma/kg/j en 2x

>9kg: 10 gamma/kg/j en 2x

#### → Diurétiques: (diminue précharge)

= **Lasix** (Furosémide) PO/IV 0,5-1mg/kg/dose 1-4x/j (! hypokaliémie)

= **Dytenzide** (assoc hydrochlorothiazide 25mg/triamtérène 50mg /comprimé de Dytenzide)

NN 1/10-1/8 co 1-2x/j

1an ¼ co 1-2x/j

3ans 1/2 co 1-2x/j

>3 ans 1co 1-2x/j

viser +- 1mg/kg 1-2x/j de Hydrochlorothiazide

stop en cas de traitement en parallèle par IEC car risque d'hyperkaliémie

Aldactone po agit sur l'hyperaldostéronisme toujours présent dans la déc card (à utiliser en combinaison au Lasix, attention hyperkaliémie en cas d'IEC)

2-3mg/kg/j en 2x

#### → Inhibiteurs d'enzyme de conversion (diminue postcharge)

améliore fonction myocardique, diminue postcharge par vasodilatation artérielle et veineuse.

Lors de l'introduction: contrôle rapproché de Tension Artérielle: ceci se fait donc en hospitalisation

TA 1x/15min pd 1h puis 1x/30min pd 1 h puis 1x/h pd 6h

= **Lisinopril** (Zestril) dose test : 0.05mg/kg/j en 1x J0, x 2 J1 (0,1mg/kg/j), x2 J2 (0,2mg/kg/j) ensuite retour à domicile, augmentation ensuite en consult (viser 0.3-1mg/kg/j)

= **Captopril** (Capoten) dose test : 0.05mg/kg/dose 3x puis augmenter (de 0.25mg/kg/j) et viser 1-2mg/kg/j (nourrisson 0.5-1mg/kg/j)

= **Enalapril** (Renitec) dose test 0,05mg/kg/dose 2x puis majorer progressivement à 0,5-1mg/kg/j en 2x

ARRET des thiazides (Dytenzide) et de spironolactone et remplacer par Lasix car risque d'hyperK+  
STOP si déshydratation, GE

→ **Beta-bloquants (diminue postcharge)**

bloque surstimulation du système catécholaminergique, améliore fonction systolique et diastolique, vasodilatation artérielle systémique

= **Indéral**: (pour instaurer le traitement chez le petit enfant) 0,2-0,5mg/kg/dose 2-4x/j, augmenter jusque 1,5mg/kg/dose (max 80mg) 2-4x/j

= **Carvedilol** (Kredex): 0,08mg/kg/12h puis /sem de 0,08mg/kg jusque 0,5-0,75 mg/kg/12h

Bisoprolol (moins utilisé): 0,02mg/kg/j à augmenter à 0,15 mg/kg/j en 1x

Attention à l'association à la digoxine car potentialise l'effet bradycardisant

Contre-indication: en cas de Bloc Auriculo Ventriculaire type II et III, Bronchite Chronique et asthme prononcé.

→ Veiller à un taux d'Hb suffisant :

toujours >10g/dl (voire >15g/dl en cas de gros shunt G-D chez les tous petits non opérable d'emblée pour augmenter la viscosité sanguine et diminuer les résistances vasculaires pulmonaires ;

→ Traiter les troubles du rythme

**Treatment of hypertension in children and adolescents**

**INTRODUCTION** — It has become clear that hypertension (HTN) begins in childhood and adolescence and that it contributes to the early development of cardiovascular disease (CVD). In hypertensive adults, multiple randomized trials have shown that reduction of BP by antihypertensive therapy reduces cardiovascular morbidity and mortality. (See "Hypertension: Who should be treated?"). Based upon these observations, identifying children with HTN and successfully treating their HTN should have an important impact on long-term outcomes of CVD.

Issues related to the treatment of HTN in children and adolescents will be reviewed here. The epidemiology, etiology, diagnosis, and evaluation of HTN are discussed separately. (See "Epidemiology, risk factors, and etiology of hypertension in children and adolescents", see "Definition and diagnosis of hypertension in children and adolescents", and see "Evaluation of hypertension in children and adolescents").

**DEFINITIONS** — In children, the following definitions based upon the 2004 National High Blood Pressure Education Program Working Group (NHBPEP) are used to classify BP measurements in the United States [1]. BP percentiles are based upon gender, age, and height derived from normative data (show table 1A-1B and show table 2A-2B). The systolic and diastolic BP are of equal importance; if there is a disparity between the two, the higher value determines the BP category. The age- and height-specific blood pressure percentiles may be determined using calculators for boys (show calculator 1) or for girls (show calculator 2). Normal BP — Both systolic and diastolic BP <90th percentile. Prehypertension — Systolic and/or diastolic BP  $\geq$  90th percentile but <95th percentile or if BP exceeds 120/80 mmHg (even if <90th percentile for age, gender, and height). Hypertension — HTN is defined as either systolic and/or diastolic BP  $\geq$  95th percentile measured upon three or more separate occasions. The degree of HTN is further delineated by the two following stages.

- Stage 1 HTN — Systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile.

- Stage 2 HTN — Systolic and/or diastolic BP  $\geq$  99th percentile plus 5 mmHg.

A more complete discussion on the classification of BP, and the definition and diagnosis of HTN in children and adolescents is found separately. (See "Definition and diagnosis of hypertension in children and adolescents", section on Definition).

Childhood HTN is also divided into two categories depending upon whether or not an underlying cause can be identified. Essential or primary HTN — No identifiable cause is found. Secondary HTN — An underlying cause is identified.

**RATIONALE FOR INTERVENTION** — The rationale for initiating therapy to lower BP in children and adolescents with chronic HTN, or those with prehypertension and other cardiovascular risk factors is based upon the following observations: Children and adolescents who are hypertensive or have prehypertension are more likely to be hypertensive as adults. (See "Definition and diagnosis of hypertension in children and adolescents", section on Tracking). HTN is a well-established risk factor for CVD in

adults. In adults, multiple trials have shown that reduction of BP by antihypertensive therapy reduces cardiovascular morbidity and mortality. The magnitude of the benefit increases with the severity of the HTN. (See "Overview of the risk factors for cardiovascular disease", section on Hypertension, and see "Hypertension: Who should be treated?"). HTN is a risk factor for accelerated atherosclerosis in children and young adults. (See "Identifying the child at-risk for atherosclerosis", section on Hypertension).

These observations suggest lowering the BP in hypertensive children would reduce the risk of accelerated atherosclerosis and subsequently premature CVD. In addition, treatment of childhood HTN, which continues resulting in lower BP values in adulthood, may reduce the likelihood of premature CVD.

Treatment for HTN includes both nonpharmacologic and pharmacologic interventions. Management decisions are dependent upon the severity of HTN, the underlying cause, and the presence of other CVD risk factors. (See "Management approach" below).

**NONPHARMACOLOGIC THERAPY** — Nonpharmacologic therapy is recommended by the 2004 NHBPEP guidelines for children with HTN (defined as BP >95th percentile) or prehypertension (defined as BP >90th to the 95th percentile or if BP exceeds 120/80 mmHg) (show table 1A-1B and show table 2A-2B) [1,2]. The age- and height-specific blood pressure percentiles may be determined using calculators for boys (show calculator 1) or for girls (show calculator 2). (See "Definitions" above).

In our practice, the following nonpharmacologic measures, which are consistent with the NHBPEP therapeutic lifestyle changes, are used to treat hypertensive and prehypertensive children [1]: Weight reduction for obesity-related HTN. Regular exercise and restriction of sedentary activity. Dietary modification including salt restriction. Nonpharmacologic measures to reduce other CVD factors such as smoking and dyslipidemia.

Children and adolescents with prehypertension who are treated with nonpharmacologic interventions should have their BP monitored every four to six months [3]. Those with HTN should be monitored more often depending upon the severity of their HTN.

**Weight reduction** — The BP lowering effect of weight reduction in obese hypertensive adult patients has been well-documented, with systolic and diastolic blood pressures falling by approximately 1 mmHg for each 1 kg of weight loss. (See "Obesity and weight reduction in hypertension").

Although the data in children are not as robust, several studies have reported results of lower BP values with weight reduction in hypertensive children similar to those seen in adult studies [4-7]. In the only randomized trial, 72 overweight adolescents were assigned to regimens of diet plus exercise, diet alone, and no intervention [5]. At the end of 20 weeks, there was a similar mean weight loss in the two intervention groups of 2.5 kg but a mean weight gain of 4 kg in the control group. The changes in systolic pressure in the three groups were -16, -10, and +4 mmHg, respectively. Weight loss was associated with an increase in serum HDL-cholesterol [5], reductions in serum triglycerides and body fat [5], and a decrease in BP sensitivity to sodium intake [6].

Dietary counseling with a nutritionist can be useful in providing customized recommendations to decrease daily caloric intake. Dietary modification should be coupled

with a decrease in time spent on sedentary activities and initiation of a regular exercise regimen. In some cases, referral to pediatric obesity centers for appropriate dietary, pharmacologic, and/or surgical therapy may be warranted. (See "Clinical evaluation of the obese child and adolescent").

**Exercise** — Exercise appears to lower BP in children [5,8-11] . A meta-analysis of 12 randomized trials with 1266 children and adolescents found that short-term physical activity led to a small but not significant reduction of 1 percent in systolic BP and 3 percent in diastolic BP [10] .

Sustained regular physical activity appears to be more effective in lowering BP. This was illustrated in a trial of 137 children, approximately one-half hypertensive ( $\geq$  95th percentile) and one-half normotensive, who were randomly assigned to three extra weekly school physical education sessions or no added exercise for eight months [8] . The extra exercise was associated with improved physical fitness and with significant reductions in systolic and diastolic BP in both the hypertensive (4.9 and 3.8 mmHg, respectively) and normotensive children (6.5 and 4.1 mmHg, respectively).

As cited above, the antihypertensive effect of physical activity combined with weight loss is greater than that with weight loss or exercise alone. However, the combination of weight loss and physical training may not improve the adverse effects of obesity on left ventricular function or size in adolescents [12] .

Aerobic exercise prescriptions should define the type, frequency, intensity, and duration of activity. Aerobic exercise involves low resistance movements usually over a period of greater than 10 minutes. Activities include walking, running, swimming, and bike riding. The optimal amount and intensity of exercise in children are uncertain. The following recommendations have been made: The American College of Sports Medicine recommends 20 to 60 minutes of aerobic exercise three to four times a week, including warm-up and cool-down periods that involve stretching or walking [13] . Exercise intensity should reach a heart rate of 60 to 85 percent of the patient's age-related maximum heart rate. The average maximum heart rate in children and adolescents is considered to be 200 beats/min with a wide range of individual values. The NHBPEP recommends regular moderate aerobic physical activity of 30 to 60 minutes on most days and limitation of sedentary activities to less than two hours per day [1] .

In contrast to the effects of regular aerobic exercise, strength-training isometric exercise, which involves high resistance, low repetition movements over short periods of time (one to three minutes) does not appear to lower the BP [14] . Furthermore, these activities (eg, weight lifting) can acutely raise both the systolic and diastolic BP [15] . Isometric exercise should be discouraged until the BP is well controlled.

**Sports participation** — Definitive long-term data concerning the safety of participation in athletics by children with borderline or mild hypertension (Stage 1 HTN) are not available. It is generally believed that these children should be allowed to participate in dynamic aerobic exercise in the absence of end-organ damage (eg, echocardiographic evidence of left ventricular hypertrophy). Patients who become symptomatic should be reevaluated. Because of its possible hypertensive response, weight lifting should be avoided in children with hypertension [1] .

Competitive sports participation should be restricted in the presence of uncontrolled stage 2 HTN [1] . Children with stage 2 HTN, once treated with pharmacologic therapy and documented to be normotensive, can participate in aerobic activity with ongoing monitoring. (See "Pharmacologic therapy" below).

Diet — There are limited data on the effect of dietary changes upon BP in children. However, it is generally accepted based upon adult trials that a reduction in salt intake and an increase intake of fresh fruits and vegetables and low-fat dairy products (eg, the Dietary Approaches to Stop Hypertension [DASH] diet [16] ) have beneficial effects in children and adolescents with HTN [1] .

Salt restriction — Increased salt intake (both sodium and chloride) is associated with higher blood pressures. Essential hypertension is seen primarily in societies in which salt intake is above 100 meq/day (2.3 g sodium); in contrast, hypertension is a rare disorder in societies in which salt intake is less than 50 meq/day (1.2 g sodium) [17] . Salt sensitivity is more marked in African-Americans and patients with established hypertension or renal insufficiency [6,18] . Among children with essential hypertension, increased salt intake may promote the development of left ventricular hypertrophy, independent of any effect on BP [19] . (See "Salt intake, salt restriction, and essential hypertension").

The effect of salt intake on BP may begin early in life. This was illustrated in a clinical trial in which 476 newborn infants were randomly assigned to a low-sodium diet (about one-third of normal intake) or a normal-sodium diet for the first six months of life [20] . At the end of the study, the systolic BP was 2.1 mmHg lower in infants who received the low-sodium diet. When 167 children from this cohort were examined 15 years later, systolic and diastolic BP were 3.6 and 2.2 mmHg lower in those originally assigned to a low-sodium intake versus those who received a normal sodium diet [21] .

Well-controlled randomized trials in adults have shown that the overall impact of moderate sodium restriction is a fall in systolic and diastolic BP in hypertensive (4.8 and 2.5 mmHg, respectively) and normotensive (1.9 and 1.1 mmHg, respectively) adults (show figure 1) [22] . Although not all hypertensive adults are salt-sensitive, the general recommendation is to reduce dietary intake from the usual 150 to 200 meq/day (approximately 9 to 12 g of salt) to 100 meq/day (approximately 6 g of salt). (See "Salt intake, salt restriction, and essential hypertension").

The evidence for a benefit from salt restriction in children and adolescents with essential hypertension is less clear [1] . Two short-term trials showed no significant BP lowering from sodium restriction in groups of adolescents who represented the entire range of BP percentiles [23,24] . Another short-term trial of obese adolescents found a benefit from marked sodium restriction (30 versus 250 mmol/day) that was no longer present after a weight loss of more than 1 kg [6] .

Despite the limited data in children, the NHBPEP has recommended an aggressive and probably difficult to achieve degree of salt restriction, reducing sodium intake to 1.2 g/day which corresponds to a salt intake of 3.1 g/day (53 meq/day) in four to eight year old children, and sodium intake of 1.5 g/day which corresponds to a salt intake of 3.8 g/day (65 meq/day) in older children [1] .

In our practice, we begin dietary salt modification with a no-added-salt diet. This also includes a reduction in or elimination of foods containing large amounts of salt (eg, potato chips, pretzels, processed foods). Parents and care providers are encouraged to read food package labels to determine the sodium content of prepared foods and avoid those with high salt content. In addition, lunches provided by school programs need to be evaluated to ensure avoiding foods with high salt content. (See "Patient information: Low sodium diet").

Potassium intake and the DASH diet — Studies in hypertensive adults have shown that increasing potassium intake can modestly lower the BP. This effect is attenuated or lost in patients also on a low-sodium diet [25] , and benefit has not been confirmed in children [26] . (See "Potassium and hypertension").

In adults, diets that are rich in fresh vegetables and fruits (eg, the Dietary Approaches to Stop Hypertension [DASH] diet), which are low in fat but relatively rich in potassium, have been shown to decrease BP [16,27] . In one study of 57 adolescents with either hypertension or prehypertension, there was a greater reduction of systolic BP in patients assigned to the DASH diet versus routine outpatient hospital-based nutrition care (mean SBP change of 10.4 versus 1.9 mm Hg) three months after nutrition counseling [28] . Although not significant, there was a trend towards lower systolic BP in the patients assigned to the DASH diet six months after nutrition counseling (9.3 versus 4.3 mm Hg). At the six-month follow-up, 50 percent of the patients assigned to the DASH diet were normotensive versus 36 percent of those who were assigned routine nutritional care.

Based upon this study as well as those in adults, a diet rich in fresh vegetables and fruits, such as the DASH diet, is suggested in patients with HTN. (See "Diet in the treatment and prevention of hypertension", section on the DASH diet).

Avoidance of excess alcohol — Multiple studies in adults have shown a clear association between excess alcohol intake and the development of hypertension. Adults who have more than two drinks per day have a 1.5- to twofold increase in the incidence of hypertension compared to nondrinkers. This effect is dose-related and is most prominent when intake exceeds five drinks per day. The applicability of these findings to children has not been well studied. Nevertheless, excess alcohol intake should be avoided to improve weight loss, BP control, and other health concerns. (See "Cardiovascular benefits and risks of moderate alcohol consumption").

Other CVD risk factors — Smoking should be avoided in hypertensive children and adolescents because it increases the risk of CVD as well as lung cancer. In addition, smoking by family members should be avoided to prevent second-hand smoke exposure, which has been associated with premature atherosclerosis in exposed children. (See "Smoking and hypertension" and see "Secondhand smoke exposure: effects in children", section on Coronary heart disease).

Dietary measures should be initiated in children with dyslipidemia, which is discussed separately. (See "Management of the child at-risk for atherosclerosis", section on Dyslipidemia).

PHARMACOLOGIC THERAPY — Although antihypertensive drug therapy in children has the potential to produce side effects and has not been proven to improve long-term

cardiovascular outcome, there is indirect supporting evidence that lowering elevated childhood BP reduces the risk of premature CVD. These data include findings that demonstrate hypertensive children are at risk for accelerated atherosclerosis and are likely to remain hypertensive as adults, who are at risk for CVD. (See "Rationale for intervention" above and see "Identifying the child at-risk for atherosclerosis").

As a result, drug therapy for HTN in children should be limited to those who are most likely to benefit and a regimen should be chosen to minimize the incidence of side effects and provide the best possible compliance.

Who to treat — In our practice, we utilize the 2004 NHBPEP guidelines to initiate pharmacologic therapy in children with one or more of the following conditions [1] : Symptomatic HTN (eg, headache, seizures, changes in mental status, focal neurologic complaints, visual disturbances, and cardiovascular complaints indicative of heart failure, such as chest pain, palpitations, cough, or shortness of breath). Stage 2 HTN defined as BP levels that are 5 mmHg greater than the 99th percentile. Stage 1 HTN (without any evidence of target-organ damage) that persists despite a trial of four to six months of nonpharmacologic therapy. Hypertensive target-organ damage, most often left ventricular hypertrophy (LVH). LVH, defined as left ventricular mass above the 95th percentile, is present in up to 40 to 50 percent of children with essential HTN and is severe (>99th percentile) in as many as 14 percent [29] . Retinal changes are a less common manifestation of target-organ damage in children. (See "Ocular effects of hypertension" and see "Evaluation of hypertension in children and adolescents", section on Initial evaluation). Stage 1 HTN in patients with diabetes mellitus or other risk CVD factors, such as dyslipidemia. (See "Treatment of hypertension in diabetes mellitus" and see "Management of the child at-risk for atherosclerosis", section on Hypertension).

Antihypertensive drugs — The number of antihypertensive drugs in children that have been systematically studied has increased due to the 1997 Food and Drug Administration Modernization Act (FDAMA) and the 2002 Best Pharmaceuticals for Children Act. However, this legislation did not affect older commonly used drugs whose patent protection had expired.

The 2004 NHBPEP report included dosing recommendations for antihypertensive drugs (show table 3) [1] . These recommendations were based upon data from industry-sponsored clinical trials and single center observational studies. When data were not available, recommendations were based from collective clinical experience and consensus opinions from experts in the field.

The initial choice of anti-hypertensive agent is discussed in the section on management approach. (See "Choice of drug" below).

Thiazide diuretics — There is an extensive clinical experience confirming the efficacy and safety of thiazide diuretics in children [30] . In addition to being used as primary therapy, a thiazide diuretic also enhances the effect of many other antihypertensive drugs (eg, ACE inhibitors and beta blockers) when given as combination therapy [31,32] . Optimal efficacy of thiazides, given alone or in combination with other drugs, requires concurrent salt restriction [33,34] . (See "Salt intake, salt restriction, and essential hypertension").

A number of clinical trials in adults with essential hypertension have shown that low-dose thiazide therapy (eg, 12.5 to a maximum of 25 mg/day of hydrochlorothiazide or chlorthalidone) is effective in lowering BP (show figure 2) and is not associated with prominent metabolic complications (show figure 3). Despite these observations, many pediatric specialists in hypertension have recommended primary therapy with ACE inhibitors, beta blockers, or calcium channel blockers rather than diuretic therapy because of concerns about the metabolic complications (eg, hypokalemia, glucose intolerance, adverse lipid effects) associated with diuretic therapy and the need for periodic blood chemistry monitoring [30] . (See "Thiazide dosage in essential hypertension").

Based upon adult data and recommendation regarding the use of thiazide diuretics as initial therapy in most patients, we suggest that initial use of low-dose thiazide diuretic therapy should be considered as initial therapy in post-pubertal adolescents with essential HTN because of its established efficacy and low cost. (See "Essential hypertension" below).

ACE inhibitors/ARBs — ACE inhibitors (eg, captopril, enalapril, lisinopril, and fosinopril) are well tolerated and widely used in hypertensive children. Captopril was the first available ACE inhibitor used in pediatrics but it has been supplanted by longer acting ACE inhibitors. In children, efficacy and dosing data are available for enalapril, lisinopril, benazepril, and fosinopril.

Enalapril has received Food and Drug Administration (FDA) approval as an antihypertensive drug for children following completion of both a pharmacokinetic and a dose-dependent trial. The former demonstrated similar pharmacokinetics in infants and children when compared to adults [35] , while the latter demonstrated a dose-dependent response with a low incidence of side effects [36] .

Lisinopril has been shown to be effective and safe based on a randomized placebo controlled study of 115 children between the ages of 6 and 16 years [37] . In another study, pharmacokinetic data were obtained in 46 children between the ages of 6 months and 15 years [38] . Based upon a dose that ranged between 0.1 and 0.2 mg/kg, pharmacokinetics of lisinopril in children were similar to those reported in adults with a peak serum concentration between five and six hours after administration. There were no drug-related adverse effects. Lisinopril is FDA approved for children between 6 and 16 years of age.

Fosinopril has been shown to reduced blood pressure in children [39] , although dosing recommendations are limited to children greater than 50 kg. There appears to be differences in dose response based upon ethnicity. Black children appear to require a higher dose per body weight to achieve similar BP reduction compared to non-black children (ie, white, Asian, and Latino children). This was illustrated in a clinical trial of 250 children between 6 and 16 years of age who were randomly selected to receive varying doses of fosinopril [40] . Non-black children had a mean decrease of 12 mmHg in their systolic BP whether a low or high dose of fosinopril was used. In contrast, black children who received a low dose of fosinopril had a lower decrease in systolic BP of a mean of 5 mmHg decrease, while those who received a high dose had a mean reduction of 13 mmHg in SBP, similar to the response in non-black children.

Studies in adults suggest that the antihypertensive effect of ACE inhibitors is increased by concurrent salt restriction [41] . Salt restriction increases renin release, making the BP

more angiotensin II-dependent and therefore more responsive to therapy with an ACE inhibitor. (See "Renin-angiotensin system inhibition in the treatment of hypertension").

Angiotensin-receptor blockers (ARBs) are a relatively new class of antihypertensive drugs in pediatrics. Both irbesartan and losartan have been FDA approved based upon clinical trials [1,42,43]. However, in a larger efficacy study, irbesartan failed to show a beneficial effect in hypertensive children between 6 and 16 years of age. This study has not been published but FDA review of the data is available [44,45]. As a result, irbesartan is not recommended as a pediatric antihypertensive agent [44].

In patients who have bilateral renovascular hypertension or are volume depleted, ACE inhibitors or ARBs may reduce the glomerular filtration rate, as manifested by a rise in the plasma creatinine concentration [46]. In these patients, another class of antihypertensive agents should be chosen. ACE inhibitors and ARBs are contraindicated in pregnancy and should be avoided in sexually active girls because of known adverse effects on the fetus. (See "Angiotensin converting enzyme inhibitors and receptor blockers in pregnancy").

Beta blockers — Beta blockers were among the first and most widely used antihypertensive drugs in children. Most of the original studies were performed with propranolol, which has been largely replaced by better tolerated, longer acting, and more selective drugs such as atenolol, metoprolol, and bisoprolol. These agents are available in combination with hydrochlorothiazide. Labetalol is another beta blocker agent, which also has alpha-blocking activity [31,47,48]. Esmolol is an intravenous beta blocker agent, primarily used to treat postoperative or intraoperative tachycardia and HTN [45].

The efficacy of an extended-release (ER) form of metoprolol, a cardioselective beta blocker, was demonstrated in a randomized trial of 140 hypertensive children [49]. Systolic blood pressure was significantly reduced in patients who received 1 or 2 mg/kg doses of ER metoprolol compared to those who received placebo. Diastolic blood pressure was only lowered in patients who received 2 mg/kg doses. During an open label, separate, 52-week trial of 100 patients, five patients discontinued metoprolol because of adverse effects (fatigue, nightmare, anxiety, dizziness, and asthma). Two patients had a serious adverse events; one patient each with pneumonia and menometrorrhagia.

Beta blockers are contraindicated in patients with asthma or heart block.

Calcium channel blockers — Increasing experience with long-acting calcium channel blockers (such as nifedipine and amlodipine) demonstrate their efficacy and safety in children with hypertension, particularly essential HTN [50-53].

A multi-center, randomized, double blinded study of amlodipine that included 268 children between 6 and 16 years of age with Stage 1 HTN demonstrated the effectiveness of amlodipine over a short period of time (eight weeks) with a relatively small number of significant side effects [52]. The causes of HTN varied and included essential HTN in 50 percent of the patients. In addition, an observational study of 33 children treated for more than six months demonstrated continued effectiveness of amlodipine without significant side effects [54].

In contrast, a randomized, placebo controlled three-week trial of another long-acting calcium channel blocker, extended release felodipine, failed to show a fall in systolic BP greater than placebo at any dose in 133 children with essential HTN [55].

One problem with these long-acting preparations is the minimum dose formulation that is currently available resulted in a range of mean daily dose from 0.06 to 0.23 mg/kg per day in these studies [50,52]. Thus, smaller children who received larger dose of medication per body weight may be more likely to experience dose-related adverse effects. (See "Major side effects and safety of calcium channel blockers").

Calcium channel blockers are contraindicated in patients with sick sinus syndrome, but may be the desired class of antihypertensive agents in patients with HTN and asthma.

**MANAGEMENT APPROACH** — Our management approach is to use nonpharmacologic and/or pharmacologic interventions based upon defined target blood pressure thresholds and goals.

**Target blood pressure goals** — In children and adolescents with elevated BP, the desired goal is to lower BP to an optimal level that reduces the risk of premature CVD. However, no data are available to define these pediatric goals because long-term epidemiologic data linking cardiovascular events to childhood BP values are lacking. As a result, target blood pressure goals have been determined by expert opinion and are based upon statistically defined BP classification [1]. (See "Definition and diagnosis of hypertension in children and adolescents", section on Definition).

In 2004, the National High Blood Pressure Education Program Working Group (NHBPEP), which was comprised of experts in the field, revised target blood pressure goals for the treatment of HTN [1]. In our practice, we use the following NHBPEP goals: In children and adolescents with HTN and no evidence of target-organ damage, comorbid risk factors, or diseases associated with CVD; the targeted goal for blood pressure (BP) is less than the 95th percentile based upon age, height, and gender (show table 1A-1B and show table 2A-2B). The age- and height-specific blood pressure percentiles may be determined using calculators for boys (show calculator 1) or for girls (show calculator 2). If there are comorbid CVD risk factors (eg, obesity or dyslipidemia), diseases associated with CVD (eg, diabetes mellitus) (show table 4), and/or evidence of target-organ damage (eg, left ventricular hypertrophy [LVH], renal scarring, or retinopathy), the BP targeted goal is lowered to below the 90th percentile for age, height, and gender. (See "Identifying the child at-risk for atherosclerosis" and see "Treatment of hypertension in diabetes mellitus").

**Our approach** — The initiation and aggressiveness of the therapy are generally based upon the severity of HTN, and the presence of target-organ damage, symptoms, or other CVD risk factors. Therapy includes nonpharmacologic and pharmacologic interventions and is focused upon achieving the previously discussed BP target goals.

Our management approach is consistent with the following NHBPEP guidelines. The choice of antihypertensive agent is discussed below. (See "Choice of drug" below). In children who are pre-hypertensive (BP >90th percentile and <95th percentile), nonpharmacologic therapy (eg, diet and exercise) is initiated to reduce their BP to below the 90th percentile. If there are comorbid CVD factors or diseases associated with CVD

(eg, obesity or diabetes mellitus), evaluation for target-organ damage is suggested. In children with stage 1 essential HTN without evidence of target-organ damage, nonpharmacologic therapy is the initial intervention. If BP target goals are not met within four to six months after initial therapy (ie, BP below the 95th percentile), pharmacologic therapy is suggested. The choice of antihypertensive agents is discussed below. (See "Choice of drug" below). In children with stage 1 HTN who are symptomatic or have evidence of target-organ damage (eg, LVH), both nonpharmacologic and pharmacologic therapy are started. In children with stage 2 HTN, we recommend treatment with both nonpharmacologic and pharmacologic therapy rather than nonpharmacologic therapy alone. Patients with stage 2 HTN and neurologic symptoms including headache, mental status changes, and neurologic findings should be emergently evaluated and treated. In children with secondary HTN, therapy should be directed to correcting the underlying cause, if possible. If the underlying cause can not be corrected so that HTN is abolished, pharmacologic therapy and nonpharmacologic therapy are initiated. (See "Epidemiology, risk factors, and etiology of hypertension in children and adolescents", section on Secondary hypertension).

Choice of drug — In adults, long-term clinical outcome trials have evaluated the comparable effectiveness of specific antihypertensive drugs directly. However, in children with hypertension there are no similar comparative data on which to base a recommendation for initial therapy [44]. Therefore, the NHBPEP guidelines do not make recommendations on the choice of agent for initial therapy and suggest that the choice is based upon the preference and experience of the responsible physician. However, adult outcome data have demonstrated that certain classes of antihypertensive drugs may be more appropriate for children with a specific underlying medical conditions, such as essential hypertension, chronic kidney disease, and diabetes mellitus. (See "Indications for use of and contraindications to specific antihypertensive drugs").

In children more likely to have a secondary cause of HTN (eg, prepubertal patients or those with stage 2 HTN), we prefer to use calcium channel blockers during the preliminary investigations because of concerns of undiagnosed bilateral renal artery stenosis or renal artery stenosis in a single kidney.

Essential hypertension — In children, there has not been a consensus on the best initial pharmacologic agent to treat essential HTN. The available classes of drugs include thiazide diuretics, ACE inhibitors, beta blockers, and calcium channel blockers [1] (show table 3). Thiazide diuretics and beta blockers have a long history of safety and efficacy based on clinical experience. Clinical short term trials have shown that ACE inhibitors and calcium channel blockers are effective, safe, and well-tolerated in children, but these two classes of drugs are more expensive.

Based upon clinical trials in adults, low-dose thiazide therapy (12.5 to 25 mg of hydrochlorothiazide per day) is the recommended initial therapy of choice for most patients with essential HTN. Although similar data in hypertensive children do not exist, it is reasonable to assume that low-dose thiazide diuretic therapy would have similar efficacy in adolescents with essential HTN. Initial therapy begins with a dose of 12.5 mg/day of hydrochlorothiazide (approximately 0.2 mg/kg per day) and is increased as necessary to a maximum of 25 mg/day. (See "Thiazide diuretics" above and see "Thiazide dosage in essential hypertension").

Data on the use of combination therapy of thiazide diuretics and other classes of antihypertensive medications (beta blockers, ACE inhibitors, and calcium channel blockers) are limited in children. (See "Choice of therapy in essential hypertension: Recommendations", section on Combination therapy).

In our practice, we use hydrochlorothiazide at a starting dose of 12.5 mg daily as initial therapy in adolescents with essential hypertension without evidence of target-organ damage. The dose is increased to 25 mg daily if the target blood pressure goal is not met after two to three months of therapy. If there is no significant response in four to six months after the start of hydrochlorothiazide, we will either add or change to an ACE inhibitor or calcium channel blocker.

Chronic kidney disease — In adults with chronic renal disease, prospective randomized trials have shown the benefit of ACE inhibitors and ARBs in delaying the progression of renal insufficiency. Studies on the use of ACE inhibitors in children are limited but are consistent with the adult data. ACE inhibitor therapy appears most beneficial in patients with glomerular disease and proteinuria and should be considered as the initial therapy in these patients [56]. Close monitoring for possible increases in creatinine and potassium is needed. A more complete discussion on treatment of HTN in children with CKD is discussed separately. (See "ACE inhibitors/ARBs" above and see "Overview of the management of chronic kidney disease in children", section on Hypertension).

There are few data on the use of ARBs in children with chronic renal failure but, based upon the adult data, these drugs are a reasonable alternative if ACE inhibitors cannot be used because of intolerable side effects (most often cough). (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease").

Diabetes mellitus — Randomized controlled trials in adults have demonstrated that ACE inhibitors and ARBs delay the progression of diabetic nephropathy and decrease albuminuria in patients with both type 1 and type 2 diabetes. (See "Treatment and prevention of diabetic nephropathy").

More limited studies in children with type 1 diabetic nephropathy suggest a similar benefit with ACE inhibitors [56]. Thus, ACE inhibitors, or, if not tolerated, ARBs, are the preferred drugs in children with diabetes because of their potential renoprotective properties. Because of the increased risk of premature CVD, therapy is targeted to decrease blood pressure values below the 90th percentile for age, gender, and height for patients with either type 1 or 2 diabetes. (See "Complications and screening in children and adolescents with type 1 diabetes mellitus", section on Hypertension, and see "Comorbidities and complications of type 2 diabetes mellitus in children and adolescents", section on Hypertension).

HTN in type 2 diabetes is usually related to obesity; thus, weight reduction is an important component of hypertension therapy in these patients.

Drug management — The management of antihypertensive therapy is based upon the following considerations [1]: First-line drug therapy should combine efficacy with minimum side effects. Starting doses should be the lowest known effective dose (see table 3). If the target blood pressure goal is not met, a second drug from a different class is added when the initial drug dose reaches the highest recommended level or if the patient

begins to experience side effects from the initial drug. (See "Target blood pressure goals" above). To improve compliance, long-acting agents should be used whenever possible.

Continued follow-up is required to monitor the response to therapy and to detect any drug-related adverse effect.

Discontinuation of therapy — In adults with well-controlled mild hypertension, studies have demonstrated that between 5 and 55 percent remain normotensive for at least one to two years after discontinuation of treatment, while other patients do well with a decrease in drug dose [57,58]. The wide reported range is dependent upon the characteristics of the population studied. Factors such as white-coat hypertension and use of nonpharmacologic therapies are associated with a greater likelihood of successful treatment withdrawal. (See "Can therapy be discontinued in well-controlled hypertension?").

The application of these observations to children is clearly speculative. Gradual discontinuation of therapy is most likely to be effective in children with mild initial hypertension who are well controlled on a single drug and who can be maintained on nonpharmacologic therapy such as weight loss and sodium restriction [57]. This "step-down" approach can be tried in those selected patients who fulfill these criteria. These patients will require ongoing nonpharmacologic therapy and BP monitoring after drug therapy is discontinued.

**SUMMARY AND RECOMMENDATIONS** — Therapeutic decisions are dependent upon the severity of HTN, the underlying cause, and the presence of other CVD risk factors. Treatment for childhood HTN includes both nonpharmacologic and pharmacologic interventions. Nonpharmacologic therapy (ie, lifestyle changes) includes weight reduction for children who are overweight, a regular aerobic exercise regimen, dietary measures (eg, salt restriction), and avoidance of excess alcohol consumption and smoking. (See "Nonpharmacologic therapy" above). Pharmacologic agents used frequently in children that are efficacious and safe include thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers (show table 3). (See "Antihypertensive drugs" above). Treatment is directed towards achieving the following BP target goals recommended by the National High Blood Pressure Education Program Working Group (NHBPEP). (See "Target blood pressure goals" above).

- In children and adolescents with HTN and no evidence of target-organ damage or comorbid CVD conditions, the targeted goal for blood pressure (BP) is less than the 95th percentile based upon age, height, and gender (show table 1A-1B and show table 2A-2B). The age- and height-specific blood pressure percentiles may be determined using calculators for boys (show calculator 1) or for girls (show calculator 2).

- If there are comorbid CVD conditions (eg, obesity, dyslipidemia, or diabetes mellitus) (show table 4), and/or evidence of target-organ damage (eg, left ventricular hypertrophy [LVH], renal scarring, or retinopathy), the BP targeted goal is lowered to below the 90th percentile for age, height, and gender. (See "Identifying the child at-risk for atherosclerosis").

In 2004, NHBPEP defined BP classes based upon BP percentiles derived from normative data (show table 1A-1B and show table 2A-2B). Our management approach is to initiate nonpharmacologic and/or pharmacologic interventions based upon these blood pressure

classes and is consistent with the NHBPEP guidelines. In general, all patients who are treated should initiate lifestyle changes whether or not pharmacologic therapy is used. (See "Definitions" above and see "Our approach" above). We suggest treating children and adolescents with prehypertension with lifestyle changes (Grade 2C). We suggest not initiating pharmacologic therapy in such patients even if lifestyle changes are ineffective (Grade 2C). We suggest treating children and adolescents with asymptomatic stage I HTN and no comorbid conditions with lifestyle changes (Grade 2B). In cases where BP does not come down to the targeted BP goal with lifestyle changes alone, we suggest initiating pharmacologic therapy (Grade 2B). We recommend treating children and adolescents with stage I HTN with other CVD risk conditions (eg, dyslipidemia or diabetes mellitus) (Grade 1B). We suggest initiating pharmacologic therapy rather than a trial of lifestyle changes alone (Grade 2C). We recommend treating children and adolescents with stage I HTN with symptoms or evidence of target-organ damage, or with stage II HTN (Grade 1B). We recommend initiating pharmacologic therapy rather than a trial of lifestyle changes alone (Grade 1B). In children with secondary HTN, therapy should be directed to correcting the underlying cause, if possible. If the underlying cause cannot be corrected so that HTN is abolished, we suggest treatment with both antihypertensive pharmacologic and lifestyle changes (Grade 1B). (See "Epidemiology, risk factors, and etiology of hypertension in children and adolescents", section on Secondary hypertension).

There are no long-term clinical outcome measures to evaluate the comparative effectiveness of specific antihypertensive drugs in children with HTN. Based upon data from adult studies, we suggest that the following underlying medical conditions be treated with a specific class of antihypertensive drugs. In adolescents with essential HTN without target-organ damage, we suggest that low-dose thiazide diuretic therapy be used as the first antihypertensive agent (Grade 2B). (See "Essential hypertension" above). In children with chronic kidney disease, we suggest that ACE inhibitors be used as the initial antihypertensive agent (Grade 2B). In patients who cannot tolerate ACE inhibitors, angiotensin-receptor blockers (ARBs) are a reasonable alternative. (See "Chronic kidney disease" above). In children with either type 1 or type 2 diabetes mellitus, we suggest that ACE inhibitors be used as the initial antihypertensive agent (Grade 2B). In patients who cannot tolerate ACE inhibitors, angiotensin-receptor blockers (ARBs) are a reasonable alternative. (See "Diabetes mellitus" above).

## Metabolism of vitamin D

**INTRODUCTION** — Very few foods contain vitamin D (fatty fish livers are the exception) and dermal synthesis is the major source of the vitamin. Vitamin D3 (cholecalciferol) is synthesized nonenzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet rays in sunlight. This system is exceedingly efficient and it is estimated that brief casual exposure of the arms and face is equivalent to ingestion of 200 international units per day. Infants, disabled persons and the elderly may have inadequate sun exposure, while the skin of those older than 70 years of age also does not convert vitamin D effectively. In addition, at northern latitudes, there is not enough radiation to convert vitamin D, particularly during the winter. For these reasons (in the United States), milk, infant formula, breakfast cereals, and some other foods have been fortified with synthetic vitamin D2 (ergocalciferol) or vitamin D3. However, strict vegetarians who do not eat fish are at risk of vitamin D deficiency in the winter unless vitamin D supplements are included in the diet.

**METABOLISM OF VITAMIN D** — Dietary vitamin D is absorbed in the small intestine as a fat soluble vitamin incorporated into chylomicrons. It travels to the liver, bound to vitamin D-binding protein and in continued association with chylomicrons and lipoproteins, where it and endogenously synthesized vitamin D3 are metabolized. The hepatic enzyme 25-hydroxylase places a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D or calcidiol. The association of oral vitamin D with chylomicra and lipoproteins permits more rapid hepatic delivery when compared to endogenously synthesized or parenterally administered hormone, which circulates exclusively on vitamin D-binding protein. This difference results in a rapid but less sustained increase in plasma calcidiol levels obtained with oral as opposed to parenteral administration .

Calcidiol has activity at bone and intestine, but is only about 1 percent as potent as the final hormone, calcitriol or 1,25-dihydroxyvitamin D. There is some feedback regulation of the hepatic 25-hydroxylase, but it is insufficient to prevent vitamin D intoxication following the ingestion of large amounts of vitamin D. The liver is the usual storage system for vitamin D with a half-life of approximately 14 days. When large amounts of vitamin D are ingested, much of the excess vitamin D is stored in adipose tissue. As these sites become saturated, the vitamin D remains in serum and is converted to toxic levels of calcidiol. The liver also has the capacity to metabolize 25-hydroxyvitamin D to inactive

metabolites. This is accomplished by the P-450 system and is enhanced by alcohol, barbiturates, and phenytoin. Calcidiol produced by the liver enters the circulation and travels to the kidney, again bound to vitamin D binding protein. This protein has a single binding site which binds vitamin D and all of its metabolites. Only 3 to 5 percent of the total circulating binding sites are normally occupied; as a result, this protein is not rate-limiting in vitamin D metabolism unless large amounts are lost in the urine as in the nephrotic syndrome.

In the tubule, entry of the filtered calcidiol-vitamin D binding protein complex into the cells is facilitated by receptor-mediated endocytosis [9]. At least two proteins working in tandem are involved in this process: cubilin, which, in the intestine, is the receptor for the intrinsic factor-vitamin B12 complex, and megalin. Deficiency of either of these proteins results in increased calcidiol excretion in the urine and, at least in experimental models, calcitriol deficiency and bone disease. Within the tubular cell, calcidiol is released from the binding protein. The renal tubular cells contain two enzymes (1-alpha-hydroxylase and 24-alpha-hydroxylase) that can further hydroxylate calcidiol, producing 1,25-dihydroxyvitamin D (calcitriol), the most active form of vitamin D, or 24,25-dihydroxyvitamin D, an inactive metabolite. Both enzymes are members of the P-450 system. Studies in vitamin D-deficient animals suggest that the proximal tubule is the important site of synthesis. In contrast, studies in the normal human kidney indicate that the distal nephron is the predominant site of 1-alpha-hydroxylase expression under conditions of vitamin D sufficiency.

The plasma calcitriol concentration is a function both of the availability of calcidiol and of the activities of the renal enzymes 1-alpha-hydroxylase and 24-alpha-hydroxylase. The 1-alpha-hydroxylase enzyme is primarily regulated by three factors:

- Parathyroid hormone (PTH)
- Plasma phosphate concentration
- Plasma calcitriol concentration [14]

Increased PTH secretion (most often due to a fall in the plasma calcium concentration) and hypophosphatemia stimulate the enzyme and enhance calcitriol production. The importance of low phosphate concentrations is suggested by the finding of markedly increased levels of 1-alpha-hydroxylase messenger RNA in mice with renal phosphate wasting and hypophosphatemia due to the targeted inactivation of the sodium-phosphate

cotransporter gene. Calcitriol synthesis may also be modulated by vitamin D receptors on the cell surface; downregulation of these receptors may play an important role in regulating vitamin D activation. Calcitriol production by the kidney is also regulated by fibroblast growth factor 23 (FGF23), a phosphaturic hormone. Impaired degradation of this hormone results in the abnormalities associated with autosomal dominant hypophosphatemic rickets. Experimental data suggest that FGF 23 may have a function opposite to calcitriol to help maintain phosphate homeostasis. Both calcitriol and calcidiol are degraded in part by being hydroxylated at the 24-position by a 24-hydroxylase. The activity of the 24-hydroxylase gene is increased by calcitriol (which therefore promotes its own inactivation) and reduced by PTH (thereby allowing more active hormone to be formed).

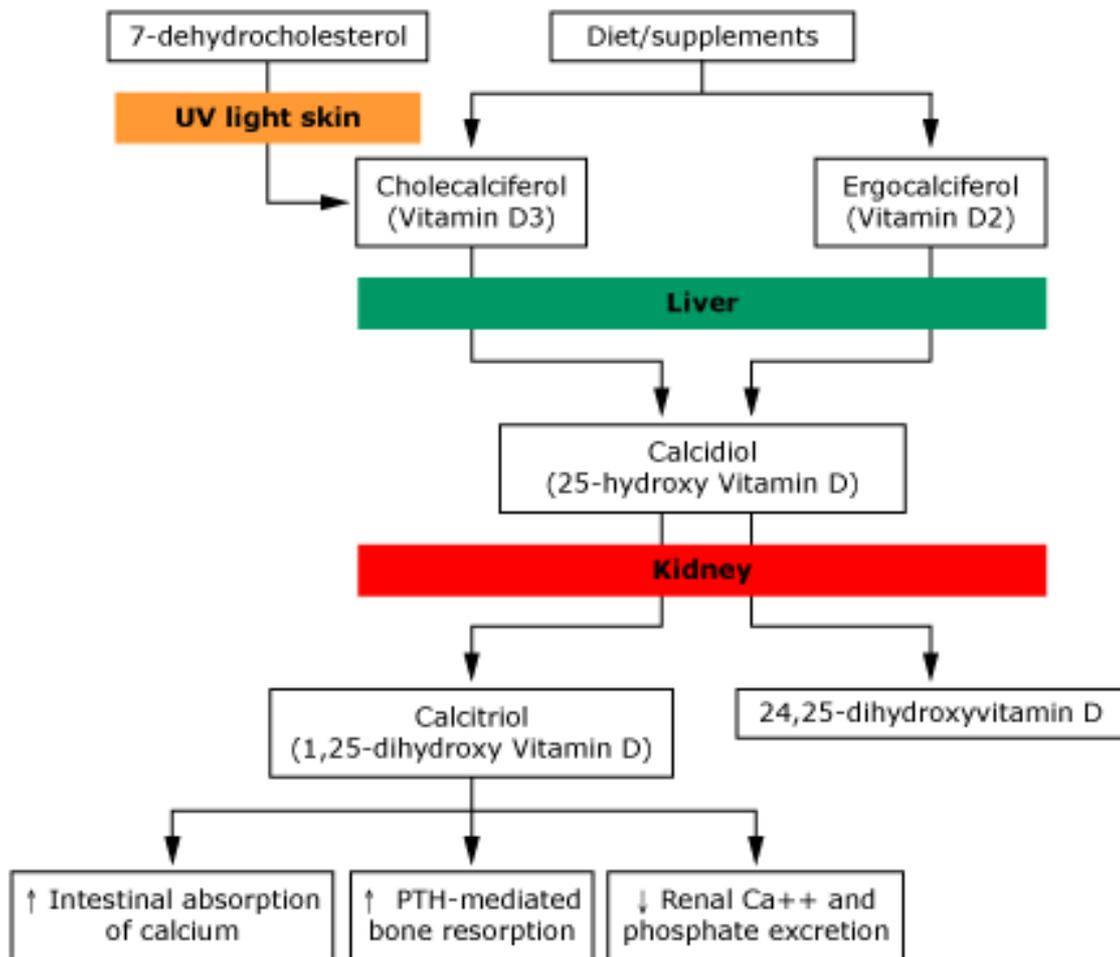
**FUNCTIONS OF CALCITRIOL** — Calcitriol binds to intracellular receptors in target tissues and regulates gene transcription. It appears to function through a single vitamin D receptor (VDR). The receptor is a member of the class II steroid hormone receptor, and is closely related to the retinoic acid receptor and the thyroid hormone receptor. Its most important biological action is to promote enterocyte differentiation and the intestinal absorption of calcium. Other effects include a lesser stimulation of intestinal phosphate absorption, direct suppression of PTH release from the parathyroid gland, regulation of osteoblast function, and permissively allowing PTH-induced osteoclast activation and bone resorption. Through these actions, calcitriol contributes to the maintenance of normal plasma concentrations of calcium and phosphate, thereby allowing mineralization of newly formed bone to take place and preventing symptomatic hypocalcemia or hypophosphatemia.

The importance of calcitriol in mineral metabolism is illustrated by the findings that can occur in hypervitaminosis D (hypercalcemia) and vitamin D deficiency (hypocalcemia, hypophosphatemia, and rickets or osteomalacia).

**Other actions** — Calcitriol has other important actions, including regulation of hematopoietic cell and probably muscle cell function. Its immunomodulatory activity may explain why calcitriol can also be synthesized by macrophages and why increased calcitriol levels and hypercalcemia can be seen in patients with granulomatous diseases such as sarcoidosis and tuberculosis.

## GRAPHICS

### Pathways of vitamin D synthesis



Metabolic activation of vitamin D to calcitriol and its effects on calcium and phosphate homeostasis. The result is an increase in the serum calcium and phosphate concentrations.

## **Bone metabolism and renal osteodystrophy in children with chronic kidney disease**

**INTRODUCTION** — Abnormalities in mineral metabolism and bone structure are an almost universal finding with progressive chronic kidney disease (CKD) [1] . The changes that occur in the homeostatic mechanisms that regulate serum concentrations of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) lead to development of renal osteodystrophy or renal bone disease. (See "Chapter 6F: Hormonal regulation of calcium and phosphate balance" and see "Parathyroid hormone secretion and action").

In children with CKD, renal osteodystrophy results in significant complications. Many are similar to those seen in adults with CKD (eg, fractures, bone pain, and avascular necrosis) but others are unique to children (eg, growth failure and skeletal deformities).

The prevention and management of renal osteodystrophy in children with CKD will be reviewed here. The pathogenesis of renal osteodystrophy is discussed separately. (See "Pathogenesis of renal osteodystrophy").

This review and its recommendations are consistent with the Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in children with CKD [1] . The K/DOQI clinical practice guidelines for bone metabolism and disease in children with CKD, as well as other K/DOQI guidelines, can be accessed through the National Kidney Foundation's web site at [www.kidney.org/professionals/kdoqi/guidelines.cfm](http://www.kidney.org/professionals/kdoqi/guidelines.cfm).

**STAGES OF CHRONIC RENAL DISEASE** — Many of the complications of CKD (including renal osteodystrophy) can be prevented or delayed through early detection and treatment. This observation has led to the development of a staging system by the K/DOQI working group that is based upon the estimated glomerular filtration rate and is independent of the primary renal diagnosis. This staging system is used to help guide management of metabolic abnormalities in children with CKD (show table 1) [2] . (See "Epidemiology, etiology, and course of chronic kidney disease in children"). Stage 1 — Normal glomerular filtration rate (GFR)  $\geq 90$  mL/min per 1.73 m<sup>2</sup>. Stage 2 — GFR between 60 to 89 mL/min per 1.73 m<sup>2</sup> Stage 3 — GFR between 30 and 59 mL/min per 1.73 m<sup>2</sup> Stage 4 — GFR between 15 and 29 mL/min per 1.73 m<sup>2</sup> Stage 5 — GFR of  $<15$  mL/min per 1.73 m<sup>2</sup> or requires dialysis treatment.

Children with CKD stage 2 usually have no signs or symptoms of bone abnormalities. However, these children may have evidence of abnormalities on laboratory testing (eg, decreased serum calcitriol [1,25 dihydroxyvitamin D] and elevated serum parathyroid hormone [PTH]) [3] . This period should be used to educate the child and family about CKD and its impact on bone metabolism. This discussion should highlight the need for laboratory monitoring and future interventions that will prevent renal osteodystrophy.

Subtle signs of renal osteodystrophy begin to be observed when the GFR decreases to 50 percent of normal (stage 3 disease). These children should be monitored for evidence of bone disease by physical examination and laboratory evaluation. Physical findings include muscle pain, weakness, and bony changes such as varus and valgus deformities of the long bones. Laboratory abnormalities of bone metabolism (eg, elevated PTH) are

common in stage 3 disease and require therapeutic interventions. (See "Management" below).

**TYPES** — There are several forms of renal osteodystrophy, including osteitis fibrosa cystica, adynamic bone disease, and osteomalacia. In some patients, there is evidence of more than one type, which is called mixed osteodystrophy.

In 51 children undergoing dialysis, the prevalence of the different types of bone disease was determined by bone biopsy [4] . Normal histology, adynamic bone disease, osteitis fibrosa cystica, mixed osteodystrophy, and osteomalacia were observed in 37, 27, 24, 10, and 2 percent of patients, respectively. In children with CKD stages 2 to 4, osteitis fibrosa cystica is the most common form of renal osteodystrophy.

The following is a brief review of the different forms of renal osteodystrophy. A more complete description of their pathogenesis is found separately. (See "Pathogenesis of renal osteodystrophy").

**Osteitis fibrosa cystica** — Osteitis fibrosa cystica results from secondary hyperparathyroidism. Bone biopsies of affected patients demonstrate increased bone turnover activity and defective mineralization compared to normal bone (show histology 1 and show histology 2). The aim of therapy is to prevent secondary hyperparathyroidism, thus preventing osteitis fibrosa cystica. (See "Parathyroid hormone" below and see "Pathogenesis of renal osteodystrophy", section on Secondary hyperparathyroidism and osteitis fibrosa).

**Adynamic bone disease** — Adynamic bone disease is characterized by low osteoblastic activity and bone formation rates (show histology 3). It represents the major bone lesion seen in children who require dialysis therapy and is related to excess suppression of the parathyroid gland (due to the administration of calcium-containing phosphate binders and vitamin D analogues) [4] . These patients typically have a low serum intact PTH concentration (eg, <100 pg/mL), which is frequently accompanied by an elevated serum calcium. Adynamic bone disease is uncommon among predialysis patients. (See "Pathogenesis of renal osteodystrophy", section on Adynamic bone disease).

In the past, adynamic bone disease also resulted from aluminum toxicity due to the administration of aluminum-containing phosphate binders. (See "Aluminum toxicity in end-stage renal disease").

Adynamic bone disease increases the risk for fractures and metastatic calcification. It is best treated by allowing the intact PTH level to rise to increase bone turnover by decreasing or discontinuing the dose of the calcium-based phosphate binders and/or vitamin D therapy. (See "Pathogenesis of renal osteodystrophy", section on Adynamic bone disease).

**Osteomalacia** — Osteomalacia is a low turnover bone lesion that is characterized by an increased volume of unmineralized bone (osteoid) (show histology 4). It is characterized by reductions in bone turnover, the number of bone-forming and bone-resorbing cells, and an increase in the volume of unmineralized bone. In the past, this disorder resulted from aluminum toxicity due to the administration of aluminum-containing phosphate binders, which are no longer recommended. Osteomalacia is now much less common [4]

and, when it occurs, is thought to reflect vitamin D deficiency. (See "Pathogenesis of renal osteodystrophy", section on Osteomalacia).

Mixed osteodystrophy — Bone lesions in patients with mixed osteodystrophy include elements of both high and low bone turnover (show histology 5).

Other factors — Other factors that may impact on renal osteodystrophy in children include corticosteroid therapy, metabolic acidosis, hypophosphatemia (due to excessive dietary phosphate restriction or use of phosphate binders), nutritional vitamin D deficiency, medications that interfere with vitamin D metabolism (eg, anticonvulsants), and prolonged immobilization. (See "Drugs that affect bone metabolism", see "Overview of rickets in children").

DIAGNOSIS — Bone biopsy is the gold standard for establishing the type of renal osteodystrophy. In most clinical settings, it is not necessary to identify the specific form of renal osteodystrophy but rather determine if bone turnover activity is high or low. In children with CKD stage 5, a combination of serum PTH and calcium can distinguish between high (eg, osteitis fibrosa cystica) and low (eg, adynamic bone disease) turnover bone disease [5,6] . In one study of children on chronic peritoneal dialysis, a serum PTH level >200 pg/mL and a serum calcium value <10 mg/dL (2.5 mmol/L) identified patients with high turnover bone disease from secondary hyperparathyroidism with 85 percent sensitivity and 100 percent specificity [5] . Serum PTH concentrations <200 pg/mL and serum calcium value >10 mg/dL (2.5 mmol/L) were 100 percent sensitive but only 79 percent specific for identifying patients with adynamic bone lesions. In another study of children on hemodialysis, all patients with a serum PTH concentration >125 pg/ml and a serum calcium value <10 mg/dL (2.5 mmol/L) had either osteitis fibrosa or mixed osteodystrophy.

Indications for bone biopsy are not well established because clinical situations, in which having the diagnosis of bone disease is helpful, have not been identified. The K/DOQI guidelines suggest that a bone biopsy be considered to determine the type of renal osteodystrophy and guide therapy in children with stage 5 disease in whom there is nontraumatic bone fractures, suspected aluminum exposure, or persistent hypercalcemia with serum PTH between 400 and 600 pg/ml [1] . The site of biopsy is typically the iliac crest. The specimen is obtained after the administration of tetracycline markers, which are used to determine the rate of new bone formation. (See "Bone biopsy and the diagnosis of renal osteodystrophy").

In children with CKD stage 2 to 4, the most likely form of renal osteodystrophy is osteitis fibrosa cystica and a bone biopsy is not routinely needed. In these patients, an elevated serum PTH concentration is indicative of increased bone turnover disease. The K/DOQI working group has established target serum PTH values at different stages of CKD (show table 2).

MANAGEMENT — The goals of therapy are to prevent phosphate retention, hypovitaminosis D, and hypocalcemia. Management is focused on early detection and correction of these abnormalities because each contributes to the development of secondary hyperparathyroidism, which causes renal osteodystrophy.

Monitoring — Serum concentrations of calcium, phosphate, and PTH should be measured on an ongoing basis in all children with CKD, even those with mild disease

who often have evidence of abnormalities in bone metabolism. In a study in adults, for example, a reduction in the glomerular filtration rate (GFR) below 80 mL/min per 1.73 m<sup>2</sup> was associated with a reduction in serum calcitriol and a progressive increase in serum PTH [3]. As the GFR fell below 60 mL/min per 1.73 m<sup>2</sup>, serum PTH rose above normal values.

Early detection of bone metabolic abnormalities ensures that therapeutic interventions can be initiated, thereby preventing or minimizing renal osteodystrophy. The frequency of these measurements is based upon the stage of CKD (show table 3).

For calcium and phosphorus measurements, the K/DOQI guidelines recommend [1]:  
Stage 2 disease — Measurements at least yearly  
Stage 3 disease — Measurements at least every six months  
Stage 4 disease — Measurements at least every three months  
Stage 5 disease — Measurements at least monthly

For PTH measurements, the K/DOQI guidelines recommend: Stage 2 disease — Measurements at least yearly. Stage 3 disease — Measurements at least every six months  
Stage 4 and 5 disease — Measurements at least every three months

If therapy is initiated to correct serum abnormalities or to treat renal osteodystrophy, laboratory evaluation should be performed more frequently to ensure a response to therapy or to identify the need to adjust therapy.

Phosphate — Phosphate is a salt of oxidized phosphoric acid and is a key component of bone matrix.

Normally, the serum phosphorus concentration is highest in infants less than three months of age. As the child ages, the normal range of phosphorus values decreases (show table 4).  
0 to 3 months of age — 4.8 to 7.4 mg/dL (1.55 to 2.39 mmol/L)  
1 to 5 years of age — 4.5 to 6.5 mg/dL (1.45 to 2.1 mmol/L)  
6 to 12 years of age — 3.6 to 5.8 mg/dL (1.16 to 1.87 mmol/L)  
13 to 20 years of age — 2.3 to 4.5 mg/dL (0.74 to 1.45 mmol/L)

Phosphorus retention begins in the early stages of CKD and plays a central role in the development of hyperparathyroidism (show figure 1). This is first mediated by reduced production of calcitriol in the kidney, thereby removing part of the inhibitory effect of calcitriol on PTH release. The ensuing hyperparathyroidism appropriately increases urinary phosphate excretion. This adaptation is not complete as small increments in serum phosphorus persist. In more advanced CKD, this adaptation becomes less successful and the ensuing hyperphosphatemia promotes increasing hyperparathyroidism both by inhibition of calcitriol production and by a direct effect on the parathyroid glands. (See "Treatment of hyperphosphatemia in chronic kidney disease" section on Background and see "Pathogenesis of renal osteodystrophy" section on Hyperphosphatemia).

The clinical correlate of these pathophysiologic changes is that a child with CKD stage 2 and 3 disease has an elevated serum PTH but a serum phosphorus that, although increased, remains within the normal range. When the GFR falls below 30 mL/min per 1.73 m<sup>2</sup> (stage 4 disease), hyperphosphatemia will usually occur unless appropriate therapy is given.

Goals — In children, the K/DOQI practice guidelines recommend the following targeted goals for serum phosphate concentrations at different stages of CKD (show table 4) [1] : Stages 1 to 4 (GFR between 15 and 89 mL/min per 1.73 m<sup>2</sup>) — The serum phosphorus should be maintained at or above the age-appropriate lower limit but no higher than the age-appropriate upper limit. Stage 5 (GFR <15 mL/min per 1.73 m<sup>2</sup> or dialysis requirement) — The serum phosphorus should be maintained between 4 to 6 mg/dL (1.29 to 1.93 mmol/L) in children 1 to 12 years of age and between 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) in adolescents.

Interventions — In children with CKD, two therapeutic interventions to attain and maintain the targeted serum phosphorus concentration include restriction of dietary phosphorus and the use of calcium-based phosphate binders.

In controlled studies of both children and adults, dietary phosphorus restriction results in decreased serum PTH and increased serum 1,25-dihydroxyvitamin D (calcitriol) concentrations (show figure 1) [7,8] . Conversely, an intake of phosphorus that is twice the Dietary Reference Intake in children with CKD stage 3 increases serum PTH and decreases serum 1,25-dihydroxyvitamin D [7] . (See "Treatment of hyperphosphatemia in chronic kidney disease").

As a result of these studies, the K/DOQI practice guidelines recommend restricting dietary phosphorus in children with CKD who have an elevated serum PTH level to 100 percent of the Dietary Reference Intake (DRI) for age. 0 to 0.5 years - 100 mg/day 0.5 to 1 year - 275 mg/day 1 to 3 years - 460 mg/day 4 to 8 years - 500 mg/day 9 to 19 years - 1250 mg/day

Dietary phosphorus is restricted to 80 percent DRI if the serum PTH is above the target range and the serum phosphate concentration is above the age-appropriate normal range (show table 4) [1] . 0 to 0.5 years - 80 mg/day 0.5 to 1 year - 220 mg/day 1 to 3 years - 368 mg/day 4 to 8 years - 400 mg/day 9 to 19 years - 1000 mg/day

After the initiation of dietary restriction, serum phosphorus should be monitored at least every three months in children with CKD stages 3 and 4, and monthly in those with CKD stage 5.

Studies in children with CKD report no association of dietary phosphorus restriction with poor linear growth [9-12] . However, serum phosphorus concentrations below the target range for age should be avoided because of the potential adverse effects of hypophosphatemia on linear growth.

Compliance with dietary phosphate restriction in children is poor as most of their favorite foods are rich in phosphate. Thus, despite attempts to restrict phosphorus intake, phosphate binders often become necessary to prevent phosphate absorption from the gastrointestinal tract.

In children, several observational studies have shown that calcium-based phosphate binders are effective and safe in lowering serum phosphate and PTH levels [13,14] . These agents are recommended as the initial phosphate binder in children with CKD because other agents have significant side effects (such as aluminum [15] ) or have not been adequately studied in children (such as sevelamer) [1] .

Phosphate binders should be taken 10 to 15 minutes before or during the meal. The effect is less when taken between meals, since most dietary phosphorus has already been absorbed.

Phosphate binders, regardless of the agent used, have a limited phosphate-binding capacity. As examples, 1 g of calcium carbonate binds 39 mg of phosphate, 1 g of calcium acetate binds 45 mg of phosphate, and 400 mg of sevelamer HCl binds 32 mg of phosphate. Thus, phosphate-binding compounds will be effective in lowering serum phosphate levels only if dietary phosphate restriction is continued.

The choice among the many different calcium-containing phosphate binders, such as calcium carbonate, calcium acetate, calcium gluconate, and calcium ketoglutarate, is in large part dependent upon the patient's tolerance of the binder and the choice of the clinician. Several studies in adults have not shown an overall advantage of one preparation over another [1]. The total dose of elemental calcium should not exceed twice the DRI for calcium based on age with a maximum of 2500 mg/day, including the dietary calcium intake (show table 5). An exception is that calcium citrate should not be administered, since it markedly increases intestinal aluminum absorption. (See "Treatment of hyperphosphatemia in chronic kidney disease", section on Phosphate binders).

In contrast to this general recommendation, calcium-based phosphate binders should not be used as the sole agent in patients who are hypercalcemic (serum calcium >10.2 mg/dL, [2.55 mmol/L]). The preferred drug in this setting is sevelamer (Renagel®), a noncalcium and nonaluminum phosphate binder [16]. It may be used alone or in conjunction with a calcium-containing phosphate binder. (See "Treatment of hyperphosphatemia in chronic kidney disease" section on Phosphate binders).

With the concern that calcium-containing phosphate binders may contribute to soft tissue calcification, noncalcium and nonaluminum phosphate binders are used more frequently as initial therapy in adults. In children, data are limited comparing sevelamer to calcium-containing agents. Until further studies demonstrate the safety and efficacy of sevelamer in children, it should be reserved for children with hypercalcemia [1,17].

Other phosphate binders should be avoided in children with CKD: Aluminum hydroxide because of aluminum bone toxicity [15]. Aluminum deposition can cause low bone turnover, leading to renal osteodystrophy (eg, adynamic bone disease and osteomalacia). (See "Types" above and see "Aluminum toxicity in end-stage renal disease"). Magnesium-containing antacids (such as magnesium hydroxide), because of the risk of hypermagnesemia and the frequent development of diarrhea. Calcium citrate, because it markedly increases the absorption of dietary aluminum.

Calcium and vitamin D — In children with CKD, the homeostatic mechanisms that maintain normal serum calcium and 1,25-dihydroxyvitamin D (calcitriol) concentrations are disrupted. In the early stages of CKD, impaired production of 1,25 dihydroxyvitamin D is partly due to phosphate retention. In the later stages of CKD, decreased synthesis may also be due to loss of the renal enzyme required for the final step of 1-hydroxylation of 25-hydroxyvitamin D (calcidiol). In adults with CKD stage 2 through 4, there are reports of low serum 25-hydroxyvitamin D concentrations, which may contribute to low

serum values of 1,25 dihydroxyvitamin D. Comparable studies have not been performed in children. (See "Metabolism of vitamin D" and see "Active vitamin D analogs and calcimimetics to control hyperparathyroidism in chronic kidney disease").

Phosphate retention and 1,25 dihydroxyvitamin D deficiency decrease serum calcium and, as noted above, contribute directly to secondary hyperparathyroidism and renal osteodystrophy. (See "Pathogenesis of renal osteodystrophy" and see "Parathyroid hormone" below).

Vitamin D — In adults with CKD and elevated serum PTH, randomized controlled trials have shown that active vitamin D analogue therapy suppresses serum PTH secretion and improves bone disease in patients with CKD stages 3 through 5.

In children, calcitriol (1,25-dihydroxyvitamin D) has been reported in observational studies to decrease serum PTH concentrations and improve the linear growth of children with CKD [18,19] . (See "Active vitamin D analogs and calcimimetics to control hyperparathyroidism in chronic kidney disease").

The K/DOQI practice guidelines recommend the following evaluation for detection and treatment of vitamin D deficiency [1] . In children with stage 2 to 4 disease (GFR of 15 to 89 mL/min per 1.73 m<sup>2</sup>) and serum PTH values above the target range for the stage of CKD (show table 2), serum 25-hydroxyvitamin D concentrations should be measured.

If serum 25-hydroxyvitamin D is <30 ng/mL (75 nmol/L), treatment with ergocalciferol should be started (show table 6). Reassessment of serum 25-hydroxyvitamin D is recommended three months after the initiation of therapy.

If serum 25-hydroxyvitamin D is >30 ng/mL (75 nmol/L) in children with stage 2 to 4 disease, treatment with calcitriol should be started only if the serum PTH is above the target range, and the serum calcium level is <10 mg/dL (2.37 mmol/L) and the serum phosphorus level is less than age appropriate upper limits for the stage of CKD (show table 7). The recommended starting dose for is based on the body weight of the child:  
Weight <10 kg — 0.05 microgram every other day  
Weight between 10 and 20 kg — 0.1 to 0.15 microgram per day  
Weight >20 kg — 0.25 microgram per day

The use of calcitriol in patients with an elevation of serum calcium or phosphorus can lead to soft tissue calcification due to an increase in the calcium phosphate product. (See "Active vitamin D analogs and calcimimetics to control hyperparathyroidism in chronic kidney disease" and see "Soft tissue and vascular calcification" below).

Once vitamin D therapy is started, serum calcium and phosphorus concentrations should be measured after one month of therapy and at least every three months thereafter. Serum PTH should be measured at least every three months. The dose of ergocalciferol or calcitriol should be held if hypercalcemia develops or the serum PTH falls below the target range for the stage of CKD (show table 7). If hyperphosphatemia develops or persists, the dose of vitamin D should be decreased, and phosphate binders and dietary phosphate restriction intensified. In children with stage 5 disease (GFR <15 mL/min per 1.73 m<sup>2</sup>) and serum PTH >300 pg/mL, calcitriol should be administered to reduce the serum PTH to 200 to 300 pg/mL. Once calcitriol is started, serum calcium and phosphorus concentrations should be measured every two weeks for one month and at

least monthly thereafter. Serum PTH should be measured monthly for three months and then at least every three months. Serum PTH concentrations <100 ng/L should be avoided to prevent adynamic bone disease. Based upon the laboratory results, dosing of calcitriol should be appropriately adjusted. (See "Adynamic bone disease" above).

Calcitriol increases the gastrointestinal absorption of calcium and phosphate, which can lead to an elevated calcium phosphate product, possibly resulting in soft tissue calcification.

More selective vitamin D analogues, such as alfacalcidol, paricalcitol [20] , or doxercalciferol, have been developed that may reduce the risk of hypercalcemia and hyperphosphatemia. In one small controlled double-blinded study of 29 pediatric hemodialysis patients, paricalcitol compared to placebo decreased PTH levels but did not affect serum calcium, phosphorus, or calcium phosphate product [21] . In adult patients, the one clinical trial that directly compared paricalcitol to calcitriol found no significant differences between the two agents. Similar comparative data are lacking in children. As a result, there is no convincing evidence supporting the use of a specific vitamin D analogue over another. (See "Active vitamin D analogs and calcimimetics to control hyperparathyroidism in chronic kidney disease", section on Vitamin D derivatives).

In adults, calcimimetics have been increasingly used to suppress PTH secretion and decrease the risk of hypercalcemia associated with calcitriol. These agents, which increase the sensitivity of the calcium-sensing receptor (CaSR) in the parathyroid gland to calcium, have not been adequately studied in children. The use of calcimimetics has been anecdotal in children with severe and/ or refractory hyperparathyroidism, and is not part of standard care. (See "Active vitamin D analogs and calcimimetics to control hyperparathyroidism in chronic kidney disease", section on Calcimimetics).

**Hypocalcemia** — The total serum calcium should be maintained within a normal range for the laboratory used, generally between 8.8 and 9.7 mg/dL (2.2 to 2.37 mmol/L). With progressive loss of kidney function, phosphate retention and 1,25-dihydroxyvitamin D deficiency can result in hypocalcemia if appropriate therapy is not given.

Symptomatic hypocalcemia should initially be treated with parenteral calcium chloride [1] . Long-term therapy requires appropriate management of hyperphosphatemia and vitamin D deficiency as described above. (See "Treatment of hypocalcemia").

**Hypercalcemia** — Children with CKD who are treated with vitamin D therapy and calcium-containing phosphate binders may develop hypercalcemia. If total serum calcium values exceed 10.2 mg/dL (2.55 mmol/L), the dose of calcium-based phosphate binders should be reduced and/or therapy changed to sevelamer. Vitamin D therapy should also be discontinued until the serum calcium returns to the targeted range and then restarted with an appropriate dose adjustment.

**Parathyroid hormone** — High bone turnover seen in osteitis fibrosa and mixed osteodystrophy is a result of secondary hyperparathyroidism. The pathogenesis of secondary hyperparathyroidism in chronic renal failure is mediated via several complex and interactive pathways. The major factors stimulating parathyroid gland function are hyperphosphatemia, which initially acts by decreasing serum 1,25-dihydroxyvitamin D; the fall in calcitriol diminishes its suppressive effect on the parathyroid gland, leading to

hyperparathyroidism. In the late stages, hyperphosphatemia itself can directly increase PTH release. Hypocalcemia, if it develops, is an additional stimulus to PTH secretion. (See "Pathogenesis of renal osteodystrophy", section on Secondary hyperparathyroidism and osteitis fibrosa).

Serum PTH concentration is inversely correlated with renal function and is almost always elevated when the glomerular filtration rate falls below 60 mL/min per 1.73 m<sup>2</sup> [4]. Although the optimal serum PTH values in children with CKD are uncertain, the K/DOQI guidelines recommend targeted levels of serum intact PTH at different stages of CKD as follows (show table 2) [1]: Stage 2 and 3 disease — 35 to 70 pg/mL Stage 4 disease — 70 to 110 pg/mL Stage 5 disease — 200 to 300 pg/mL

The management and prevention of secondary hyperparathyroidism is complex and requires frequent monitoring and adjustment of therapy. The initial step is to correct phosphate retention by dietary restriction usually combined with either calcium-containing phosphate binders and/or sevelamer. (See "Phosphate" above).

This is followed by either calcium supplementation and/or vitamin D therapy. In the early stages of CKD, the clinician also should assess and replenish 25 hydroxyvitamin D (if the level is low) with oral ergocalciferol or cholecalciferol prior to initiating therapy with calcitriol. (See "Calcium and vitamin D" above).

In most children with stage 5 disease, the combination of dietary phosphate restriction, phosphate binders, and active vitamin D therapy is required to maintain normal age-appropriate serum phosphate value and a serum PTH concentration that is no more than two to four times normal. Severe secondary hyperparathyroidism requiring parathyroidectomy is rare in children.

Aluminum in chronic kidney disease — Aluminum-related disorders in CKD, although now extremely rare, can present with the findings of hypercalcemia, osteomalacia, microcytic anemia, and dialysis encephalopathy. The purpose of monitoring the plasma aluminum level in the late stages of CKD is to identify excessive aluminum intake or absorption that might have occurred so that corrective measures can be taken. To prevent aluminum toxicity, the regular administration of aluminum, historically provided most commonly in the form of phosphate binders, should be avoided and, in hemodialysis patients, the dialysate concentration of aluminum should be maintained at <10 mcg/L [1]. (See "Aluminum toxicity in end-stage renal disease").

Patients who are ingesting aluminum-containing phosphate binders or medications such as sucralfate that contain aluminum should not receive citrate simultaneously as the latter medication enhances the gastrointestinal absorption of aluminum. Serum aluminum levels should be measured yearly in patients with Stage 5 CKD, and the baseline level of serum aluminum should be <20 mcg/L. A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (>60 mcg/L) or clinical signs and symptoms of aluminum toxicity, or prior to parathyroid surgery if the patient has had aluminum exposure [1]. To help avoid toxicity, the low dose DFO test should not be performed in patients with serum aluminum levels above 200 mcg/L. (See "Aluminum toxicity in end-stage renal disease").

**COMPLICATIONS** — The sequelae of renal osteodystrophy in children include growth retardation, musculoskeletal deformities, and soft tissue calcification [1] .

**Growth failure** — Growth failure in children with CKD is multifactorial in origin. Potential contributing factors in addition to renal osteodystrophy include chronic metabolic acidosis, anorexia, inadequate caloric intake, and inadequate insulin-like growth factor. The relative importance of these factors in growth failure is uncertain. However, treatment is aimed at correcting all correctable abnormalities.

There is evidence of increased growth after interventions such as vitamin D therapy and normalization of serum PTH concentrations [18,19] . In addition to these standard goals of the treatment of CKD as described above, growth hormone therapy is also effective. The data supporting this conclusion are presented separately. (See "Management" above and see "Growth hormone treatment in children with chronic kidney disease").

**Musculoskeletal deformities** — Children with renal osteodystrophy are at increased risk for nontraumatic fractures. In addition, other skeletal deformities may develop, given that these children can be vitamin D deficient, hypophosphatemic, acidotic, on drugs that induce cytochrome P450 pathways, etc. The deformities are similar to those seen in children with vitamin D deficiency rickets. (See "Overview of rickets in children").

In children with CKD, the growth plate is vulnerable to injury with disruption of the connection between the epiphyseal plate and the metaphysis [22] . This abnormality, along with hyperparathyroid erosions of bone, puts the child at an increased risk for slipped epiphysis and genu valgum. (See "Slipped capital femoral epiphysis").

**Soft tissue and vascular calcification** — Soft tissue calcifications (also called calcinosis) can lead to long-term morbidity in patients with CKD. The sites include vascular, ocular, periarticular, and visceral calcifications and may be severe enough to produce calciphylaxis. Most of the data have been derived from studies in adults and are presented separately. The following discussion will emphasize the more limited data related to children. (See "Vascular calcification in chronic kidney disease" and see "Calciphylaxis" and see "Eye disorders associated with chronic kidney disease").

The etiology of soft tissue calcification is multifactorial in children. This issue was addressed in a retrospective autopsy review of 120 children with CKD from 1960 to 1983, 60 percent of whom had soft tissue calcification [23] . On multiple logistic regression analysis, the use of vitamin D or its analogues, the peak calcium phosphate product, the age at onset of renal failure, and male sex were associated with calcinosis. Vitamin D therapy showed the strongest independent association with calcinosis.

Soft tissue calcification can involve the vasculature, including the coronary arteries [23-25] . The frequency of coronary artery calcifications, as detected by electron beam CT, was evaluated in a series of 39 dialysis patients (age 7 to 30 years, mean 19 years) [24] . The following findings were noted: Coronary artery calcification was present in 14 of the 16 dialysis patients who were over 20 years of age, but not in any of the younger dialysis patients and in only 3 of 60 normal subjects 20 to 30 years of age. In addition to older age, the patients with coronary artery calcification had been dialyzed longer (14 versus 4 years) and had a significantly higher calcium phosphate product (65 versus 56 mg<sup>2</sup>/dL<sup>2</sup>).

In an attempt to minimize the risk of soft tissue and vascular calcification, the K/DOQI guidelines recommend that the calcium phosphate product be maintained below the following values [1] : Less than 55 mg<sup>2</sup>/dL<sup>2</sup> in children older than 12 years of age Less than 65 mg<sup>2</sup>/dL<sup>2</sup> in children younger than 12 years of age

This is best achieved by maintaining the serum level of phosphate within the target range and keeping the serum calcium within the normal range for the laboratory, generally between 8.8 and 9.7 mg/dL (2.2 to 2.37 mmol/L)

**SUMMARY AND RECOMMENDATIONS** — In children with chronic kidney disease (CKD), abnormalities in bone metabolism occur early affecting those with mild to moderate renal disease and is universal. If untreated, these patients will develop renal bone disease (renal osteodystrophy) as their renal failure progresses. Renal osteodystrophy can present as several different pathologic forms and includes osteitis fibrosa, adynamic bone disease, osteomalacia, and mixed osteodystrophy. Osteitis fibrosa cystica results from secondary hyperparathyroidism and is the form of bone disease seen in children with mild to moderate CKD. The other forms are seen in children with severe CKD and are often due to therapeutic interventions (eg, excess suppression of the parathyroid gland from calcium-containing phosphate binders and vitamin D analogues). (See "Types" above and see "Pathogenesis of renal osteodystrophy"). The Kidney Disease Outcome Quality Initiative (K/DOQI) provides guidelines to care for children with CKD who are at risk for developing renal osteodystrophy. These guidelines specifically outline measures to detect and treat abnormalities of bone metabolism and secondary hyperparathyroidism.

Our clinical practice is consistent with the K/DOQI guidelines in the management of bone metabolic abnormalities in children with CKD and includes the following: Management (frequency of monitoring and therapeutic interventions) is based upon the child's level of kidney function (show table 1 and show table 3). (See "Stages of chronic renal disease" above). Therapy focuses on prevention of phosphate retention and hypovitaminosis D because these are the main contributors to the development of secondary hyperparathyroidism, which results in renal osteodystrophy. (See "Management" above). We suggest that serum concentrations of calcium, phosphate, and parathyroid hormone should be measured on an ongoing basis in all children with stages 2 to 5 of CKD (show table 3) (Grade 2C). (See "Monitoring" above). In children with an elevated serum PTH and/or phosphate, we recommend reducing the PTH and/or phosphate concentration with dietary restriction of phosphorus and the use of phosphate binders, if necessary (show table 5) (Grade 1B). Calcium citrate, aluminum hydroxide, and magnesium-containing antacids should not be used as phosphate binders because of their adverse side effects. (See "Phosphate" above). In children with CKD stage 2 to 4, if serum PTH is above the target range, 25-hydroxyvitamin D concentration should be measured. If the 25 hydroxyvitamin D level is <30 ng/mL (75 nmol/L), we suggest that ergocalciferol be given (Grade 2C). If the level is >30 ng/mL (75 nmol/L) and the serum calcium level is <10 mg/dL (2.37 mmol/L), we recommend calcitriol therapy (Grade 1B). (See "Vitamin D" above). In children with CKD stage 5 and PTH levels >300 pg/mL, we recommend calcitriol should be administered until serum PTH is reduced to a range between 200 to 300 pg/mL (Grade 1B). (See "Vitamin D" above). Serum calcium should be maintained within a normal range for the laboratory used, generally between 8.8 and 9.7 mg/dL (2.2 to 2.37 mmol/L). If the patient is hypocalcemic, we recommend that calcium supplementation and/or vitamin D therapy be given (Grade 1B). (See "Hypocalcemia" above).

### Stages of chronic kidney disease

Stage Description GFR (mL/min/1.73 m<sup>2</sup>)

1 Kidney damage with normal or GFR 90

2 Kidney damage with mild GFR 60-89

3 Moderate GFR 30-59

4 Severe GFR 15-29

5 Kidney failure <15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m<sup>2</sup> for 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

### Phosphate restriction prevents hyperparathyroidism in renal failure

Relationship between the glomerular filtration rate (GFR) and the plasma parathyroid hormone (PTH) concentration in two groups of dogs which developed renal failure: one maintained on a regular diet (solid line); and one treated with dietary phosphate restriction (dashed line). A decline in GFR led to a progressive rise in PTH levels with the regular diet; limiting phosphate intake prevented both phosphate retention and the development of secondary hyperparathyroidism.

## **Course and treatment of autosomal dominant polycystic kidney disease**

**INTRODUCTION** — Although autosomal dominant polycystic kidney disease (ADPKD) can lead to end-stage renal disease (ESRD) in early childhood, progression to ESRD most commonly occurs in middle age and later. It is estimated that the likelihood of requiring dialysis is less than 2 percent below the age of 40, 20 to 25 percent by age 50, 35 to 45 percent by age 60, and 50 to 75 percent by age 70 to 75 [1,2]. (See "Autosomal recessive and dominant polycystic kidney disease in children").

The median age of initiation of ESRD has risen, possibly related in part to improved blood pressure control and more widespread use of inhibitors of the angiotensin system [3]. (See "Control of hypertension" below).

**COURSE** — A number of risk factors have been identified for progressive renal disease in ADPKD. These include [2,4-10]:

- Younger age at diagnosis
- Male gender
- Genotype (PKD 1 versus PKD 2)
- Episode of gross hematuria
- Hypertension
- Proteinuria
- Increased and increasing renal size

**Age at diagnosis** — The younger a patient is diagnosed with polycystic kidney disease, unless found as a result of asymptomatic family screening, the earlier end-stage renal disease is likely to develop [4,5]. Since the diagnosis is often prompted by the onset of symptoms, it is not surprising that patients diagnosed at a younger age have a worse prognosis [4,5].

In one of the largest reviews thus far of risk factors for progressive disease in ADPKD, an analysis and risk ratio calculation for the development of end-stage renal disease was performed in 834 patients [4]. Patients diagnosed before the age of 30 had a mean renal survival 10 years less than those diagnosed after the age of 30 ( $p < 0.0001$ ).

Despite improved understanding of the genetic risks for inheriting ADPKD, the proportion of patients with a diagnosis prompted by the onset of symptoms remains high (approximately 40 percent of cases) [11].

**Male gender** — The cause of the accelerated progression of renal disease among males, noted primarily in PKD 1, is unclear [12].

Hormonal manipulation in a rat model of autosomal dominant polycystic disease (ADPKD), the Han:SPRD rat, found that elevated levels of testosterone led to increased cyst growth, and female hormones may be associated with less cyst growth [13,14]. However, in a study utilizing magnetic resonance imaging (MRI) to determine renal size, no differences were seen in men versus women with regard to renal volume [15].

**Genetic abnormality** — The prognosis of ADPKD is dependent upon the gene mutation responsible for ADPKD. Approximately 85 percent of affected families have a defect in the polycystin 1 gene located on chromosome 16. Most of the remaining families have a mutation in the gene polycystin 2 located on chromosome 4 (referred to as PKD2). A few families have a defect unrelated to either locus; however, other gene mutations responsible for ADPKD have not been discovered [16]. (See "Genetics of autosomal dominant polycystic kidney disease and mechanisms of cyst growth").

Patients with PKD2 have a less severe phenotype than those with PKD1, but neither disorder is benign and early onset disease has been associated with both [17,18]. A direct comparison of outcomes between the two genetic abnormalities was assessed in a review of 333 and 291 patients with PKD1 and PKD2, respectively, as well as 398 matched controls [19]. The following results were reported:

- The median age of either death or the onset of end-stage renal failure was 53, 69, and 78 years for PKD1, PKD2, and control patients, respectively.
- The median age of presentation with renal failure was 54 and 74 years for those with PKD1 and PKD2, respectively.

Similar findings were noted in a prospective study of 136 patients with PKD1 and 60 patients with PKD2 who were followed for 22 years [20].

The better prognosis of patients with PKD2 compared to PKD1 may in part be related to slower rate of cyst growth. (See "Kidney growth rate" below).

**Kidney growth rate** — Sequential imaging studies suggest that changes in renal function correlate with renal volume growth rates, with faster growth associated with faster declines in glomerular filtration rate (GFR) [7,8,15,21-23]:

- In a longitudinal study of 229 patients, a significant correlation was observed between decreases in GFR and increases in renal volume by ultrasound [7].
- In the Consortium for Radiologic Imaging Studies of Polycystic kidney disease (CRISP) cohort of 242 patients, renal and cyst volumes and renal blood flow as determined by MRI were correlated with severity of kidney dysfunction as determined by iothalamate GFR [8,22]. Sequential measurements of these parameters over the course of three years in 232 patients demonstrated the following [15]:

— An increase in mean kidney and cyst volumes, with a mean rate of change in kidney volume of approximately 5 percent per year. Patients with larger kidneys at baseline experienced a proportionately greater increase. Interestingly, 17 patients (7 percent) had a significant decrease in kidney volume.

— Overall, there was an inverse correlation between GFR, and renal and cyst volume growth. During this relatively short study, a significant decline in GFR was found only among individuals with kidney volumes >1500 mL at baseline (-4 mL/min per year).

— Patients with the PKD2 gene had smaller kidney volumes at baseline (711 mL versus 1197 mL among those with the PKD1 gene), and a lesser absolute increase during follow-up (136 mL versus 245 mL). Measured GFR increased in the PKD2 group by +8.2 mL/min, and decreased in the PKD1 group by -2.4 mL/min ( $p=0.06$ ). A subsequent analysis demonstrated that the change in kidney volume and cyst size was proportionate in each group [24].

- In another three year sequential study from the CRISP cohort, a reduction in blood flow and an increase in total kidney volume both preceded the decline in GFR [23].

These studies suggest that baseline kidney volume and sequential measurements can provide valuable clinical and diagnostic information, since a faster rate of growth in kidney and cyst volumes is directly associated with a faster rate of decline in GFR.

Although ultrasound remains the diagnostic imaging study of choice, it does not appear to be sufficiently accurate to measure change in kidney volume over a short period of time. Its inaccuracy in measuring cyst volume relative to MRI was described in a study from the CRISP cohort [25]. The variability of renal volume measurements between ultrasonographers ranged from 19 to 42 percent.

**Interfamilial and intrafamilial heterogeneity** — It has been suggested that the prognosis in a given patient could be inferred from the course of other family members. If, for example, the patient's father and uncle developed end-stage renal disease by the age of 50, then the patient would be expected to progress at approximately the same rate.

This type of homogeneity implies that the clinical phenotype may correlate with the inheritance of a specific mutation [6]. As an example, in a comparison of outcomes of ten large families with PKD1, each of which had a unique disease-associated haplotype and at least 12 affected members, significant interfamily differences were observed in overall survival, renal survival, and prevalence of hypertension [26].

A similar correlation has been reported with PKD2 [27,28]. In the largest study to date, the correlation between the genotype and clinical phenotype was evaluated in 461 affected patients among 71 families with known mutations [28]. Milder disease was associated with splice-site mutations. In a second multicenter European study, a less severe phenotype was also observed in families with mutations in the 3' end of the gene, suggesting (but not proving) that a truncated protein product may be mildly functional [27].

However, substantial clinical heterogeneity has also been described among patients with the same genetic mutation. In the previously mentioned genotype-phenotype study of PKD2, for example, there was marked variability in the age of onset of either chronic renal failure or end-stage renal disease in patients with four specific genetic abnormalities [28]. With one mutation, for example, the reported age of onset of an adverse renal outcome varied from 40 to over 80 years of age among seven different individuals. In addition,

substantial intrafamilial heterogeneity of at least one parent-offspring pair occurs in approximately 50 percent of cases even though the genetic defect is the same [29].

A possible explanation for differing outcomes in patients with the same mutation is that late measures of disease severity (eg, significant elevation in serum creatinine) instead of renal volume may be too insensitive and affected by other factors. Alternatively, as suggested by animal studies, modifier gene(s) may increase the severity of the defect induced by the PKD gene [6]. Examples of evidence in support of modifier genes include the following:

- One study that found marked intrafamilial variability in renal disease progression among siblings and monozygotic twins [30]. The mean difference in age at the onset of end-stage renal disease was significantly less among the nine pairs of monozygotic twins (two years) than among the 56 sibships (seven years). This suggests that the observed variability is likely due to the inheritance of modifier genes.
- Among 83 PKD1 families, quantitative analysis of 315 patients without end-stage disease and an additional 389 affected family members in whom data on age of onset of ESRD or age without ESRD was available (but without clinical evaluation) found that 20 to 60 percent of the variance in clinical traits resulted from inherited differences in modifier genes [31]. More specifically, 32 percent of the differences in the creatinine clearance and 40 to 50 percent of the variation in age of onset of end-stage renal disease could be attributed to modifier genes. Although this study had some limitations [12], these findings further support the hypothesis that genetic modifiers likely play a significant role in disease manifestations.

The angiotensin I converting enzyme gene may be such a modifier gene. In one study of 189 patients from 46 families, inheritance of the DD allele (compared to the ID and II alleles) was significantly associated with early renal failure: 10 of the 11 patients with the end-stage renal disease prior to the age of 40 had the DD genotype [32].

Evidence for the cystic fibrosis transmembrane conductance regulator gene as another modifier gene was provided by the evaluation of one family with both ADPKD and cystic fibrosis (CF) [33]; in this study, two patients with both disorders had less severe disease compared to other family members. However, a wide survey of ADPKD probands failed to find such a protective effect for the most common mutation observed in CF as well as an intronic polymorphism known to be associated with Wolffian duct abnormalities [34]. These findings suggest that, if the CF gene has a modifying rule, additional mutations may be responsible. (See "Genetics of autosomal dominant polycystic kidney disease and mechanisms of cyst growth").

Although further study is required, it appears that familial phenotypes depend upon both the inherited mutation in the PKD genetic locus as well as the presence of other modifying genetic factors that interact with the suspect gene and/or gene product [6,12,35,36].

**Combination of risk factors** — The presence of multiple risk factors further enhances the risk of progressive renal disease in both men and women. In men, for example, a particularly high risk for early development of end-stage renal disease is conferred by the combination of the diagnosis of ADPKD before age 30, an episode

of gross hematuria before age 30, and documentation of hypertension before the age of 35. In one series, the probability of renal survival at age 48 was zero for the 29 men with all three risk factors, as compared to 100 percent for the 51 men without any of the risk factors [4].

**MECHANISM OF RENAL FAILURE** — Even though cysts form in only a small number of nephrons (<5 percent), it had been proposed that growth of these cysts leads to renal failure by compressing adjacent normal parenchyma. There is, however, little evidence of tissue compression in the kidney, and similar cyst growth in the liver is rarely associated with clinically significant hepatic synthetic dysfunction. There is also no evidence of increasing segmental glomerulosclerosis, as might be expected if secondary glomerular injury were responsible for disease progression [37]. The observations that protein excretion is almost always less than 1 g/day (unless there is a superimposed primary glomerular disease) [38] and that uninephrectomy does not appear to accelerate the rate of decline in renal function are also compatible with a relatively minor role for hemodynamic factors in ADPKD [39]. (See "Secondary factors and progression of chronic kidney disease").

It is therefore likely that other factors play an important role in the progressive decline in renal function. Histologic examination of tissue from patients with early and end-stage renal failure suggests that progressive renal failure in ADPKD correlates most closely with the development of vascular sclerosis and interstitial fibrosis [37]. How these changes occur and their possible relation to cyst formation are not clear.

Apoptosis (programmed cell death) also may play an important role [40]. One study found increased apoptosis in glomeruli, cyst walls, and both cystic and noncystic tubules from patients with ADPKD and renal failure, but not in patients without renal failure or those with no renal disease; tubular apoptosis was also absent in patients with primary glomerular diseases. Thus, cysts may promote progressive renal failure in part by causing apoptosis in noncystic glomerular and tubular cells.

## TREATMENT

**Inhibition of fluid secretion** — Animal models have provided some support for the theory that blocking the transporters that promote fluid movement into the cysts might be one way to slow cyst growth. At present, the best hope for an effective therapy seems to lie with the vasopressin V2 receptor antagonists.

**Vasopressin receptor antagonists** — Increasing in vitro evidence suggests that intracellular cyclic AMP (cAMP) plays a significant role in cystogenesis in polycystic kidney disease [41,42]. (See "Genetics of autosomal dominant polycystic kidney disease and mechanisms of cyst growth", for a detailed discussion of this issue).

Based in part upon these observations, the effectiveness of vasopressin V2 receptor antagonists, which lower renal epithelial cell intracellular cAMP levels, have been evaluated in animal models of this disorder:

- In a transgenic model of PKD 2, the administration of the vasopressin V2 receptor antagonist OPC-31260 prevented renal enlargement and dysfunction, and inhibited cystogenesis [43]. Renal cyclic AMP levels were decreased with this agent, resulting in decreased cystic fluid collection. Urine volume was not increased in treated animals.

- The administration of the selective V<sub>2</sub> receptor antagonist tolvaptan (OPC-41061) lowered renal cAMP levels and decreased the severity of cyst formation in the PCK rat, a model of human autosomal recessive polycystic kidney disease [44]. Significantly lower kidney weights and cyst and fibrosis volumes were observed with tolvaptan.
- PCK rats that do not express vasopressin are completely protected from renal cyst formation [45]. These animals develop renal cysts when they are exposed to the V<sub>2</sub> agonist, 1-deamino-8-D-arginine vasopressin (DDAVP) [45,46].

Both tolvaptan and OPC-31260 (the agent used in the previously cited study) inhibit mitogen-activated protein kinase (MAPK) signaling, which may mediate the proliferative response to cAMP in the kidney. Similarly, PCK rats that do not express AVP have markedly reduced MAPK signaling [45].

Phase II trials of V<sub>2</sub> antagonists in polycystic kidney disease have been completed, and phase III trials are currently active [47,48].

**Other approaches** — In animal models of cystic disease, blocking sodium channels with the potassium-sparing diuretic amiloride minimizes sodium entry and diminishes or halts cyst enlargement [49]. Amiloride has also been shown in vitro to diminish sodium transport in human low-sodium cysts [50]. Another possible way to prevent cyst enlargement is to restrict the intake of caffeine, which promotes cyst growth in in vitro studies [51].

Although these observations are intriguing, the amiloride or caffeine restriction have not been demonstrated to be effective or harmful in patients with PKD. Despite this, a potential benefit of restricting caffeine (which increases cyclic AMP levels) is strongly supported by benefits associated with vasopressin receptor antagonists; these agents appear to act in part by lowering renal cAMP levels. (See "Vasopressin receptor antagonists" below).

Experimental data suggest that fluid secretion in several animal species is in part via active chloride transport, which may be reduced by somatostatin. The finding of somatostatin receptors in the human kidney raises the possibility that it may reduce fluid accumulation in PKD. In a pilot study comparing somatostatin to placebo in patients with PKD, active therapy was associated with a smaller increase in cyst size and total kidney volume after six months of treatment [52].

Decreasing cyst fluid accumulation will slow the rate of progression only to the degree that fluid secretion into the cyst is responsible for increasing cyst size.

**Inhibition of cell proliferation** — In addition to fluid accumulation, it seems likely that activation of proto-oncogenes and subsequent tubular hyperplasia play an important role [53,54].

Studies in murine models of cystic renal disease have suggested possible slowing of disease progression from a variety of medical therapies including methylprednisolone, urinary alkalization, taxol, rapamycin, and lovastatin [55-62]. In addition, the severity of cystic kidney disease in rodent models of disease can be ameliorated using epidermal growth factor receptor tyrosine kinase inhibitors, peroxisome proliferator-

activated receptor agonists, cyclin-dependent kinase inhibitors, and mitogen-activated protein kinase inhibitors [63-67].

No clinical studies using any of these interventions are available.

**Cyst drainage** — In theory, it might also be beneficial to preserve renal function by draining large cysts. Direct reduction of cyst size by percutaneous aspiration, aspiration with sclerosis [68], or surgical drainage has been effectively used to relieve severe or refractory pain; there is, however, no evidence that these measures improve renal function or delay the rate of disease progression [69]. This lack of benefit is compatible with the observation that the degree of renal failure correlates best with vascular sclerosis and interstitial fibrosis, rather than cyst compression of adjacent tissue [37]. (See "Renal manifestations of autosomal dominant polycystic kidney disease").

**Control of hypertension** — Modalities aimed at diminishing secondary hemodynamic injury, such as control of hypertension and dietary protein restriction, have also been evaluated in patients with ADPKD. Effective treatment of hypertension may have a dual benefit: slowing the rate of decline in renal function [3]; and minimizing the risk of rupture of a cerebral aneurysm. Patients with hypertension are much more likely to develop progressive renal failure [70]. It is not clear, however, whether the renal disease causes the hypertension or the development of hypertension exacerbates the renal injury, perhaps by inducing the vascular injury described above [37].

Angiotensin converting enzyme (ACE) inhibitors can effectively lower blood pressure in most patients with ADPKD. (See "Hypertension in autosomal dominant polycystic kidney disease" for a discussion of the potential benefits and risks, such as a modest reduction in glomerular filtration rate, associated with the use of these agents in ADPKD).

ACE inhibitors can also minimize the degree of secondary glomerular injury in chronic renal diseases via a preferential reduction in intraglomerular pressure. An effect on proteinuria reduction is likely to be of less importance in ADPKD, in which the general lack of glomerulosclerosis [37] and usually minimal degree of proteinuria suggest a limited role for glomerular damage in disease progression [71,72]. In one study of 270 patients, for example, only 48 (18 percent) excreted more than 300 mg of protein per day [73]. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease" and see "Renal manifestations of autosomal dominant polycystic kidney disease", section on Proteinuria).

However, ACE inhibitors have other potential beneficial effects, including interruption of angiotensin II mediated profibrotic cytokine production. An ongoing study is examining the possibility that combination therapy with ACE inhibitors and angiotensin receptor blockers may delay progression of ADPKD (HALT-PKD). (See "Secondary factors and progression of chronic kidney disease", section on Angiotensin II).

**Protein restriction** — There are conflicting findings on the efficacy of a low protein diet (0.6 to 0.7 g/kg per day). Initial studies showed a slowing in the rate of loss of renal function [74], while a reduced rate of cyst growth was noted in experimental polycystic kidney disease [75]. However, these observations have not been confirmed by later reports [76,77]. The MDRD study, for example, showed no improvement in the course of

ADPKD with protein restriction in patients with a baseline GFR between 25 and 55 mL/min [69]. This is not surprising, since secondary glomerular injury does not appear to be important in this disorder.

At present, we do not restrict protein intake below 1 to 1.1 g/kg per day in patients with ADPKD given the limited evidence of benefit. (See "Protein restriction and progression of chronic kidney disease").

**Ammoniogenesis and alkali therapy** — Any form of chronic renal failure is associated with an adaptive increase in ammonia generation per functioning nephron in an attempt to excrete the daily acid load. The local accumulation of ammonia may contribute to the tubulointerstitial disease that is commonly seen. Ammonia may also promote cyst formation and, in a rat model of cystic disease, diminishing ammonia generation with alkali therapy led to a marked reduction in the severity of the cystic disease and interstitial inflammation [78].

The applicability of these findings to ADPKD in humans is uncertain, but prevention of metabolic acidosis is desirable for other reasons, since it appears to protect against bone disease and muscle wasting. (See "Treatment of metabolic acidosis in chronic kidney disease").

**PREGNANCY** — The effect of pregnancy in women with ADPKD is variable. Women who already have renal insufficiency may have similar difficulties as those with other chronic renal diseases. (See "Pregnancy in women with underlying renal disease"). The maternal and fetal outcome in women with relatively normal renal function has been illuminated in a report of 605 pregnancies in 235 women with a plasma creatinine concentration  $\leq 1.2$  mg/dL (105  $\mu$ mol/L) [79]. The following observations were noted:

- The fertility rate in men and women was similar to unaffected family members without ADPKD.
- Normotensive women usually had successful, uncomplicated pregnancies. However, those women who developed new-onset hypertension (16 percent) with or without preeclampsia were more likely to develop chronic hypertension.
- Hypertensive women were at increased risk for fetal loss and preeclampsia. Women who developed preeclampsia had higher rates of prematurity and perinatal mortality.
- There was an increased frequency of ectopic pregnancies in ADPKD women, suggesting that fallopian tube structure, ciliary function, or movement is abnormal in ADPKD women.
- There was a suggestion that four or more pregnancies was associated with lower creatinine clearances, suggesting that repeated pregnancy may enhance the rate of disease progression.

**RENAL REPLACEMENT THERAPY** — Patients with ADPKD who progress to end-stage renal disease require renal replacement therapy. As with all patients, the options are either dialysis or renal transplantation, but peritoneal dialysis is less commonly performed. This is due in part to the clear incompatibility between the intraabdominal space requirements for effective peritoneal exchange and the presence of massively enlarged kidneys. In addition, there may be an increased risk of peritonitis secondary to cyst infections or complications of diverticular disease [80]. Nevertheless, some centers have found that peritoneal dialysis is well tolerated and results in no specific difficulties in the patient with ADPKD requiring renal replacement therapy [81].

Patients with ADPKD and renal failure are therefore most commonly treated with hemodialysis or undergo renal transplantation. In general, such patients have equivalent or perhaps better overall outcomes with any renal replacement therapy compared to non-ADPKD patients [82-86].

**Renal transplantation** — Although the outcomes are usually good, there are some issues in the renal transplant recipient that are specific for ADPKD, including potential need for nephrectomy and higher rate of complications.

A few complications appear to be more frequent or unique in this patient population; these include posttransplant erythrocytosis, symptomatic aneurysms, urinary tract infections, diverticulitis, and gastrointestinal disorders requiring surgery [82,87-89]:

- One study of 874 consecutive renal transplant recipients, 114 of whom had ADPKD, compared the posttransplant outcomes and manifestations of patients with ADPKD with a matched control population [82]. At follow-up at 63 months, no difference in patient and graft survival was observed between the two groups. Clinical characteristics more frequently observed or unique to patients with ADPKD included elevated hematocrit levels, the requirement for nephrectomy (19 before and 7 after transplantation), diverticulitis (four patients, two with perforation) and symptomatic aortic aneurysms (death in two patients).
- A second series of 1417 renal transplant recipients, 145 of whom had ADPKD, found that gastrointestinal surgery was required twice as often in patients with polycystic disease (12 versus 6 percent for those without ADPKD) [87]. A perforated colon was the most common abnormality in the ADPKD group, a possible reflection of the high frequency of colonic diverticulosis in patients with ADPKD who progress to end-stage renal disease. (See "Extrarenal manifestations of autosomal dominant polycystic kidney disease").

**Nephrectomy** — Some patients require nephrectomy of one or both cystic kidney(s) in order to better accommodate the allograft, or for recurrent urinary tract infection, chronic pain, or chronic hematuria [90,91]. Traditionally, open nephrectomy was preferred, but newer techniques have been developed to enable laparoscopic removal of large cystic kidneys [92,93].

General results appear to be similar with nephrectomy performed pre-, during or post-renal transplantation, but concomitant nephrectomy and transplantation are associated with increased patient satisfaction [90,91]. In one series of 32 patients, 7, 16 and 9 patients underwent pre-, during and post-transplant nephrectomy, respectively [91]. As expected, blood loss, operative time and hospitalization length were somewhat greater for the concomitant nephrectomy group (by approximately 50 mL, 160 minutes, and 1.5 to 2 days, respectively), but this does not account for the transplant surgery procedure in those who had nephrectomy post-transplant. Renal allograft function at three month follow-up was the same for the concomitant and post-transplant nephrectomy groups.

**Hemodialysis** — Survival of patients with ADPKD undergoing hemodialysis appears to be superior (by 10 to 15 percent at five years) to that of patients with other causes of end-stage renal disease, including nondiabetics [83,84,86]. In one large survey using data from the United States Renal Data System, the relative risk of death

was lower among patients with ADPKD compared to nondiabetic control dialysis patients (RR of 0.57,  $p < 0.001$ ) [86].

This difference in survival is primarily due to a lower incidence of coronary artery disease in these generally more healthy patients with ADPKD. Clinical problems more frequently observed in patients with ADPKD include renal pain (36 versus 2 percent for non-ADPKD patients), gross hematuria (36 versus 16 percent), and renal infection (16 versus 2 percent) [84].

**Peritoneal dialysis** — A survival benefit among patients with ADPKD, compared to those without ADPKD, is also observed with peritoneal dialysis. In addition, limited evidence suggests that patients with ADPKD may have superior survival rates with peritoneal dialysis than with hemodialysis [85].

**CAUSES OF DEATH** — It has been reported from national registry data that the distribution of causes of death among patients with ADPKD is similar to patients with other causes of end-stage renal disease, with most deaths attributable to cardiac causes [86]. One report more closely examined the cause of death in 129 patients with ADPKD, 58 percent of whom had an autopsy [94]. The most common causes were heart disease (36 percent), infection (24 percent), and a neurologic event (12 percent). Cardiac hypertrophy was seen in 89 percent of autopsied patients and coronary disease in 81 percent. Neurologic deaths were primarily due to ruptured intracranial aneurysm (6 percent) and hypertensive intracerebral hemorrhage (5 percent). No patient died of renal cancer.

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## **Continuous renal replacement therapies: Overview**

**INTRODUCTION** — Continuous renal replacement therapies (CRRTs) involve either dialysis (diffusion-based solute removal) or filtration (convection-based solute and water removal) treatments that operate in a continuous mode [1-4]. Variations of CRRT might run 12 to 14 hours, especially during daytime periods of full staffing. This regimen has become more prevalent in Europe and has been called "go slow dialysis." The longer duration of CRRT makes it quite different from conventional intermittent hemodialysis in which each treatment lasts four to six hours or less.

The major advantage of continuous therapy is the slower rate of solute or fluid removal per unit of time. Thus, CRRT is generally better tolerated than conventional therapy, since many of the complications of intermittent hemodialysis are related to the rapid rate of solute and fluid loss.

**TERMINOLOGY** — There are many variations of CRRT and the remainder of this topic will provide a general overview of the nomenclature that has been developed. The different modalities are categorized according to the access characteristics — blood or peritoneal, venovenous or arteriovenous ([show table](#)).

**Arteriovenous or venovenous** — Arteriovenous (AV) refers to the use of an arterial catheter that allows blood to flow into the extracorporeal circuit by virtue of the systemic blood pressure. A venous catheter is placed for return. Venovenous (VV) is an alternative modality in which both catheters or one dual lumen catheter are placed in veins. An extracorporeal blood pump is required to circulate blood through the extracorporeal circuit.

The advantage of arteriovenous access is that it is simple to set up and does not require an extracorporeal blood pump. It does, however, require arterial puncture with an attendant risk of arterial embolization. Blood flow may also be unreliable in patients who are hypotensive or have severe peripheral vascular disease.

Venovenous access, on the other hand, does not require arterial access, involves less systemic anticoagulation, uses only one dual lumen catheter, and has faster and more reliable blood flow than with arterial access. The only disadvantage is the requirement for an extracorporeal blood pump.

**Hemodialysis** — Hemodialysis (HD) refers to the transport process by which a solute passively diffuses down its concentration gradient from one fluid compartment (either blood or dialysate) into the other. During HD, urea, creatinine, and potassium move from blood to dialysate, while other solutes, such as calcium and bicarbonate, move from dialysate to blood. The dialysate flows countercurrent to blood flow through the dialyzer to maximize the concentration gradient between the compartments and therefore to maximize the rate of solute removal. The net effect is the production of desired changes in the plasma concentrations of these solutes: a reduction in the blood urea nitrogen and plasma creatinine concentration; and an elevation in the plasma calcium and bicarbonate concentrations.

**Hemofiltration** — Hemofiltration (HF) refers to the use of a hydrostatic pressure gradient to induce the filtration (or convection) of plasma water across the membrane of the hemofilter. The frictional forces between water and solutes (called solvent drag) results in the convective transport of small and middle molecular weight solutes (less than 5000 Daltons) in the same direction as water. Substitution fluid is usually required to prevent excessive fluid removal.

The process of HF itself removes smaller solutes (such as urea and electrolytes) in roughly the same concentration as the plasma. There is therefore no change in the plasma concentrations of these solutes by HF, in contrast to those achieved by HD. However, the administration of substitution fluid will lower by dilution the plasma concentrations of those solutes (such as urea and creatinine) not present in the substitution fluid.

**Hemodiafiltration** — Hemodiafiltration (HDF) refers to a combination of dialysis and filtration. Solute loss primarily occurs by diffusion dialysis but 25 percent or more may occur by hemofiltration.

**CONTINUOUS REPLACEMENT THERAPIES** — The acronyms that have derived from the above concepts describe continuous therapies with the following general characteristics.

**Continuous arteriovenous hemofiltration** — Continuous arteriovenous hemofiltration or CAVH uses AV access to remove fluid and solutes by convection. Its per hour efficiency of solute removal is generally quite low, since no diffusion occurs. Thus, 24 hour/day operation or the addition of enhancing techniques is required.

**Continuous venovenous hemofiltration** — Continuous venovenous hemofiltration or CVVH is similar to CAVH except that the venovenous access mandates use of a blood pump.

Chronic hemofiltration, although not commonly used in North America as a chronic renal replacement therapy, offers some advantages compared with conventional hemodialysis, including a more physiologic process [5].

**Slow continuous ultrafiltration** — Slow continuous ultrafiltration or SCUF is strictly a dehydrating procedure with no intent to substantially remove solute. Access can be arteriovenous or venovenous. SCUF is similar to CAVH or CVVH except that the ultrafiltration rate is held at a lower rate; thus, SCUF is primarily used when the fluid removal goals are modest.

**Continuous arteriovenous hemodialysis** — Continuous arteriovenous hemodialysis (CAVHD or CAVD) is similar to CAVH with two exceptions: dialysate is run at a low flow rate countercurrent to the direction of blood flow; and the ultrafiltration rate is not maximized to protect against the development of hypotension. Fluid removal is slower than with CAVH alone, but a greater reduction in solute concentration is achieved.

**Continuous venovenous hemodialysis** — Continuous venovenous hemodialysis (CVVHD or CVVD) utilizes venovenous access and a blood pump, but is otherwise similar to CAVHD.

**Continuous arteriovenous hemodiafiltration** — Continuous arteriovenous hemodiafiltration is similar to CAVHD except that ultrafiltration is allowed at a rate beyond that necessary to reestablish euvolemia. From the viewpoint of solute removal, CAVHDF combines diffusion to aggressively removal small solutes with convection to remove large solutes. Because the volume of fluid ultrafiltered is so large, replacement fluid must be given to maintain euvolemia.

**Continuous venovenous hemodiafiltration** — Continuous venovenous hemodiafiltration or CVVHDF is similar to CAVHDF, except that venovenous access is utilized and a blood pump is required.

**Continuous equilibrium peritoneal dialysis** — Continuous equilibrium peritoneal dialysis (CEPD) is a long-dwell procedure similar to CAPD. A semipermanent peritoneal dialysis catheter is placed. Rapid exchanges are used initially to attain fluid and solute balance (as in acute PD). This is followed by longer dwell times to maintain this balance.

**Sustained low efficiency or extended daily dialysis** — Dialytic regimens have been developed which, although not necessarily continuous, have therapeutic aims in common with other CRRTs; these include lower solute clearances that are maintained for longer periods of time. Such regimens are collectively referred to as "sustained low efficiency dialysis" (SLED), but terms used in the literature include "extended daily dialysis" (EDD) and "slow continuous dialysis" (SCD).

**Choice of therapy** — The choice of modality is dependent upon several factors including availability, the expertise of the clinician, hemodynamic stability, vascular access, and whether the primary need is for fluid and/or solute removal [6]. The last factor is often an important determinant, since each of these procedures is associated with a different rate of solute and water removal.

As examples:

- SCUF, CVVH, or CAVH can be used if fluid removal is the primary goal. We generally prefer venovenous access because of its more predictable blood flow rate. However, arteriovenous access can be used if blood pumps are not available.
- CAVHD will probably be more effective than CAVH in the highly catabolic patient with a large small solute load.
- One of the forms of HDF, with its convective removal of larger solutes, may be desirable in the patient with sepsis in whom an ancillary goal is the removal of inflammatory mediators.

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**Continuous renal replacement therapies**

**Blood access**

Arteriovenous

Continuous arteriovenous hemofiltration

Continuous arteriovenous hemodialysis

Continuous arteriovenous hemodiafiltration

Venovenous

Continuous venovenous hemofiltration

Continuous venovenous hemodialysis

Continuous venovenous hemodiafiltration

Slow continuous ultrafiltration

Slow low efficiency dialysis or dialfiltration

Slow low efficiency daily dialysis

Extended daily dialysis

**Peritoneal access**

Continuous equilibrium peritoneal dialysis

## **Protein restriction and progression of chronic kidney disease**

**INTRODUCTION** — Extensive studies in animals and preliminary studies in humans suggest that progression of a variety of chronic kidney diseases (CKD) may be largely due to secondary hemodynamic and metabolic factors, rather than the activity of the underlying disorder. Identification of these factors, such as intraglomerular hypertension and glomerular hypertrophy, is clinically important because they can be treated, which may prevent or minimize further glomerular injury. (See "Secondary factors and progression of chronic kidney disease").

In a variety of animal models (such as subtotal nephrectomy and diabetic nephropathy), lowering protein intake protects against the development of glomerular scarring (called glomerulosclerosis) [1,2]. This effect is mediated, in part, by changes in glomerular arteriolar resistance, leading to a reduction in intraglomerular pressure [1,2] and decreased glomerular hypertrophy [3].

Dietary protein restriction may also be beneficial by exerting nonhemodynamic effects. In experimental focal glomerulosclerosis, for example, a very low protein diet can markedly reduce glomerular scarring in conjunction with decreased expression of the cytokines transforming growth factor (TGF) beta-1 and platelet-derived growth factor (PDGF), and of glomerular genes regulating the synthesis of excess matrix that contributes to the sclerotic lesions [4,5]. The mechanism by which protein intake affects cytokine expression is unclear, but the net effect may be preserved glomerular filtration due to diminished matrix accumulation [4,5]. (See "Pathogenesis and diagnosis of focal glomerulosclerosis"). The applicability of these findings to humans remains unproven.

Studies in humans indicate that an increase in the glomerular filtration rate can be induced by animal protein and by amino acid mixtures [6-9]; in comparison, vegetable protein and egg whites alone produce little or no effect [8,9]. Why the latter sources of protein have little hemodynamic activity is not clear, but lower concentrations of the amino acids that cause renal vasodilatation (such as glycine and alanine) and lesser stimulation of vasodilator prostaglandins may be involved [8].

A review of protein restriction, including mechanisms of action, in slowing the progression of chronic kidney disease is presented in this topic review. A detailed discussion of the use of antihypertensive therapy in CKD is presented separately. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease").

**MECHANISM OF PROTEIN-INDUCED HYPERFILTRATION** — The mechanism by which dietary protein or amino acids affect renal hemodynamics is not completely understood. Two major theories have been proposed, including the altered release of a hormone or hormones and an intrarenal effect involving sodium reabsorption and/or tubuloglomerular feedback [6,7].

**Hormonal effects** — Enhanced secretion of glucagons, a direct renal vasodilator, may be a mediator of protein-induced hyperfiltration [6,7]. A high protein diet also increases the release of at least two other hormones that can raise the glomerular filtration rate, including insulin-like growth factor I (IGF-I) and kinins [10,11]. IGF-1 is a direct renal vasodilator that can increase both renal blood flow and the glomerular filtration rate [10]. In addition to a possible role in protein-induced hyperfiltration, IGF-1 may play an important role in the hyperfiltration and glomerular hypertrophy observed in type 1 diabetes mellitus. (See "Overview of diabetic nephropathy").

The renin-angiotensin system may also modulate the effect of protein on glomerular filtration. Angiotensin II leads to a preferential increase in efferent arteriolar resistance, causing an increase in intraglomerular pressure and hyperfiltration. Lowering angiotensin II production induces efferent dilatation, which decreases intraglomerular pressure and perhaps the glomerular filtration rate. However, there are conflicting data on the effect of a low protein diet on renal renin release. Both a reduction in renin gene expression (which could contribute to the protective effect of a low protein diet in renal disease) and an increase in gene expression have been described [6,12]. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease" for a review of the potential beneficial effects of angiotensin converting enzyme inhibitors).

**Intrarenal effects** — Intrarenal mechanisms, including tubuloglomerular feedback, may contribute to protein-induced hyperfiltration [6,7]. An increase in the filtered load of amino acids may enhance proximal sodium reabsorption via sodium-amino acid cotransporters in the proximal tubule. The ensuing decrease in sodium chloride delivery to the macula densa may then activate tubuloglomerular feedback, leading to an elevation in GFR in an appropriate attempt to restore macula densa delivery to normal. (See "Chapter 2D: Regulation of GFR and renal plasma flow", section on Tubuloglomerular feedback).

**Other effects** — Protein restriction also limits phosphorus intake, which may contribute to a beneficial effect on disease progression. (See "Secondary factors and progression of chronic kidney disease").

**PROTEIN RESTRICTION** — Multiple well-designed randomized controlled human trials have evaluated both the efficacy and safety of protein restriction in patients with progressive CKD [13-17]. Moderate protein restriction (0.6 to 0.8 g/kg per day) is associated with a modest but not significant benefit of protein restriction on progression of renal disease. It is generally well tolerated and does not lead to malnutrition in patients with CKD providing caloric goals are met, dietary protein is of high biologic value, and metabolic acidosis is avoided.

Therefore, we suggest the use a low protein diet (0.6 to 0.8 g/kg per day) in select predialysis patients who are highly motivated to follow such a diet. However, the adoption of this diet should NOT preclude the initiation of dialysis in patients with severe chronic renal failure, if indicated. (See "Indications for initiation of dialysis in chronic kidney disease").

We also do not believe sufficient data support the use of a very low protein diet, especially given the significant limitation of lifestyle that is necessary to achieve this degree of protein restriction.

**Clinical trials evaluating efficacy** — Relatively small studies have suggested that a low protein diet may protect against progression of CKD in at least some diseases, such as diabetic nephropathy and chronic glomerular diseases [18-21]. In two trials in diabetic nephropathy, for example, the rate of decline in GFR was slowed by as much as 75 percent with dietary protein restriction (show figure 1) [18,19]. (See "Treatment and prevention of diabetic nephropathy"). In one small study, even patients with an initial GFR as low as 15 mL/min appeared to benefit (show figure 2) [20].

In contrast to these positive results, a much larger controlled trial (Northern Italian Cooperative Study Group) involving 456 Italian patients with a variety of renal diseases found that a low protein diet produced only a small, not statistically significant trend toward benefit at two years [22]. There were, however, two potential problems with this study: the GFR was measured indirectly by the often inaccurate creatinine clearance (see "Calculation of the creatinine clearance"); and, more importantly, noncompliance with protein restriction minimized the difference in dietary intake between control and treated groups. Protein intake (as estimated from the formula derived below) has been close to 1 g/kg per day in the control group in most studies. Whereas protein intake was reduced by 29 to 43 percent in the treated group in the smaller successful trials [18-20], it was reduced by only 16 percent in

the Italian trial [22]. This difficulty with compliance occurred despite the availability of much greater dietary counseling and monitoring than is available to the typical practitioner.

Subsequently, in the largest trial to date, the Modification of Diet in Renal Disease (MDRD) study analyzed 585 patients with nondiabetic chronic renal disease and a mean GFR of 39 mL/min (all patients with GFR less than 55 mL/min) [23]. Patients were randomly assigned to protein intakes of 1.3 or 0.58 g/kg per day with or without aggressive blood pressure control and followed for a mean of 2.2 years. The achieved protein intake in the low protein group was between 0.6 to 0.8 g/kg per day. Despite good compliance, there appeared to be little overall benefit with the low protein diet. A biphasic response was noted: patients treated with protein restriction had a greater fall in GFR in the first four months (that may have reflected a reduction in intraglomerular pressure), followed by somewhat slower progression over the ensuing months (2.8 versus 3.9 mL/min per year) (show figure 3). However, even in this later phase, the absolute benefit was still small at only 1.1 mL/min per year. A similar lack of substantial benefit was noted in a second part of this study involving 255 patients with more advanced disease (mean GFR 19 mL/min) who were randomized to a low protein diet or a very low protein diet (0.3 g/kg per day) with a keto acid-amino acid supplement.

A long-term follow-up analysis of the MDRD study was subsequently published [24]. In this 12-year study (1989 to 2000), the authors evaluated outcomes during the first six years after the trial ended (1989 to 1994), the next six year period (1995 to 2000), and the total 12-year period. Analysis of outcomes after the first six years revealed a small but significant benefit of low-protein intake on renal failure and all-cause mortality (respective hazard ratios of 0.68, CI 0.51-0.93 and 0.66, CI 0.50-0.87, respectively). However, there was no benefit of protein restriction when outcomes between 6 and 12 years were analyzed.

A major limitation of this analysis included lack of data for dietary intake after the completion of the study. Thus, it is possible that the lack of effect of the low protein diet observed beyond six years reflected a decrease in adherence to the prescribed diet. These data suggest the need for a longer follow-up period for future studies designed to assess the effects of protein restriction intervention.

The MDRD study and the Northern Italian Cooperative Study raise the question of why human trials have been unable to replicate the robust benefit observed in animal models. A number of factors may play a contributory role:

- Both control and experimental groups had excellent blood pressure control and many were being treated with ACE inhibitors. The mean blood pressure in the MDRD study was 131/81 at baseline, and 44 percent of patients were treated with an ACE inhibitor during the study. In this setting, in which hemodynamically-mediated injury should already be minimized, it may be difficult to demonstrate further benefit with dietary protein restriction. The observation that the rate of decline in GFR was only 3.9 mL/min per year in the control group is compatible with this hypothesis.
- The type of underlying disease might be important (see below). The MDRD trial, for example, included almost no patients with diabetic nephropathy (the group that might be most likely to benefit) [18,19], while 24 percent of patients had polycystic kidney disease (a disorder in which there is little evidence of hemodynamically-mediated injury). (See "Course and treatment of autosomal dominant polycystic kidney disease").
- The control groups in the large Italian and MDRD studies ingested 1.0 and 1.1 g/kg of protein per day [22,23]. Therefore, it is possible that higher levels of protein intake than these might be deleterious.
- The duration of study during which protein restriction was rigorously maintained may have been too short to reveal a beneficial effect of protein restriction.
- Some of the MDRD investigators have proposed that the seemingly small benefit from protein restriction may be clinically important [25]. According to this reasoning, a patient with a glomerular filtration rate of 40 mL/min who is losing 4 mL/min per year will require dialysis in about eight years. However, if the rate of fall were only 3 mL/min per year, then 11 years would be required to reach the same end-point. Thus, the absolute benefit would be three years without dialysis.

A later, smaller trial of 128 patients also provided evidence of modest benefit from dietary protein restriction in nondiabetic chronic renal failure [26]. The less accurate creatinine clearance was used in this study and, at 2.3 years, the likelihood of more than a 50 percent reduction in creatinine clearance was 40 percent in the control group (mean protein intake 1.06 g/kg per day) versus 29 percent in the treatment group (mean protein intake 0.8 g/kg per day, higher than the desired level of 0.6 g/kg per day).

**Meta-analyses and systematic reviews** — Several meta-analyses have examined the relationship between dietary protein restriction and the initiation of renal replacement

therapy [27-30]. A 2006 systematic review evaluated eight randomized controlled trials that compared low protein diets (0.3 to 0.6 g/kg per day) with standard protein intake (>0.8 g/kg per day) among 1524 patients with nondiabetic CKD [30]. Compared with standard protein intake, a low protein diet was associated with a decreased risk of need for dialysis, kidney transplantation, or death during follow-up (RR 0.69, 95% CI 0.56-0.86).

However, these studies were primarily performed during a period prior to the current practice of aggressive blood pressure lowering and the administration of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. As a result, it is unclear if a low protein diet provides added renal protection to that obtained with the current standard approach [31].

A Cochrane Review that was first published in 2000 and updated in 2008 analyzed nine randomized controlled trials and three before and after studies that evaluated protein-restricted diets in type 1 and type 2 diabetic CKD patients who were followed for at least four months. The authors concluded that there was modest but not significant benefit of protein restriction on progression of renal disease [32]. However, the studies had variable limits for protein restriction, heterogeneous follow-up, and did not report on quality of life.

Nevertheless, these studies provide some evidence that a low protein diet may benefit some patients with chronic renal failure [31,33].

**Effects of a very low protein diet** — A limited number of studies have evaluated the effects of a very low protein diet in patients with significant proteinuria or reduced GFR. One study evaluated the effects of a very low protein diet (0.3 g/kg per day supplemented with 10 to 20 g/day of essential amino acids), which was administered for an average of ten months in 16 patients with the nephrotic syndrome caused by various different etiologies [34]. Eleven of the 16 patients with clearances below 30 mL/min upon entrance into the study exhibited modest improvement with treatment, but all eventually required dialysis. Among the remaining five patients with clearances greater than 30 mL/min, however, dietary treatment for 3 to 14 months resulted in several beneficial effects:

- Decreased proteinuria (9.3 versus 1.9 g/day).
- Increased serum albumin concentration (2.5 versus 3.8 g/dL).
- Increased glomerular filtration rate (52 versus 70 mL/min).

- Upon resumption of a relatively normal diet, four of the five patients continued to remain in clinical remission (or near-remission) at a follow-up of 6 to 24 months.

The underlying cause(s) of nephrotic syndrome in all five of these patients was either focal glomerulosclerosis, diabetic nephropathy, or both, disorders in which a spontaneous increase in clearance and resolution of the nephrotic syndrome is rarely (if ever) observed.

The mechanism for these observations remains unclear. These striking results must be verified in larger, controlled studies prior to any possible change in our recommendations concerning the use of very low protein diets in patients with the nephrotic syndrome (see below).

Some evidence also suggests that this very low protein diet may help delay the requirement for renal replacement therapy without inducing malnutrition or increasing mortality among patients with near-end-stage renal failure (GFR of less than 6 to 10 mL/min) [35,36]. In one multicenter Italian study, 112 elderly nondialysis patients (age greater than 70 years) with end-stage renal disease (GFR of 5 to 7 mL/min) were randomly assigned to dialysis or a very low protein diet (protein at 0.3 g/kg per day; 35 kcals/day) [36]. At a median follow-up of 26.5 months, both groups had similar mortality rates, while the rate of hospitalization was higher among those assigned to dialysis. Forty patients assigned to the diet group eventually required dialysis initiation after a median of 9.8 months due to hyperkalemia and volume overload. However, patients with diabetes or nephrotic range proteinuria were excluded from this study, which limits its applicability to a general population.

**Safety** — Nutritional studies in patients with CKD suggest that protein intake can be safely lowered to 0.6 g/kg per day and, if supplemented with a ketoacid-amino acid mixture, possibly to 0.3 g/kg per day [13-17].

This issue was assessed in an analysis of patients who were enrolled in the MDRD study [14]. As previously mentioned, patients were randomly assigned to a usual protein diet (1.3 g/kg per day), a low protein diet (0.58 g/kg per day), or a very low protein diet (0.3 g/kg per day supplemented with a ketoacid-amino acid mixture at 0.28 g/kg per day) based upon their glomerular filtration rate. Patients assigned to the low protein diet achieved a protein intake between 0.6 to 0.8 g/kg per day. Patients assigned to the very low protein diet achieved a protein intake between 0.4 to 0.8 g/kg per day.

At a mean follow-up of 2.2 years, a low protein intake was not associated with increased rates of mortality, hospitalization, or malnutrition. However, lower levels of protein

ingestion were associated with diminished energy intake and significant, but small, absolute declines in serum transferrin, body weight, percent body fat, and arm muscle area. As a result, although protein restriction is safe for two to three years, declines in some nutritional indices are observed. Thus, careful monitoring must be maintained if such diets are prescribed.

Three conditions must be met to avoid malnutrition:

- Adequate caloric intake must be maintained.
- At least 60 percent of the ingested protein must be of high biologic value or contain a high percentage of essential amino acids (show table 1) [13].
- Stimulation of skeletal muscle protein breakdown should be prevented to limit net nitrogen loss. Metabolic acidosis should also be treated since metabolic acidosis stimulates skeletal muscle protein breakdown [13,37]. (See "Treatment of metabolic acidosis in chronic kidney disease"). A protein-restricted diet may, of itself, help to prevent metabolic acidosis. A post hoc analysis of the MDRD study showed that a reduction in protein intake resulted in increased serum CO<sub>2</sub> after one year of follow-up [38]. (See "Clinical trials evaluating efficacy" above).

In addition, resistance training, properly supervised, may help maintain muscle mass [39].

**Monitoring nutritional adequacy in CKD** — Unfortunately, there is no single optimal laboratory test to assess and monitor nutritional adequacy in CKD patients. The International Society of Renal Nutrition and Metabolism (ISRNM) convened an expert panel and published their recommendations [40]. The panel coined the term "kidney disease wasting," which refers to the occurrence of protein-energy malnutrition (loss of body protein mass and fuel reserve) in CKD or acute kidney injury regardless of the cause.

Protein-energy wasting can be diagnosed if three characteristics are present [40]:

- Low serum albumin, pre-albumin or cholesterol
- Reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy)
- Reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference)

Serum transferrin, which is used as a marker of protein adequacy in general population, is not useful in CKD patients due to underlying anemia in the latter group. Measurements of inflammatory markers (eg, C-reactive protein, interleukin-6, etc.) alone or in combination with albumin or pre-albumin are also not recommended at this time to guide the nutritional status of patients with CKD.

Patients with CKD who are on a protein restricted diet should be carefully monitored with close follow-up every three to six months for adequate caloric intake and evidence of protein malnutrition. We usually follow the body weight as well as serum albumin, pre-albumin, and cholesterol. More frequent monitoring (ie, monthly) may be necessary in patients with advanced CKD (ie, stages 4 and 5).

**Estimating protein intake** — Compliance with dietary protein restriction can be estimated from a 24-hour urine collection, providing daily intake is relatively constant and the patient is in a steady state (as evidenced by a stable BUN and body weight) [13,41]. (See "Patient information: Collection of a 24-hour urine specimen").

In this setting, urinary nitrogen excretion is roughly equal to nitrogen intake. The former can be estimated from:

$$\text{Urinary nitrogen excretion} = \text{Urine urea nitrogen} + \text{Nonurea nitrogen}$$

Nonurea nitrogen excretion is relatively constant, averaging 30 mg/kg per day. Moderate urinary protein loss can be ignored, but each gram excreted above 5 g/day should be added to the above formula.

Each gram of nitrogen is derived from 6.25 g of protein. Thus,

$$\text{Estimated protein intake} = 6.25 (\text{Urine urea nitrogen} + 30 \text{ mg/kg})$$

If, for example, 24-hour urine urea nitrogen excretion is 8.2 g in a 60 kg woman excreting 3.5 g of protein per day, then:

$$\text{Estimated protein intake} = 6.25 (8.2 + 1.8) = 62.5 \text{ g}$$

Thus, protein intake is approximately 1 g/kg per day.

**NEPHROTIC SYNDROME** — The safety of a low protein diet in nephrotic syndrome is uncertain. In some experimental models of nephrotic syndrome, the institution of a low

protein diet diminished hepatic albumin synthesis, which suggests protein deficiency [42,43]. However, in the same study, a low protein diet also decreased protein excretion, presumably due to a fall in intraglomerular pressure. The net effect of these opposing factors was no change in the plasma albumin concentration [42,43]. Overall, studies have not demonstrated conclusive evidence of malnutrition with protein restriction in moderately nephrotic animals [44].

One study examined this issue in five stable patients with nephrotic syndrome [45]. Despite moderate proteinuria that averaged 7.2 g/day, nitrogen balance was maintained on a diet that provided 0.8 g/kg per day of protein plus 1 g of protein for each gram of proteinuria and 35 kcal/kg per day. Positive nitrogen balance was maintained by the inhibition of amino acid oxidation and protein degradation and by stimulation of protein synthesis during feeding.

These data suggest that protein restriction can be safely implemented in patients with moderate proteinuria providing adequate caloric intake is maintained.

However, these data do not define the minimum safe protein intake nor do they prove that supplementing protein intake for the degree of proteinuria is necessary. In addition, the safety of protein restriction in patients with massive proteinuria (>15 g/day) or concurrent catabolic states (eg, due to corticosteroids or systemic lupus erythematosus) remains uncertain. Thus, we do not use protein restriction for patients with nephrotic syndrome.

## **SUMMARY AND RECOMMENDATIONS**

- Dietary protein restriction may protect against the progression of CKD by hemodynamically mediated reductions in intraglomerular pressure and by changes in cytokine expression and matrix synthesis. (See "Introduction" above). The hemodynamic effects of protein-induced hyperfiltration may be due to changes in hormones (such as glucagon and insulin-like growth factor-1), alterations in renin-angiotensin system, and intrarenal effects, including tubuloglomerular feedback. (See "Mechanism of protein-induced hyperfiltration" above).
- The benefits of moderate dietary protein restriction (0.6 to 0.8 g/kg per day) on the progression of CKD in humans remain controversial. Current data suggest that, at best, a small reduction in the rate of decline of glomerular filtration rate may be observed with a low protein diet. (See "Clinical trials evaluating efficacy" above and see "Meta-analyses and systematic reviews" above).

- Among patients with glomerular filtration rates less than 60 mL/min, we suggest the intake of approximately 0.7 g/kg of high biologic value protein per day rather than higher protein values (**Grade 2B**). This diet should also be administered in combination with other measures to slow the rate of progression of CKD, particularly rigorous blood pressure control with agents that inhibit the renin-angiotensin system. (See "Clinical trials evaluating efficacy" above and see "Meta-analyses and systematic reviews" above) and see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease").
- Patients who are on a protein restricted diet should be carefully monitored, preferably by a dietician, with close follow-up every three to six months for adequate caloric intake and evidence of protein malnutrition. We follow the body weight as well as serum albumin, pre-albumin, and cholesterol. More frequent monitoring (ie, monthly) may be necessary in patients with advanced CKD (ie, stages 4 and 5). (See "Safety" above).

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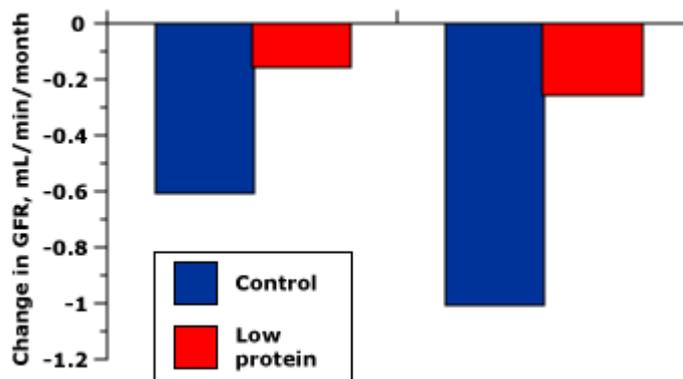
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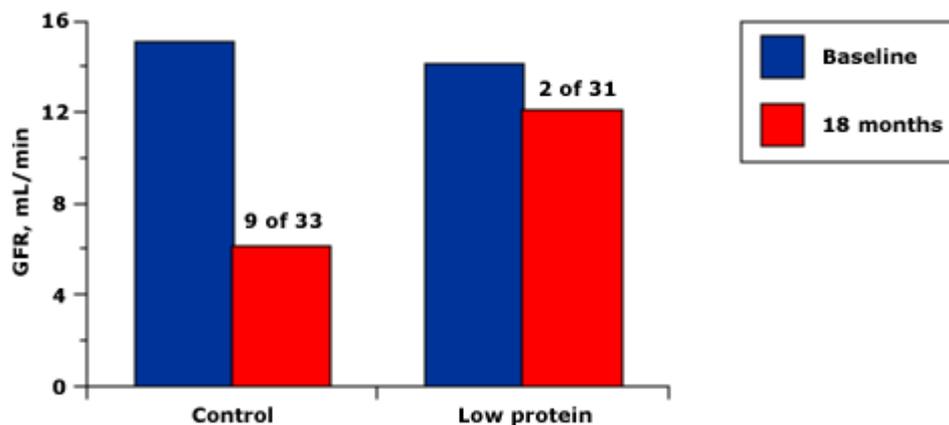
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**Protein restriction slows progression of diabetic nephropathy**



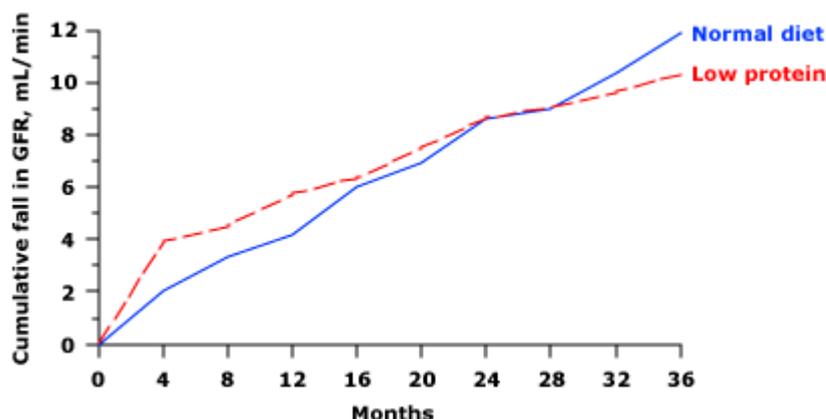
Dietary protein restriction - to about 0.6 g/kg per day or 30 to 40 percent lower than the control group - in two studies in patients with diabetic nephropathy (left and right panels) led to a 75 percent reduction in the rate of loss of glomerular filtration rate (GFR) at 18 to 36 months. *Data from Walker, JD, Bending, JJ, Dodds, RA, et al, Lancet 1989; 2:1411 and Zeller, K, Whittaker, E, Sullivan, L, et al, N Engl J Med 1991; 324:78.*

**Low protein diet slows progression in advanced chronic renal failure**



Beneficial effect of dietary protein restriction in patients with near end-stage renal disease (mean GFR 14 to 15 mL/min). At 18 months, patients on a low protein diet (right panel) had no significant further reduction in GFR and only 2 of 31 had progressed to maintenance dialysis. In comparison, the GFR fell by more than 50 percent and 9 of 33 required dialysis in the control group. *Data from Ihle, BU, Becker, GJ, Whitworth, JA, et al, N Engl J Med 1989; 321:1773.*

**Protein restriction has minimal protective effect in nondiabetic chronic renal failure**



Cumulative fall in glomerular filtration rate (GFR) over three years in patients with nondiabetic chronic renal failure (mean baseline GFR 39 mL/min) receiving a normal (solid line) and low protein (dashed line) diet. Protein restriction had little or no overall

beneficial effect. There was a trend toward more rapid loss of GFR in the first four months followed by a modest slowing of progression during the last 32 months. *Data from Klahr, S, Levey, AS, Beck, GJ, et al, N Engl J Med 1994; 330:877.*

### Protein biological value

Food item	Biological value
Egg protein	100
Whole bean	96
Whole soy bean	96
Human milk	95
Cow milk	90
Cheese	84
Rice, unpolished	83
Chicken	79
Fish	76
Beef	74
Soybean curd	72
Rice, polished	64
Corn	60
Kidney bean	49
White flour	41

This table depicts common food items with their BV values. Biological value (BV) is a measure of the proportion of absorbed protein that is incorporated into the proteins of the body. One method of determining biological value measures absorbed and excreted nitrogen and determines the ratio of incorporated nitrogen to absorbed nitrogen:

•  $BV = (Nr/Na) \times 100$ .

• Nr = nitrogen retained in the body (measured indirectly by nitrogen excretion in the urine and feces).

• Na = absorbed nitrogen from dietary protein.

• A BV of 100 suggests complete utilization of protein from a particular food. Egg protein has a BV of 100.

• BV does not take into account how readily the protein can be digested and absorbed.

*Data from: Jolliet, P, Pichard, C, Biolo, G. Enteral nutrition in intensive care patients: a practical approach. Intensive Care Med 1998; 24:848.*