Kidney Failure in Infants and Children

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Objectives

After completing this article, readers should be able to:

1. Recognize and delineate the causes of acute renal failure.
2. Formulate emergency management of fluid electrolyte disorders in acute renal failure.
3. Characterize the incidence, causes, and costs of chronic renal failure in children.
4. Explain the pathogenesis and treatment of complications of chronic renal failure.
5. Delineate a plan to help the family with the outcome of renal failure.

Introduction

The evaluation of kidney failure is challenging, despite many advances in diagnosis and treatment over the past decade. To provide pediatricians with an informed choice, this article reviews both acute and chronic renal failure, their multiple causes, the principles of treatment, and both short- and long-term outcomes.

Acute renal failure (ARF) is characterized by the abrupt failure of the kidneys to regulate water and electrolyte homeostasis. ARFs in childhood due to hemolytic-uremic syndrome, postinfectious acute glomerulonephritis, or dehydration are reversible, but a small percentage may progress to chronic renal failure (CRF). CRF is the result of slowly progressive kidney diseases and seldom is fully reversible. This condition in childhood is associated with obstructive uropathy, congenital aplastic/hypoplastic/dysplastic kidneys, and other causes. In CRF, almost every system in the body eventually becomes compromised.

Acute Renal Failure

Incidence and Causes

ARF is encountered in 3% to 10% of all admissions to neonatal intensive care units. In our experience with a regional pediatric nephrology program serving a catchment area of 1.5 million general population, 6.4% of 3,154 children referred to the program from community physicians suffered from ARF. However, precise figures on the true incidence of ARF in childhood are surprisingly sparse.

ARF is a life-threatening, abrupt reduction of urinary output to less than 300 mL/m^2 per day that is precipitated by prolonged renal ischemia in most cases. Occasionally, it may present with a high urinary output but mounting serum urea nitrogen and creatinine levels, the so-called "high output" or "nonoliguric" ARF, more often following severe burns or open heart surgery. The three leading causes of acute renal failure in children (Table 1) in developing countries are: hemolytic-uremic syndrome (31%), glomerulonephritis (23%), and postoperative sepsis/prerenal ischemia (18%). In contrast, for industrialized countries, the three most common causes are: intrinsic renal disease (44%), postoperative septic shock (especially after open heart surgery) (34%), and organ/bone marrow transplantation (13%).

Proximal tubular necrosis may follow toxic ingestions (eg, carbon tetrachloride, diethylene glycol, arsenic, mercury, gold, lead, and other heavy metals). Medications, such as

Abbreviations

ARF: acute renal failure
CAPD: continuous ambulatory peritoneal dialysis
CCPD: continuous cycling peritoneal dialysis
CRF: chronic renal failure
CVVH: continuous veno-venous hemofiltration
DHT: dihydrotachysterol
ECG: electrocardiogram
FE_{Na}: fractional excretion of sodium
GFR: glomerular filtration rate
IGF-1: insulin-like growth factor-1
IWL: insensible water loss
KFI: kidney failure index
PICU: pediatric intensive care unit

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Table 1. Causes of Acute Renal Failure in Children

Causes	Developing Country/ Referral Center n (%)	Industrialized Country/ Tertiary Center n (%)
Hemolytic-uremic syndrome	25 (31)	5 (3)
Glomerulonephritis	18 (23)	–
Intrinsic renal disease	–	64 (44)
Urinary obstruction	7 (9)	–
Postoperative sepsis	14 (18)	49 (34)
Ischemic and prerenal	14 (18)	–
Organ and bone marrow transplant	–	19 (13)
Miscellaneous	2 (3)	9 (6)
Total	80	146

From Flynn JT. Causes, management approaches, and outcome of acute renal failure in children. *Curr Opin Pediatr*. 1998;10:184–189.

sulfonamide, kanamycin, and neomycin, and radiocontrast material occasionally are reported to precipitate tubular patchy necrosis. Newer medications that may precipitate acute tubular necrosis include intravenous immunoglobulin, acyclovir, ibuprofen, angiotensin-converting enzyme inhibitors, cyclosporin, and tacrolimus.

Tubular and vascular obstruction causing prolonged renal ischemia may follow renal parenchymal uric acid accumulation, sickle cell crisis, myoglobulinemia, and renal vein thrombosis.

Cortical and tubular necrosis may occur following hemorrhagic shock, severe dehydration, crush injuries, thermal burns, and septic shock.

In neonates, asphyxia, erythroblastosis, cardiac pump oxygenation, or mechanical ventilation all may compromise renal function and predispose the infant to ARF. In addition, the maternal nephrotoxic medications used in complicated pregnancies may enter the fetal circulation and contribute to renal injury.

Laboratory Markers in the Differential Diagnosis

The differential diagnosis of various types of ARF based on urinary excretion patterns is summarized in Table 2. In prerenal (dehydration) ARF, the urine osmolality is elevated to more than 500 mOsm/kg because the renal tubule is reabsorbing all the filtered volume that it can. In acute renal tubular injury causing ARF, the renal concentrating ability is impaired, resulting in low urine osmolality of less than 350 mOsm/kg. Thus, it is important in the evaluation of ARF to obtain a spot urine for determination of urine osmolality before various treatments compromise the usefulness of this test. However, use of these indices is complicated by considerable overlap in urinary osmolality, urea, creatinine, and sodium. Thus, the best strategy for the combined use of these indices remains unclear. It has been suggested that the so-called kidney failure index (KFI) (urine sodium divided by the urine-to-plasma creatinine ratio) be used to differentiate the four categories of ARF (Table 2), with a KFI of higher than 1 designating renal and a KFI of less than 1 designating prerenal azotemia.

The fractional excretion of sodium (FE_{Na}) is just as useful. The FE_{Na}, calculated as the ratio of urine to plasma sodium divided by the ratio of urine to plasma creatinine, is less than 1% in prerenal azotemia; an FE_{Na} greater than 2% supports the diagnosis of ARF. In preterm infants, an FE_{Na} less than 2.5% suggests prerenal azotemia.

In the neonate, the KFI is higher than 2.5 in renal and less than 2.5 in prerenal azotemia. It should be recog-

Table 2. Differential Diagnosis of Acute Renal Failure Using Urinary Indices in Neonates (N) and Children (C)

	U_{osmo}		U/P Urea		U/P Creatinine		U_{Na}		U/P Osmo		KFI	
	N	C	N	C	N	C	N	C	N	C	N	C
Prerenal	>400	>500	>10	20	>30	>40	<30	<10	>1.5	>2	<2.5	<1
Renal	<400	<350		3	<10	<20	>60	>60	<1	<1	>2.5	>2
Nonoliguric		300		5		<40	>50	>50		0.5		>1
Postrenal		>350		5		<15	>60	>60		±		±

U_{osmo} = urinary osmolality (mOsm/kg); U/P Urea = urine-to-plasma urea ratio (mg/mg); U/P Creatinine = urine-to-plasma creatinine ratio (mg/mg); U_{Na} = urinary sodium (mEq/L); U/P Osmo = urine-to-plasma osmolality ratio (mOsm/mOsm); KFI = kidney failure index, calculated as urine sodium divided by the ratio of urine creatinine to serum creatinine.
From Chan JCM, Alon U, Oken DE. Clinical aspects of acute renal failure. In: Edelman CM, ed. *Pediatric Kidney Disease*. Boston, Mass: Little Brown & Company; 1992:1923–1941.

Table 3. Normal Glomerular Filtration Rate Values for Children

Age	GFR (mL/min/1.73 m^2)	Range (mL/min/1.73 m^2)
Preterm neonates (<34 wk GA)		
2 to 8 d	11	11 to 15
4 to 28 d	20	15 to 28
30 to 90 d	50	40 to 65
Term neonates (>34 wk GA)		
2 to 8 d	39	17 to 60
4 to 28 d	47	26 to 68
30 to 90 d	58	30 to 86
1 to 6 mo	77	39 to 114
6 to 12 mo	103	49 to 157
12 to 19 mo	127	62 to 191
2 to 12 years	127	89 to 165

GA = gestational age.
From Way AF, Bolonger AM, Gambertogli JG. Pharmacokinetics and drug dosing in children with decreased renal function. In: Holliday MA, Barratt TM, Avner ED, eds. *Pediatric Nephrology.* 3rd ed. Baltimore, Md: Williams & Williams; 1994:1306.

nized that glomerular filtration rates (GFRs) are lower in preterm neonates compared with term infants and older children (Table 3). The normal serum creatinine also varies with age, with higher values related to higher muscle mass in older children (Table 4).

Treatment

EMERGENCY FLUID MANAGEMENT. ARF (including the high-output variety) due to ischemic or toxic shock is managed best in the pediatric intensive care unit (PICU). Once kidney failure is established, fluid management should be guided by the principles of replacing the estimated insensible water loss (IWL) plus the loss in both volume and electrolytes from urinary or other outputs.

The increased endogenous water production of 100 mL/m^2 per day resulting from increased tissue catabolism in uremia must be subtracted from the IWL of 400 mL/m^2 per day. Thus, the IWL calculations in ARF compute to 300 mL/m^2 per day, not the IWL of 400 mL/m^2 per day under normal circumstances. Urine output should be replaced (volume for volume) with intravenous fluid solutions of approximately the same electrolyte composition as that of the urine. For this purpose, the sodium and potassium content of the urinary output should be analyzed.

The success of ARF management depends on meticulous monitoring of daily urine and other outputs and careful restoration of caloric, fluid, and electrolyte losses. A daily weight loss of up to 1% of the body weight is expected during the management of the initial oliguric phase of ARF. Weight gain or hyponatremia during this period usually indicates fluid overload.

Furosemide (administered intravenously at 1 mg/kg) promotes renal blood flow and acts as a renoprotective agent in the early stages of ARF.

Table 4. Normal Serum Creatinine Concentrations at Different Ages

Age	Serum Creatinine (mg/dL) [mcmol/L]	Range (mg/dL) [mcmol/L]
(<34 wk GA)		
<2 wks old	0.9 [79.6]	0.7 to 1.4 [61.9 to 123.8]
≥2 wks old	0.8 [70.7]	0.7 to 0.9 [61.9 to 79.6]
Term neonates (>34 wk GA)		
<2 wks old	0.5 [44.2]	0.4 to 0.6 [35.4 to 53.0]
≥2 wks old	0.4 [35.4]	0.3 to 0.5 [25.6 to 44.2]
2 wk to 5 y	0.4 [35.4]	0.2 to 0.5 [17.7 to 44.2]
5 to 10 y	0.6 [53.0]	0.3 to 1.0 [26.5 to 88.4]
>10 y	0.9 [79.6]	0.6 to 1.4 [53.0 to 123.8]

GA = gestational age
From Way AF, Bolonger AM, Gambertogli JG. Pharmacokinetics and drug dosing in children with decreased renal function. In: Holliday MA, Barratt TM, Avner ED. *Pediatric Nephrology.* 3rd ed. Baltimore, Md: Williams & Williams; 1994:1306.

CALORIC MANAGEMENT. A minimum of 25% of the daily caloric requirement must be supplied to reduce the catabolism of ARF. This can be achieved by a 25% dextrose solution delivered via an indwelling cannula inserted into the superior vena cava to avoid peripheral venous thrombosis from such a hypertonic solution. Intravenous infusion of essential amino acids has been advocated as therapy for patients who have ARF, based on the theory that accumulations of urea, creatinine, potassium, and phosphate are removed in the synthesis of nonessential amino acids from essential amino acids and the formation of new tissue. Paradoxically,

when essential amino acids are infused, these variables increase significantly. Thus, the use of essential amino acid in ARF has not gained much acceptance.

The oliguric phase of ARF usually lasts from a few days to 2 weeks. A popular high-caloric supplement, given when the child regains his or her appetite (toward the end of that period) is corn syrup in ginger ale or lemon juice.

HYPERKALEMIA AND HYPONATREMIA. A number of treatment complications may occur during the oliguric phase. Hyperkalemia (>6.5 mEq/L [6.5 mmol/L]), with T-wave elevation on electrocardiogram (ECG) examination, requires prompt treatment with one or a combination of the following maneuvers: 1) infusion of 0.5 mL/kg of 10% calcium gluconate solution over 2 to 4 minutes with stethoscopic or ECG monitoring of the heart; 2) intravenous crystalline insulin at 1 U of insulin in 5 g dextrose to promote movement of potassium intracellularly through enhanced gluconeogenesis, monitored by serial blood glucose determinations; or 3) kayexalate cation exchange resins at a dose of 1 g/kg body weight in a 20% sorbitol or dextrose solution, administered either as a high-retention enema or orally, to help rid the potassium burden from the body.

Hyponatremia (<130 mEq/L [130 mmol/L]), which almost invariably results from fluid overload, must be corrected promptly by fluid restriction.

METABOLIC ACIDOSIS AND OTHER COMPLICATIONS. Other complications of ARF include metabolic acidosis, seizures, and such clinical entities as pericarditis, infection, and anemia. Metabolic acidosis results from impairment of renal net acid excretion and requires judicious use of sodium bicarbonate therapy when the serum total bicarbonate falls below 10 mEq/L (10 mmol/L). At the other extreme of acid-base disturbance, metabolic alkalosis can develop from the combined loss of hydrochloric acid and potassium depletion from nasal gastric suction. Seizures may occur in an oliguric child because of hypokalemia, hypertension, hypocalcemia, or the rapid elevation of blood urea nitrogen. Each of these specific causes should be sought and the appropriate treatment instituted. Seizures from other causes can be controlled with slow intravenous infusion of diazepam at 0.1 mg/kg, followed by maintenance therapy with diphenylhydantoin at dosages of 3 to 8 mg/kg orally.

DECISION TO DIALYZE. Peritoneal or hemodialysis should be considered when any of the complications become severe, as represented by the following conditions: 1) serum urea nitrogen in excess of 150 mg/dL (53.6 mmol/L); 2) serum creatinine in excess of 10 mg/dL (884 mcmol/L); 3) potassium in excess of 6.5 mEq/L (6.5 mmol/L), with T-wave elevation on ECG unrelieved by medical means; 4) severe metabolic acidosis with serum bicarbonate persistently below 10 mEq/L (10 mmol/L) and unrelieved by bicarbonate therapy; and 5) congestive heart failure and fluid overload. The serum urea nitrogen can be expected to be reduced by at least 50% within 48 hours of the institution of peritoneal dialysis; serum potassium can be expected to fall to a normal range and metabolic acidosis to be reversed within 24 hours. Hemodialysis achieves these ends at a fraction of the time of peritoneal dialysis. If vascular access is available, hemodialysis is now the preferred dialysis modality in North American PICUs. In developing countries, peritoneal dialysis has the advantages of lower cost and no dependency on expensive hemodialysis machinery.

Continuous veno-venous hemofiltration (CVVH) is especially useful in hemodynamically unstable patients in PICUs. CVVH is comparable to intermittent hemodialysis, although a recent retrospective study indicated a lower survival rate among patients treated with CVVH.

GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR. Despite initial claims of increasing renal blood flow, the use of either recombinant human growth hormone or insulin-like growth factor in ARF has not improved survival or resulted in demonstrable alleviation of significant renal injury. Thus, their continued use in treating ARF is being called into question.

Outcome

There are three phases in the course of ARF: the oliguric phase, the diuretic phase, and the recovery phase. Each of the oliguric and diuretic phases usually lasts a few days to 2 weeks. With conservative management, the diuretic phase of ARF usually begins 7 to 14 days after the onset of oliguria. However, blood urea nitrogen and serum potassium levels may continue to rise during the first few days of diuresis, possibly because the intracellular urea and potassium that have accumulated during oliguria are moving into the extracellular compartment. Daily body weight, precise intake and output volumes, and urinary losses of electrolytes and fluids must be monitored continuously and these losses scrupulously replaced during the diuretic phase. Seizures, urinary tract infections, and psychoses are not uncommon during the diuretic phase. The recovery phase may vary from a few weeks to several

Table 5. Percent Distribution of Primary Renal Disease in Children Resulting in Renal Transplantation

	(3,673)	%
Gender		
Male	2,168	59.0
Female	1,504	40.9
Race and ethnicity		
White	2,391	65.1
Black	551	15.0
Hispanic	531	14.5
Other	200	5.4
Diagnosis		
Obstructive uropathy	605	16.5
Aplastic/hypoplastic/dysplastic kidneys	603	16.4
Focal segmental glomerulosclerosis	426	11.6
Reflux nephropathy	209	5.7
Systemic immunologic disease	174	4.7
Chronic glomerulonephritis	160	4.4
Syndrome of agenesis of abdominal musculature	112	3.0
Congenital nephrotic syndrome	103	2.8
Hemolytic-uremic syndrome	101	2.7
Polycystic kidney disease	100	2.7
Medullary cystic disease/juvenile nephronophthisis	94	2.6
Cystinosis	92	2.5
Pyelonephritis/interstitial nephritis	84	2.3
Membranoproliferative glomerulonephritis type I	84	2.3
Familial nephritis	83	2.3
Renal infarct	75	2.0
Idiopathic crescentic glomerulonephritis	65	1.8
Membranoproliferative glomerulonephritis type II	37	1.0
Oxalosis	29	0.8
Membranous nephropathy	23	0.6
Wilms tumor	22	0.6
Drash syndrome	20	0.5
Sickle cell nephropathy	5	0.1
Diabetic nephropathy	4	0.1
Other	203	5.5
Unknown	160	4.4

From Warady BA, Hebert D, Sullivan EK, Alexander SR, Tejani A. Renal transplantation, chronic dialysis, and chronic renal insufficiency in children and adolescents. The 1995 Annual Report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Nephrol.* 1997;11:49–64.

months for all urinary abnormalities (eg, hematuria and proteinuria) to disappear.

The expected overall survival rate for children who have ARF is 70%. The 30% mortality usually is due to secondary complications, such as sepsis.

Chronic Renal Failure

Incidence and Causes

CRF affects nearly 500/1 million population per year; 1% to 2% are in the pediatric age range. The provision of dialysis and transplantation for these individuals in the United States costs $15.64 billion, with 75% of the total cost paid by the United States Treasury via Medicare. (These data are from 1997, the latest year in which the data analysis was completed by the United States Renal Data System, and are available in the August 1999 issue of the *American Journal of Kidney Diseases.*) Despite ongoing debate concerning treatment availability and costs, the industrialized nations of the world have affirmed government support for these treatments for the immediate future, despite worldwide fiscal constraints on health care expenditures. The aims of the next decade must be focused on optimizing the medical management of chronic renal diseases to improve the quality of life, slow the rate of progression of renal disease, and alleviate the tax burden. In children, the future aims also must include maximizing growth and development. Table 5 summarizes the causes of CRF in children.

Clinical Presentation: The Four Stages of Chronic Renal Disease

The first stage of chronic renal disease coincides with a GFR of 50% to 75% of normal for age. This is an asymptomatic stage. Increases in serum urea nitrogen, creatinine, and parathyroid hormone ensue only after the GFR falls below 50% of normal. The second stage of chronic renal disease generally is referred to as chronic renal insufficiency and coincides with the GFR of 25% to 50% of normal for age. Heavy, asymptomatic proteinuria of more than 1,000 mg/d often is present. Hyposthenuria and nocturia also are characteristic features. Whereas infection and dehydration seldom cause significant problems in the first stage because of a wider margin of renal functional reserve, these conditions may precipitate severe azotemia in the second stage. The third stage of chronic renal disease, generally known as CRF, is related to a GFR of 10% to 25% of normal and is

characterized by the clinical features of anemia, acidosis, hyperphosphatemia, and hypocalcemia as well as renal osteodystrophy and rickets. The fourth and final stage of chronic renal disease, known as end-stage renal disease, coincides with the GFR of less than 10% of normal. Because of the severe neurologic, cardiovascular, intestinal, hematologic, and skeletal abnormalities that usher in this final stage, preparation for the initiation of dialysis and transplantation must begin as the child enters the transition into end-stage disease. Although the first two stages of CRF are distinct, the features of the last two stages overlap.

Reversible Renal Failure

Chronic renal disease is slowly progressive. Depending on the underlying cause, it may progress over the course of a dozen years or longer to end-stage renal disease. The first two stages of CRF (vide supra) often are asymptomatic, but functional impairment is accelerated by various reversible causes (eg, dehydration, hypertension, congestive heart failure, hypercalcemia, hyperuricemia, hypokalemia, alkalosis, and nephrotoxic agents including certain antibiotics, cyclooxygenase inhibitors, converting enzyme inhibitors, and nonsteroidal anti-inflammatory agents). Persistent metabolic alkalosis in association with diuretic-induced hypokalemia may be early clues of interstitial nephritis. If the diagnosis is established and the appropriate treatment instituted, accelerated deterioration of renal function could be reversed. Dehydration and salt depletion exacerbate chronic renal insufficiency. Hypercalcemia impairs renal function. Early recognition and treatment of these defects should alleviate further immediate renal damage. The control of hypertension limits arteriolar nephrosclerosis and retards the rate of renal function deterioration. Hyperuricemia gives rise to renal tubular deposition of uric acid crystals. Early recognition and treatment by alkalinization of the urine or by the use of allopurinol may preserve renal function.

Patients who have CRF not only have depressed renal function, but they also are predisposed to urinary tract infections, which must be treated promptly with the appropriate antibiotics to conserve the marginal renal reserve. The physician must guard against such reversible deterioration of renal function, thereby conserving residual function. In vivo studies have shown that antioxidants (eg, acetylcysteine) prevent injury from radiocontrast agents. Just as importantly, animal studies have demonstrated that antioxidants (eg, alpha-tocopherol) reverse renal injury in progressive renal diseases. Buddhist monks who had CRF and ate one low-protein vegetarian meal per day demonstrated a slower rate of progression to end-stage renal failure than did controls. However, such studies are faulted for methodologic difficulties, including the lack of renal histologic evaluation of the study groups. Treatments to slow the progression of CRF are summarized in Table 6.

Table 6. Slowing the Progression of Chronic Renal Failure

Lowering intraglomerular hyperfiltration
• Converting enzyme inhibitors (eg, captopril, enalapril, lisinopril)
• Calcium channel blockers (eg, diltiazem)
• Low-protein diets, low-phosphate diet, vegetarian diet
Antioxidants (eg, alpha-tocopherol, acetylcysteine)
Lipid-lowering agents
• Rate-limiting enzyme inhibitors (eg, levostatin, pravastatin)

Major Complications

As the kidney fails, major disturbances in calcium, phosphate, and acid-base metabolism develop, resulting in renal rickets and growth retardation. With the increasing recognition of the kidneys as an endocrine organ, CRF can be said to give rise to malfunctions of all endocrine systems. The lack of erythropoietin production associated with kidney failure results in anemia. Insulin resistance, thyroid, and other endocrine dysfunctions complicate CRF. Growth hormone resistance in uremia, coupled with renal osteodystrophy, contributes to the often severe growth failure seen in children who have CRF. Anorexia frequently complicates the late stages, resulting in nutritional deficiency. These and related complications of CRF are reviewed to provide the pediatrician with a better understanding of how to help the child who has this major organ failure and to address the family's concerns.

RENAL OSTEODYSTROPHY. Figure 1 illustrates the three major consequences of CRF. The first is impaired phosphate excretion, which results in an elevation of serum phosphate and a reciprocal drop in calcium, stimulating the development of secondary hyperparathyroidism and renal osteodystrophy. The second and probably major consequence of CRF on calcium metabolism is the impaired formation of active metabolites of vitamin D, resulting in malabsorption of calcium across the intesti-

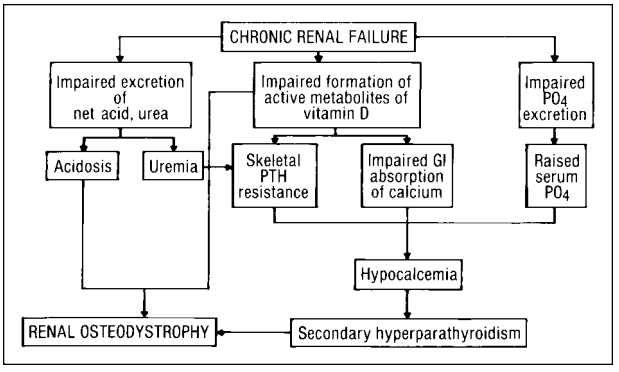

Figure 1. Chronic renal failure leading to major consequences in calcium and phosphate metabolism and the development of renal osteodystrophy.

nal tract, giving rise to hypocalcemia. With uremia, there is increasing evidence of a skeletal parathyroid hormone resistance, which also contributes to the development of secondary hyperparathyroidism. Finally, the third major consequence of CRF is the impaired excretion of net acid and retention of urea. The resultant development of metabolic acidosis and uremia contributes to skeletal parathyroid hormone resistance and also may contribute directly to the development of renal osteodystrophy. The signs and symptoms of renal osteodystrophy are summarized in Table 7.

GROWTH FAILURE. Growth hormone is secreted from the anterior pituitary (Fig. 2), but it does not exert a growth effect directly at the target site, except in the liver, where it stimulates the formation of insulin-like growth factor-1 (IGF-1), previously known as somatomedin C. IGF-1 acts as a paracrine hormone at the growth plate of the long bone to stimulate growth, augmented to a small degree by growth hormone directly. Feedback regulation to the further secretion of growth hormone is negative.

Tissue resistance to endogenous and exogenous growth hormone has been documented carefully in recent studies showing that the expression of IGF-1 in uremia is significantly blunted compared with that of control and pair-fed animals. Growth hormone receptor mRNA also is inhibited by the uremic condition. The increased IGF-binding proteins encountered in CRF also interfere with growth hormone action. Thus, the use of recombinant human growth hormone for treatment of growth disturbance due to CRF now can be defended based on the rationale of the need to overcome such clearly demonstrated tissue resistance.

Table 7. Clinical Features of Renal Osteodystrophy in Childhood

Clinical manifestations
• Growth retardation
• Bone pain
• Myopathy
• Skeletal deformities
• Rickets signs in infants
Biochemical data
• Increased serum AP activity
• Elevated serum PTH concentrations
• Lower serum 1,25-$(OH)_2$-D_3
Radiologic abnormalities
• Subperiosteal resorption
• Epiphyseal slipping
• Osteopenia
Pathologic findings
• Osteitis fibrosa

AP = alkaline phosphatase, PTH = parathyroid hormone, 1,25-$(OH)_2$-D_3 = 1,25-dihydroxyvitamin-D_3

The majority of children who have CRF suffer from significant growth retardation. Recombinant human growth hormone augments linear growth in children who have chronic renal insufficiency, with the potential for 3 to 4 inches of additional growth over 2 years. Despite concerns about the possibility of hypercalciuria associated with conjoint use of calcitriol and recombinant human growth hormone in uremic animals and the risk of focal glomerulosclerosis in growth hormone transgenic mice experiments, the use of conventional doses of recombinant human growth hormone (0.3 IU/kg per week) has been found to be safe and efficacious. No increased risk of malignancy has been encountered with use of recombinant human growth hormone in CRF over the past decade.

ANEMIA. When renal function falls below 15% of normal for age, anemia appears with increasing frequency in children who have CRF. Table 8 summarizes the multiple factors contributing to the pathogenesis of the normocytic, normochronic anemia that characterizes CRF. To prevent nutritional anemia due to folate deficiency, oral supplementation with folic acid 1 mg/d is recommended. In addition, if serum ferritin levels are low, oral iron supplementation is required. Recombinant

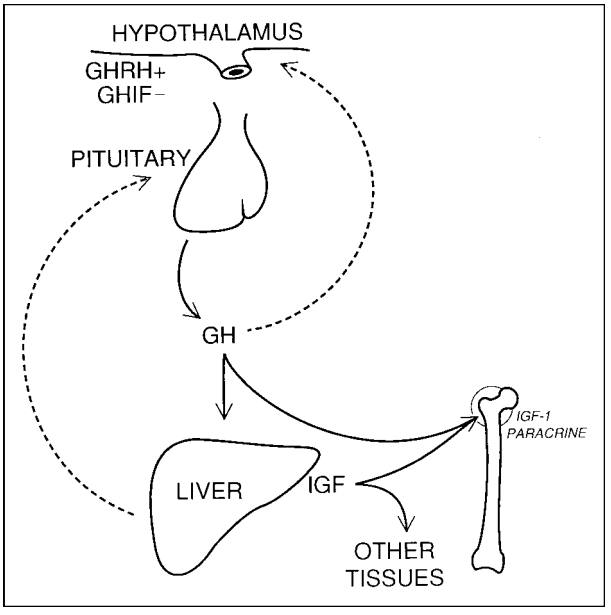

Figure 2. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) axis. Action of GH on hepatic production of IGF-1. Negative feedback regulation to the further secretion of GH is represented by the interrupted lines. From Krieg RJ Jr, Santos F, Chan JCM. Growth hormone, insulin-like growth factor, and the kidney. *Kidney Int.* 1995;48:321–336. By permission of International Society of Nephrology.

human erythropoietin at 50 to 100 IU/kg per week to reverse anemia usually becomes necessary in those undergoing dialysis.

METABOLIC ACIDOSIS AND GROWTH FAILURE. Increased proteolysis occurs in response to a relatively small decrease in serum bicarbonate from 20 mEq/L to 17 mEq/L. More importantly, the recognition that metabolic acidosis inhibits growth hormone pulsatile secretion and expression has led to the recommendation by the Kidney Foundation (K/DOQI 2000) that serum bicarbonate be maintained at 22 mEq/L with bicarbonate therapy (Table 9).

Table 8. Pathogenic Factors of the Anemia of Chronic Renal Failure

Decreased erythropoiesis
• Reduced availability of erythropoietin
• Inhibitor(s) of erythropoiesis*
• Bone marrow fibrosis*
Shortened red blood cell survival*
• Hemolysis due to extracorpuscular factor(s)
Excessive blood losses
Deficiency states
• Iron deficiency
• Folic acid deficiency

*These factors seem to be exacerbated by hyperparathyroidism.

NUTRITION DEFICIENCIES IN GROWTH FAILURE. The importance of energy intake on growth is illustrated by the significant correlation between growth velocity (expressed as percentage of normal) and energy intake (expressed as percentage of that recommended for age). Reduced growth velocity almost invariably is present in children who have uremia and an energy intake below 80% of the recommended dietary allowance. Caloric intake should be maintained at the recommended dietary allowance for healthy children of the same height and age (Table 10). These calories should be provided as carbohydrate (50%) and fat (40%), with protein kept to only 10% of the total.

CALORIC AND NUTRIENT MAXIMIZATION OF GROWTH IN INFANCY. Infants who have early chronic renal insufficiency grow poorly. However, dialysis and transplantation in such infants do not result in catch-up growth. Abitbol et al demonstrated that nutritional deficiencies are pivotal contributors to this growth failure. With vigorous caloric and protein supplementations to reach close to 100% of the recommended dietary allowance, weight gain without linear growth acceleration was demonstrated. Im-

Table 9. Oral Preparations for Alkali Therapy

Drug	Preparation	Sodium Content	Base Content
Shohl solution or Bicitra	Solution	1 mL = 1 mEq	1 mL = 1 mEq
Sodium bicarbonate	Solution	1 mL = 1 mEq	1 mL = 1 mEq
	Powder	1 g = 12 mEq	1 g = 12 mEq
	Tablet	8 mEq tablet	8 mEq tablet
Calcium carbonate	Tablets	Free	1 g = 19 mEq

Table 10. Estimated Safe and Adequate Daily Dietary Intake for Calories, Protein, Sodium, Potassium, Calcium, and Phosphorus in Chronic Renal Insufficiency

Age (y)	Energy (kcal/kg)	Protein (g/kg)	Sodium (mg)	Potassium (mg)	Calcium (mg)	Phosphorus (mg)
0 to 0.5	115	2.2	230	650	360	240
0.5 to 1	105	2.0	500	850	540	360
1 to 3	100	1.8	650	1,100	800	800
3 to 6	85	1.5	900	1,550	800	800
6 to 10	85	1.5	1,200	2,000	800	800
10 to 14						
Male	60	1.0	1,800	3,025	1,200	1,200
Female	48	1.0	1,800	3,025	1,200	1,200
14 to 18						
Male	42	.85	1,800	3,025	1,200	1,200
Female	38	.85	1,800	3,025	1,200	1,200

provement in body mass indices did not extend to length and head circumference. For this reason, it was recommended that protein intake in infants be restricted to 75% of the recommended dietary allowance to minimize protein waste product accumulation in CRF.

Despite early treatment with vitamin D metabolites, the elevated parathyroid hormone concentration in these infants correlated inversely with linear growth, suggesting that better treatment of subclinical bone disease is essential in infancy.

CARBOHYDATE, LIPID, NITROGEN DISORDERS. The glucose intolerance in uremia is associated with peripheral insulin resistance. Elevated serum cholesterol and triglyceride and reduced high-density lipoprotein cholesterol levels may be related to this dysfunction in carbohydrate metabolism.

The retention of nitrogenous products results in anorexia, nausea, vomiting, and uremic stomatitis, but no specific agent or single "uremic toxin" has been identified to account for these symptoms of the uremic syndrome

OTHER SYSTEMIC DISORDERS. Impaired immunologic defenses and delayed wound healing give rise to a higher incidence of infection in uremic patients. A progressive encephalopathy, developmental delay, seizures, myoclonus, hypotonia, ataxia, and chorea have been noted in infants who have CRF. Uremic encephalopathy in a child or adult presents with nonspecific complaints (eg, listlessness, fatigue, depression), with late signs consisting of myoclonus, slurred speech, confusion, seizures, and psychosis. Uremic peripheral neuropathy is distal and symmetric.

The incidence of duodenal ulcers is increased in those who have uremia, which may be related to a rise in serum gastrin concentration due to inadequate excretion by the failing kidney. Pericardial effusion and pericarditis may occur at a higher frequency when the serum urea nitrogen concentration exceeds 80 mg/dL. Uremic pneumonia is an extreme form of pulmonary edema. Pulmonary edema may follow fluid overload and left heart failure from malignant hypertension.

Sexual dysfunction follows decreased concentrations of follicle-stimulating hormone and testosterone in CRF. The pruritis of uremia is due to microscopic subcutaneous calcium deposition associated with secondary hyperparathyroidism. If orally administered diphenhydramine 10 to 25 mg two to three times per day (maximum, 300 mg/d) fails to alleviate the pruritis, the final resort is parathyroidectomy, which may alleviate this symptom.

Recommendations

CRF progresses in an orderly fashion; when 25% to 50% of the renal functions are lost, secondary hyperparathyroidism can be expected in most children (Fig. 3). When kidney functions are reduced to 50%, parathyroid hormone concentrations will be elevated. Thus, secondary hyperparathyroidism invariably is present at 50% reduction in GFR, warranting the use of calcium carbonate as a phosphate binder and dihydrotachysterol (DHT) or calcitriol (1,25-dihydroxyvitamin D_3) or the nonhypercalcemic vitamin D metabolite 22-oxacalcitriol to control the secondary hyperparathyroidism. When only 30% of the normal GFR remains (with rising serum urea nitrogen and creatinine and hypertension), protein and salt restriction, multiple vitamins, antihypertensives, and diuretics should be introduced into the treatment regimen. At 5% to 10% of normal GFR, nausea and vomiting from the uremia require treatment with antiemetics, and planning for dialysis and kidney transplantation must begin.

In children who have CRF, the standard of care now consists of using DHT 0.01 mg/kg per day or calcitriol

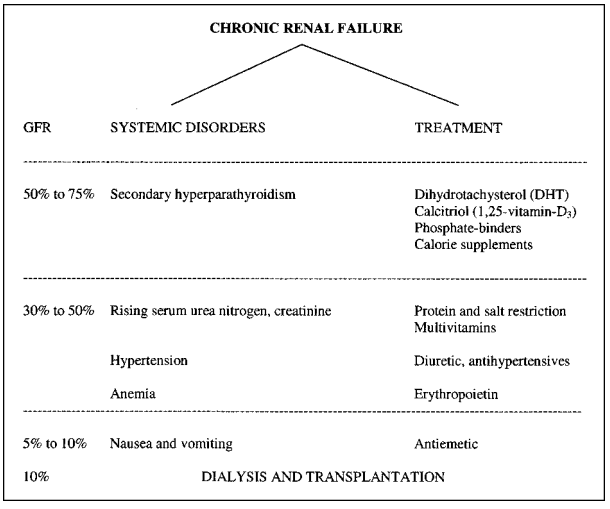

Figure 3. Sequence of initiation of treatment modalities in relation to the progressive decline in glomerular filtration rate (GFR) at % of normal for age.

(1,25-dihydroxyvitamin D_3) to treat the renal osteodystrophy, suppress the hyperparathyroidism, and promote linear growth. DHT is available in liquid droplets and can be calibrated more easily for use in infants. Calcitriol is available only in 0.25 and 0.5 mcg capsules. Aluminum hydroxide should be avoided because the aluminum may be absorbed through the gastrointestinal tract in the presence of hyperparathyroidism and uremia. Calcium carbonate 20 mg/kg per day is an excellent phosphate binder that also provides additional calcium intake and is mildly alkalogenic. It is important to use a higher dosage of calcium carbonate with the major meals (eg, dinner) to bind the increased amounts of phosphate. Sevelamer hydrochloride, a new and effective phosphate binder, as well as calcium acetate are gaining patient acceptance due their improved taste. Alkali therapy (Bicitra 2 mEq/kg per day in two to three divided doses, Table 9) should be used to correct metabolic acidosis and reduce proteolysis due to acidosis.

Protein should be restricted to 0.8 to 2.2 g/kg per day, according to the age, body weight, and gender (Table 10). Energy provisions should be 38 to 42 kcal/kg per day in females and males 15 to 18 years of age and as high as 100 kcal/kg per day in those between 1 and 3 years of age (Table 10). Phosphate should be restricted to generally less than 12 mg/kg per day.

Recombinant human growth hormone should be administered at 0.05 mg/kg per day before renal transplantation. This therapy is stopped when the child attains the 50th percentile for midparental height or receives a kidney transplant.

Nonpharmacologic antihypertensive therapy consists of weight control, exercise, stress reduction, and dietary sodium restriction. Such lifestyle changes need the participation of the entire family to succeed.

Pharmacologic antihypertensive therapy may employ a host of new medications to suppress the renin-angiotensin system (Table 11) as well as old, well-tested medications such as diuretics, which reduce the volume expansion of CRF. Diuretics lose their effectiveness in CRF when 70% of renal function is lost because of the inability to increase distal tubular sodium delivery and free water loss.

Generally, anemia significant enough to require blood transfusions or erythropoietin is not encountered until the GFR is less than 10 mL/min per 1.73 m^2, which usually is only after the patient enters into the dialysis program. At this time, recombinant human erythropoietin at 50 to 100 IU/kg per week is an important therapeutic maneuver to reverse the normochromic, normocytic anemia. Because of the rapid formation of red cells after recombinant human erythropoietin administration, serum transferrin concentrations need to be followed, and if the serum transferrin saturation is less than 20%, iron supplementation at 0.5 mg/kg per day should be initiated. In many centers, iron always is administered with erythropoietin therapy.

The rate of progression of kidney failure can be slowed with careful dietary control, judicious protein restriction, a low-phosphate diet, reduction of glomerular hyperfiltration by converting enzyme inhibitor, and control of systemic hypertension.

Prognosis in End-stage Renal Failure

Coincidental to a GFR of less than 10% of normal for age, when conservative management of CRF reaches its limits, dialysis and transplantation become the next therapeutic modalities. In the past 2 decades, continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD) have gained wide acceptance as the dialysis modalities of choice for children.

In contrast to the usual peritoneal dialysis in which the dialysate dwells in the peritoneal space for 30 minutes, the "dwell" time in CAPD is usually 4 to 8 hours. Thus, the dialysis exchanges are minimized to four or five per day. Besides the advantage of costing less than hemodialysis, CAPD usually is performed at home (after a 2-week training course) without expensive equipment or interference with the child's schooling. The principal disadvantage is the unreasonably high frequency of peritonitis (averaging two episodes per

Table 11. Selected Antihypertensive Drugs for Children Who Have Chronic Renal Failure

Drug	Formulation	Dose (oral)	Adjustment in CRF	Effect on Renin
Diuretics				Increase
Hydrochlorothiazide	25, 50, 100 mg tabs	0.5 to 2.0 mg/kg per dose qd or bid	Thiazides not effective at GFR <30% of normal	
Hydrochlorothiazide	50 mg/5 mL, 100 mg/mL			
Furosemide	20, 40, 80 mg tabs; 10 mg/mL	0.5 to 4.0 mg/kg per dose qd or bid	None	
Bumetanide	0.5, 1, 2 mg tabs	0.01 to 0.03 mg/dose qd	Unknown	
Metolazone	2.5, 5, 10 mg tabs; 0.1 mg/mL	0.2 mg/kg per dose qd or bid	Unknown	
Chlorthalidone	25, 50 mg tabs	25 to 50 mg qd in single dose	None	None
Chlorthiazide	250, 500 mg tabs; 250 mg/5 mL suspension	<6 mo: up to 30 mg/kg per day in bid dosage 6 mo to 2 y: 10 to 20 mg/kg per day qd or in bid dosage with maximum 375 mg/d 2 to 12 y: 10 to 20 mg/kg per day with maximum 1 g/d in single or divided doses	Decrease or discontinue	None
Beta blockers				Decrease
Acebutolol	200, 400 mg tabs	200 to 800 mg qd (adults)	Decrease dose	
Atenolol	25, 50, 100 mg tabs	50 to 100 mg (adults)	Decrease 50% at GFR <50 mL/min/1.73 m^2, give qid GFR <10 mL/min/1.73 m^2	
Labetolol	100, 200, 300 mg tabs	50 to 100 mg bid (>10 y)	None	
Metoprolol	50, 100 mg tabs	100 to 200 mg qd or bid (adults)	None	
Propranolol	10, 20, 50, 100 mg tabs; 20, 40, 80 mg/mL	0.5 to 1.0 mg/dose bid	None	
Vasodilators				Increase
Hydralazine	10, 25, 50, 100 mg tabs; 0.2 mg/mL	0.5 to 2.0 mg/kg per dose bid or qid	None	
Minoxidil	2.5, 10 mg tabs	0.1 to 0.5 mg/kg per dose bid to qd	None	
Central sympatholytic				Decrease
Clonidine	0.1, 0.2, 0.3 mg tabs or patch	0.05 to 0.3 mg/dose bid or tid	None	
Methyldopa	125, 250, 500 mg tabs	10 mg/kg per day in 2 to 4 doses; maximum 65 mg/kg or 3 g daily	Patients may be sensitive to lower dosages	Decrease
Angiotensin-converting enzyme inhibitors				Increase
Captopril	12.5, 25, 50, 100 mg tabs	0.5–2.0 mg/kg per day bid	Caution with all ACE when GFR <50 mL/min/1.73 m^2	
Enalapril	2.5, 5, 10, 20 mg tabs	0.15 mg/kg per day bid		
Fosinopril	10, 20 mg tabs	5 to 20 mg qd (adults)		
Lisinopril	2.5, 5, 10, 20, 40 mg tabs	2.5 to 20 mg/day bid or qd (adults)		

(continued)

Table 11. Selected Antihypertensive Drugs for Children Who Have Chronic Renal Failure (cont)

Drug	Formulation	Dose (oral)	Adjustment in CRF	Effect on Renin
Calcium channel blockers				None
Nifedipine	10, 20 mg caps 30, 60, 90 sustained release	0.25 to 2.0 mg/kg per dose bid to qid sustained release qd or bid	May need to limit dose	
Diltiazem	30, 60, 90, 120 tabs; 120, 180, 240, 300 mg caps	0.4 to 1.25 mg/kg per dose qid; sustained release qd to bid	Unknown	
Verapamil	120, 180, 240 mg	4 to 10 mg/kg per day tid	With caution	
Amlodipine	2.5, 5, and 10 mg tabs	2.5 mg qd 10 mg qd maximum	None	None
Nicardipine (cardene)	20, 30 mg caps	20 mg tid	Patients should be closely monitored	Small, temporary increase
Isradipine	2.5, 5 mg caps	0.1 mg/kg per dose initially increase to maximum of 1.2 mg/kg per day	Patients should be closely monitored	Small, temporary increase

Updated from Feld L, Lieberman E, Mendoza SA, Springate JE. Management of hypertension in the child with chronic renal disease. *J Pediatr.* 1996;129:S18–S26.

year) attributed to inadvertent breakdowns in sterile techniques.

Although the long-term prognosis for patients receiving CAPD is not yet available, the long-term survival rates for children undergoing chronic hemodialysis and renal transplantation are. Of children receiving long-term chronic hemodialysis, all survived at 6 months and 95% at 5 years. Of living-related transplantations in all age groups, 92% survived at 6 months and 72% at 5 years, with allograft half-lives of 13 years. For cadaveric transplantations, survival was 86% at 6 months and 65% at 5 years, with allograft half-life of 9 years. In contrast to live unrelated organ donors, parent donor transplants do significantly better than cadaveric transplants. Survival is 74% at 5 years, and allograft half-life is 12 years. Over the years, kidney transplants have improved due to the many new and powerful antirejection medications.

Dialysis and transplantation in infants and children, with cumulative experience over the past 3 decades, have become widely accepted treatments in end-stage renal disease.

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PIR Quiz

Quiz also available online at *www.pedsinreview.org*

5. An 18-month-old boy is hospitalized after 2 days of diarrhea and persistent vomiting. He has had no wet diapers in the past 12 hours. As part of the evaluation, you obtain the following laboratory results: urine sodium, 25 mmol/L (25 mEq/L); urine creatinine, 60 mg/dL (5,304 mcmol/L); plasma creatinine, 0.8 mg/dL (70.7 mcmol/L). The diagnosis that *best* accounts for the clinical and laboratory findings is:

   A. Glomerulonephritis.
   B. Hemolytic-uremic syndrome.
   C. Polycystic kidney disease.
   D. Posterior urethral valves.
   E. Rotaviral infection.

6. An 18-month-old girl is hospitalized for diarrhea, persistent vomiting, and continued anuria overnight despite receiving 20 mL/kg normal saline as an intravenous bolus. The laboratory results this morning reveal a plasma creatinine of 1.0 mg/dL (88.4 mcmol/L), with a fractional excretion of sodium of 3%. The *best* choice of intervention at this time is to replace urinary output and:

   A. Infuse insensible water loss.
   B. Infuse insensible water loss adjusted for tissue catabolism.
   C. Infuse maintenance fluids.
   D. Maintain an open vein for medications only.
   E. Repeat a 20 mL/kg normal saline fluid bolus.

7. The *most* common cause of chronic renal failure in children requiring transplantation is:

   A. Familial nephritis.
   B. Hemolytic-uremic syndrome.
   C. Obstructive uropathy.
   D. Polycystic kidney disease.
   E. Reflux nephropathy.

8. A 7-year-old boy who has chronic renal failure due to posterior urethral valves has a plasma creatinine of 1.2 mg/dL (106 mcmol/L). At this level of renal function, optimal management would require:

   A. Calcium acetate.
   B. Captopril.
   C. Erythropoietin.
   D. No treatment.
   E. Transplantation.

9. The boy's renal function progressively deteriorates over the next several years. His growth can *best* be maximized in the years before transplantation by:

   A. Assuring intake of 120 kcal/kg per day.
   B. Injecting growth hormone weekly.
   C. Maintaining hemoglobin at 13 g/dL (130 g/L) or higher.
   D. Maintaining plasma bicarbonate at 16 mmol/L.
   E. Providing a protein-rich diet.