

Section 4 - Tubular Disorders

Chapter 536 - Tubular Function

Jerry M. Bergstein

Except for reduced protein levels, the ultrafiltrate of blood that enters the proximal tubule is similar to plasma. Body homeostasis is maintained by tubular reabsorption of salts and water.

SODIUM.

After the 1st year of life, the tubules have the reabsorptive capacity to lower the urinary sodium concentration to 1 mEq/L (1 mmol/L). Approximately 65% of filtered sodium is isotonically reabsorbed in the proximal tubule. Glucose and amino acids are also reabsorbed in the proximal tubule in conjunction with sodium transport. An additional 25% of filtered sodium is reabsorbed from the ascending limb of the loop of Henle in association with the active transport of chloride. The remainder of sodium reabsorption is accomplished in the distal tubule and collecting duct, mediated in part by aldosterone. Sodium excretion is closely related to the extracellular fluid (ECF) volume and may be modified by factors that regulate the ECF volume.

POTASSIUM.

Essentially all of the filtered potassium is reabsorbed, primarily in the proximal tubules. The potassium excreted is derived from distal tubular and collecting duct potassium secretion, as modified by the pH of the ECF, by aldosterone, and by the urinary flow rate and sodium concentration.

CALCIUM.

Approximately 98% of filtered calcium is reabsorbed by the tubules. Proximal tubular reabsorption (65% of the filtered load) is linked to sodium reabsorption. Calcium reabsorption is enhanced by parathyroid hormone, thiazide diuretics, and reduction of the ECF volume. Calcium excretion is increased by saline infusion and furosemide.

PHOSPHATE.

The majority of the filtered phosphate is reabsorbed in the proximal tubule. Reabsorption is inhibited by parathyroid hormone.

MAGNESIUM.

About 25% of filtered magnesium is reabsorbed in the proximal tubule; the major site of magnesium reabsorption and the principal moderator of magnesium excretion is the thick ascending limb of the loop of Henle.

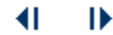
ACIDIFICATION AND CONCENTRATING MECHANISMS.

These are discussed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus ([Chapters 537](#) and [538](#))

MATURATION OF TUBULAR FUNCTION.

At birth and for several months thereafter, tubular functional capabilities are at less than adult levels. Tubular function is adequate for healthy infants, but limitations may contribute to fluid and electrolyte abnormalities in sick infants. Maximal urinary concentrating capacity in a healthy full-term newborn is 600-700 mOsm/kg (mmol/kg) H₂O. This reduction in concentrating capacity in comparison with older children and adults (who can concentrate to more than 1,000 mOsm/kg [mmo1/kg] H₂O) is related to reduced glomerular filtration rate (GFR), to tubular cell immaturity, to reduced nephron length, to reduced medullary solute gradient due to increased medullary blood flow and low urea production, and to diminished tubular responsiveness to antidiuretic hormone. Although the ability of newborn infants to dilute the urine is comparable to that of adults, their capacity to excrete a water load is diminished, owing to the reduced GFR. The capacity of neonates to excrete sodium, potassium, hydrogen ion, and phosphate is also limited, owing in part to the low GFR or immaturity of tubular function.

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Chapter 537 - Renal Tubular Acidosis

Jerry M. Bergstein

Renal tubular acidosis (RTA) is a clinical state of systemic hyperchloremic acidosis resulting from impaired urinary acidification. Three types exist: distal RTA (type I), proximal RTA (type II), and mineralocorticoid deficiency (type IV). A proposed type III has been found to be a variant of type I. All types are associated with a normal anion gap.

NORMAL URINARY ACIDIFICATION.

After the first few months of life, approximately 85% of the filtered bicarbonate is reabsorbed in the proximal tubules, but in premature infants and neonates such reabsorption of bicarbonate is transiently reduced, and bicarbonate wasting results when the serum bicarbonate level exceeds 20-22 mEq/L (mmol/L). Proximal tubular reabsorption of bicarbonate involves the secretion of hydrogen ion into the tubular lumen in exchange for sodium ([Chapter 52](#)). The hydrogen ion combines with filtered bicarbonate to form carbonic acid, which, under the influence of carbonic anhydrase, dissociates into carbon dioxide and water. The carbon dioxide diffuses into the proximal tubular cells, where, under the influence of carbonic

anhydrase, it is reconverted to carbonic acid. The carbonic acid dissociates to yield a hydrogen ion that is again secreted to absorb additional bicarbonate and to yield a bicarbonate ion that enters the peritubular capillary. The remaining 15% of filtered bicarbonate is reabsorbed in the distal tubule. A normal kidney reabsorbs all filtered bicarbonate, but this does not make the urine acid. Acidification of the urine is mediated by distal tubular and collection duct secretion of hydrogen ion (which is in part mineralocorticoid dependent) and of ammonia (which forms ammonium ion in an acidic urine).

537.1 Proximal Renal Tubular Acidosis

PATHOGENESIS.

Proximal RTA results from reduced proximal tubular reabsorption of bicarbonate, presumably owing to deficient carbonic anhydrase production or hydrogen ion secretion. Rather than reabsorbing the normal 85% of filtered bicarbonate, the proximal tubules in this condition may reabsorb only 60%, thus presenting the distal tubules with 40% rather than the usual 15% of the filtered load. Because the distal tubules can, at a maximum, reabsorb only 15% of the normal filtered load of bicarbonate, up to 25% may be lost in the urine. Proximal RTA is generally more severe than distal RTA, because complete loss of the distal bicarbonate recovery mechanism (which is rare) would waste only 15% of filtered bicarbonate. With urinary bicarbonate loss, the serum bicarbonate level falls until it reaches a level (bicarbonate threshold) at which bicarbonate wasting ceases. At this level (15-18 mEq/L [mmol/L]), the quantity of filtered bicarbonate is reduced to an amount that can be totally reabsorbed by the tubules. Because distal tubular acidification mechanisms remain intact, the urine may then be acidified (pH < 5.5). Flooding the distal tubule with sodium bicarbonate stimulates sodium reabsorption in exchange for potassium, leading to hypokalemia. Contraction of the extracellular fluid volume (as a result of the loss of sodium bicarbonate) stimulates chloride reabsorption (resulting in hyperchloremia) and aldosterone secretion (enhancing potassium loss).

Proximal RTA ([Table 537-1](#)) may occur as an isolated disorder not associated with other diseases or with other abnormalities of proximal tubular function. Isolated proximal RTA may be transient or persistent, sporadic or inherited (usually autosomal dominant). Proximal RTA may also occur as part of a generalized defect in proximal tubular transport (Fanconi syndrome), characterized by proteinuria, glucosuria, phosphaturia, aminoaciduria, citraturia, and proximal RTA. A primary form of Fanconi syndrome, not associated with other disease states, has been reported to show both autosomal dominant and recessive modes of inheritance. Secondary Fanconi syndrome may develop during the course of several different inherited or acquired disease states (see [Table 537-1](#)).

INHERITED FORMS OF FANCONI SYNDROME

Cystinosis ([Chapters 537 .3](#) and [82 .4](#)).

Lowe Syndrome. See [Chapter 537 .4](#).

Galactosemia(see [Chapter 84 .2](#)).

The renal manifestations of this disorder result from prolonged galactose accumulation in the proximal tubules.

Hereditary Fructose Intolerance (see [Chapter 84 .3](#)).

This autosomal

TABLE 537-1 -- Classification of Renal Tubular Acidosis
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Proximal	Distal	Mineralocorticoid Deficiency*
Isolated	Isolated	Adrenal disorders (↓ A, ↑ R)
Sporadic	Sporadic	Addison disease
Hereditary	Hereditary	Congenital hyperplasia
Fanconi syndrome	Secondary	Primary hypoaldosteronism
Primary	Interstitial nephritis	Hyporeninemic hypoaldosteronism (↓ A, ↓ R)
Secondary	Obstructive	Obstruction
Inherited	Reflux	Pyelonephritis
Cystinosis	Pyelonephritis	Interstitial nephritis
Lowe syndrome	Transplant rejection	Diabetes mellitus
Galactosemia	Sickle cell nephropathy	Nephrosclerosis
Hereditary fructose intolerance	Lupus nephritis	Pseudohypoaldosteronism (↑ A, ↑ R)
Tyrosinemia	Ehlers-Danlos syndrome	
Wilson disease	Nephrocalcinosis	
Medullary cystic disease	Hepatic cirrhosis	
Mitochondrial cytopathies	Elliptocytosis	
Acquired	Medullary sponge kidney	
Heavy metals	Toxins	
Outdated tetracycline	Amphotericin B	
Proteinuria	Lithium	
Interstitial nephritis	Toluene	
Hyperparathyroidism		
Vitamin D-deficiency rickets		
Gentamicin		
Cyclosporine		

* A = aldosterone; R = renin.

recessive deficiency of fructose-1-phosphate aldolase leads to proximal tubular dysfunction.

Tyrosinemia.

Generalized proximal tubular dysfunction is common in hereditary tyrosinemia (see [Chapter 82](#) .2).

Wilson Disease.

The clinical manifestations of this autosomal recessive disorder include proximal tubular dysfunction; it is discussed in [Chapters 357](#) .2 and [606](#) .3.

Medullary Cystic Disease.

This disorder is inherited as an autosomal dominant trait, whereas a similar disorder, juvenile nephronophthisis, is inherited as an autosomal recessive trait. Whether these are separate disorders or the same disorder with variable inheritance is uncertain. Children more commonly have the recessive form, whereas the dominant form is more common in adults. The major pathologic finding is cysts in the medulla. Because the "cysts" seem to be dilatations of the distal tubules and collecting ducts, some may also be found in the renal cortex. Progressive interstitial inflammation and fibrosis lead to glomerular sclerosis, cortical atrophy, and renal insufficiency. Some children suffer no clinical problems until reaching end-stage renal failure. Others show manifestations of tubular dysfunction such as polyuria and polydipsia (concentrating defect), sodium wasting, and proximal RTA. Affected children commonly have red or blond hair. Urinalysis may yield normal results or show minimal abnormalities. Radiographic studies show small, poorly functioning kidneys. The diagnosis is confirmed by biopsy or at nephrectomy if either is warranted in preparation for transplantation.

CAUSES OF ACQUIRED FANCONI SYNDROME.

These include tubular toxins such as heavy metals (lead, mercury, cadmium, uranium), outdated tetracycline, proteinuric states (myeloma, nephrotic syndrome), and interstitial nephritis. Excessive parathyroid hormone secretion (primary and secondary hyperparathyroidism, vitamin D-deficient rickets) may also cause proximal RTA, presumably by inhibition of carbonic anhydrase.

537.2 Distal Renal Tubular Acidosis

PATHOGENESIS.

The genesis of distal RTA is best explained as a deficiency of hydrogen ion secretion by the distal tubule and collecting duct, although other mechanisms may also be involved. Independent of the precise mechanism, the excretion of ammonium ion is also decreased. The lack of secreted hydrogen ion reduces the formation of carbonic acid and then carbon dioxide in the tubular lumen. The loss of bicarbonate in the urine may be 5-15% of the filtered load. Owing to the nature of the defect, the pH of the urine cannot be reduced below 5.8 despite severe systemic acidosis. Loss of sodium bicarbonate results in hyperchloremia and hypokalemia. The hypokalemia is usually less severe than that found in proximal RTA because less bicarbonate is wasted. Hypercalciuria, nephrocalcinosis, and nephrolithiasis may be present. Distal RTA may occur as an isolated condition not associated with any other disorder; as such it may be sporadic or inherited as an autosomal dominant or recessive trait. Secondary distal RTA may develop during the course of several diseases and intoxications involving the distal tubules and collecting ducts (see [Table 537-1](#)).

MEDULLARY SPONGE KIDNEY.

This noninherited disorder is characterized by cystic dilatation of the terminal portions of the collecting ducts as they enter the renal pyramids. Although renal function and life span are typically normal, the disorder may be complicated by pyelonephritis, hypercalciuria, nephrocalcinosis ([Fig. 537-1](#)), nephrolithiasis, impaired concentrating capacity, and distal RTA.

MINERALOCORTICOID DEFICIENCY

PATHOGENESIS.

This form of RTA results from inadequate production of or reduced distal tubular responsiveness to aldosterone.

Figure 537-1 Ultrasound examination of a child with distal renal tubular acidosis demonstrating medullary nephrocalcinosis.

The lack of aldosterone effect impairs the establishment across the tubular cell membrane of an electrochemical gradient (with negative electrical potential in the tubular lumen) favorable to hydrogen ion secretion. In the absence of aldosterone-mediated sodium reabsorption, hyperkalemia develops. Hyperkalemia suppresses renal ammonia production, resulting in a reduction of ammonium ion excretion and, thus, net acid excretion. The net effect is a hyperkalemic, hyperchloremic acidosis. The systemic acidosis may render the urine pH acid (< 5.5).

Mineralocorticoid-deficiency RTA may result from diseases of the adrenal gland (Addison disease, congenital adrenal hyperplasia, primary hypoadosteronism) in which aldosterone production is deficient. In these disorders, renal function is normal, urinary sodium wasting is common, and the plasma renin level is elevated. Hyporeninemic hypoadosteronism is a form of RTA that may result from kidney diseases associated with interstitial damage and destruction of the juxtaglomerular apparatus; it may also be observed with volume expansion and prostaglandin inhibition. In these conditions, plasma levels of renin and, as a result, of aldosterone are reduced; renal function may be compromised. Rarely, type IV RTA may be a result of distal tubular unresponsiveness to aldosterone (pseudohypoadosteronism); plasma renin and aldosterone levels are elevated, renal function is usually normal, and salt wasting is the rule. In adults, this form of RTA may be observed in patients with medullary disease and renal insufficiency.

CLINICAL MANAGEMENT OF RENAL TUBULAR ACIDOSIS

CLINICAL MANIFESTATIONS.

Children having isolated forms of proximal or distal RTA commonly present with growth failure toward the end of the 1st yr of life. Symptoms may include polyuria, dehydration, anorexia, vomiting, constipation, and hypotonia. Children having secondary forms of proximal or distal RTA may present in a similar fashion or with complaints unique to their fundamental disease. Mineralocorticoid deficiency is usually found as an underlying feature of a primary kidney disease.

Distal RTA is complicated by hypercalciuria, which may lead to nephrocalcinosis, nephrolithiasis, and renal parenchymal destruction. The causes of the hypercalciuria are unknown; potential mechanisms include bone breakdown to release calcium carbonate (the carbonate to be converted to bicarbonate

in an attempt to control the acidosis) and diminished levels of urinary citrate (which chelates calcium).

Proximal RTA may be complicated by rickets, which may be due to phosphate wasting or insufficient production of 1,25 (OH)₂ D.

DIAGNOSIS.

Before the diagnosis of RTA is considered, other causes of systemic-acidosis, such as diarrhea, inborn errors of metabolism, ingestion, lactic acidosis, diabetes mellitus, and renal failure, should be precluded. The biochemical features of proximal and distal RTA include low serum bicarbonate and potassium levels in association with hyperchloremia. In mineralocorticoid-deficiency RTA, systemic acidosis is associated with hyperkalemia. The anion gap in all forms of RTA is usually normal (see [Chapter 52](#)).

Patients suspected of having proximal or distal RTA should be evaluated by comparing the pH (by pH meter) of a first morning urine specimen (collected under mineral oil to prevent the loss of carbon dioxide) with simultaneous measurements of serum electrolytes. In patients who have substantial systemic acidosis (serum bicarbonate level < 18 mEq/L), a urine pH of less than 5.6 supports the diagnosis of proximal RTA, whereas patients with distal RTA have a urine pH of 5.8 or greater. The urinary anion gap (urine concentrations of sodium plus potassium minus chloride) may be an indirect index of ammonium ion excretion that distinguishes proximal from distal RTA. Normal individuals and patients with proximal RTA have a negative gap during metabolic acidosis owing to an increase in ammonium chloride production. Patients with distal RTA have a positive anion gap owing to impaired excretion of hydrogen and ammonium ions.

In patients having mild acidosis (serum bicarbonate level 18-20 mEq/L [mmol/L]), ammonium chloride loading may be required to distinguish between the two types. If proximal RTA is detected, then other defects of proximal tubular function should be sought (glucosuria, phosphaturia, proteinuria, aminoaciduria). When any form of RTA is confirmed, potential underlying causes (see [Table 537-1](#)) should be investigated.

TREATMENT.

The goals of therapy are correction of the acidosis and maintenance of normal serum bicarbonate and potassium levels. Most patients' conditions can be corrected with oral therapy; in infants having severe acidosis and hypokalemia, intravenous therapy may be required initially. The least expensive and easiest alkalinizing solution for oral use is Shohl solution (Bicitra, Willen Drug Company, Baltimore, MD) containing 1 mEq/mL of "bicarbonate equivalent" as sodium citrate. For patients requiring potassium supplementation, potassium citrate can be added (Polycitra, Willen Drug Company, Baltimore, MD) to form a solution that contains 1 mEq/mL each of sodium and potassium, and 2 mEq/mL of bicarbonate equivalent. Sodium bicarbonate tablets (325 and 650 mg) may be used for older patients. Infants may also require oral sodium chloride supplements. Patients with Fanconi syndrome may require phosphate and vitamin D supplements. Patients having mineralocorticoid-deficiency RTA may require diuretics or polystyrene sulfonate resin (Kayexalate, Winthrop Pharmaceuticals, New York, NY) to reduce the serum potassium level to normal.

PROGNOSIS.

Isolated proximal RTA, although initially more severe than the distal variety, may resolve during the 1st decade of life. Isolated distal RTA seems to be a lifelong disease; in some instances, renal failure may develop. The prognosis is excellent, however, if the disease is recognized and therapy initiated before the development of nephrocalcinosis. A continuing need for alkali therapy and for lifelong monitoring of clinical status is the rule.

Mineralocorticoid-deficiency RTA most frequently results from obstructive uropathy and usually resolves within 12 mo after correction of the obstruction. In other secondary forms of RTA, the ultimate prognosis may depend on the severity of the primary disorder.

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537.3 Cystinosis

(Lignac Syndrome; Fanconi Syndrome with Cystinosis)

Cystinosis is an autosomal recessive disorder mapped to chromosome 17. The severe form of the disease (*infantile or nephropathic cystinosis*) presents in the 1st 2 yr of life and proceeds to renal failure by the end of the 1st decade. Adolescents may be affected by a milder form of the disease characterized by normal growth, minimal renal tubular abnormalities, and slow progression to renal failure. A benign adult form with no renal involvement also exists.

PATHOGENESIS.

The disease results from accumulation of cystine within the lysosomes of the bone marrow, liver, spleen, lymph nodes, kidneys, fibroblasts, leukocytes, corneas, conjunctivae, thyroid, pancreas, intestine, and brain. Normally, lysosomal degradation of proteins yields free cysteine, which is transported out of the cell. In cystinosis, a defect in the membrane transport system traps cystine within the lysosome.

CLINICAL MANIFESTATIONS.

In the nephropathic variety, initial clinical manifestations may include polyuria and polydipsia (concentrating defect), fever (dehydration, decreased sweat production), growth retardation, rickets, blond hair and fair skin (diminished pigmentation), photophobia, and Fanconi syndrome. Later manifestations may include hypothyroidism, retinopathy leading to decreased visual acuity and occasional blindness, hepatosplenomegaly, and delayed sexual maturation. Intracellular accumulation of cystine in the kidneys leads to chronic nephritis and end-stage renal failure by the end of the 1st decade of life.

DIAGNOSIS.

The diagnosis of cystinosis may be suggested by the detection of cystine crystals in the cornea. Because these may be absent, the diagnosis should be confirmed in suspected cases by measurement of leukocyte cystine content. For families at risk, prenatal testing is available.

TREATMENT.

Treatment includes correction of the metabolic abnormalities associated with Fanconi syndrome. Specific therapy involves depletion of cystine from tissues with the thiol-containing agent cysteamine. This drug penetrates lysosomal membranes to convert trapped cystine to cysteine, which forms a complex with cysteamine. The complex is then transported out of the lysosome. Early initiation of the drug may prevent or delay deterioration in renal function. Cysteamine eye drops may be helpful in removing corneal cystine crystals.

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PROGNOSIS.

Patients whose disease progress to end-stage renal failure are satisfactory transplant candidates. After transplantation, which extends survival, patients may develop additional complications of the disease including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic endocrine and exocrine insufficiency.

537.4 Oculocerebrorenal Syndrome of Lowe **(Lowe Syndrome)**

This rare X-linked recessive disorder is characterized by congenital cataracts, mental retardation, and Fanconi syndrome.

PATHOGENESIS.

The gene responsible for this disorder, termed OCRL-1, has been cloned. Gene mutations lead to deficient production of a phosphatase that is important in the transport of vesicles within the Golgi apparatus. Pathologic studies of the kidneys show nonspecific tubulointerstitial changes. Electron microscopy shows thickening of the glomerular basement membranes and changes in the mitochondria of the proximal tubules. At autopsy, brain lesions have been variable and inconsistent. CT and MRI studies show abnormalities in the cerebral white matter.

CLINICAL FEATURES.

Prominent initial features of the disease include centrally located congenital cataracts, sometimes associated with glaucoma, moderate to severe mental retardation, hypotonia, and Fanconi syndrome. Although birthweight is usually normal, patients show progressive growth failure over time. Blindness and renal insufficiency may ultimately develop.

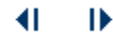
TREATMENT.

Management includes early removal of the cataracts, adequate nutrition, correction of the biochemical abnormalities, and genetic counseling. Slit-lamp examination of carriers may reveal punctate lenticular opacifications.

537.5 Rickets Associated with Renal Tubular Acidosis

Russell W. Chesney

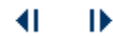
Rickets may be present in primary renal tubular acidosis (RTA), particularly in type II or proximal RTA. See [Chapters 44](#) . [10](#) and [712](#) . Hypophosphatemia and phosphaturia are common in these syndromes, which are characterized by hyperchloremic metabolic acidosis, various degrees of bicarbonaturia, and frequently hypercalciuria and hyperkaliuria. Bone demineralization without overt rickets usually is detected in type I and distal RTA. The metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and occasionally pathologic fractures. Although acute metabolic acidosis in vitamin D-deficient animals may impair the conversion of 25(OH)D to 1,25(OH)₂ D, resulting in reduced levels of this active metabolite, the circulating levels of 1,25(OH)₂ D in patients with either type of RTA are normal. If patients with RTA have azotemia and loss of renal mass, serum 1,25(OH)₂ D levels are often reduced. Bone demineralization in distal RTA probably relates to dissolution of bone, because the calcium carbonate in bone may serve as a buffer against the metabolic acidosis that is due to the hydrogen ions retained by patients with RTA. Administration of sufficient bicarbonate to reverse acidosis stops bone dissolution and the hypercalciuria that is common in distal RTA. Proximal RTA is treated with both bicarbonate and oral phosphate supplements to heal bone disease. Doses of phosphate similar to those used in familial hypophosphatemia should be used ([Chapter 711](#)) . Vitamin D is needed to offset the secondary hyperparathyroidism that complicates oral phosphate therapy.



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Chapter 538 - Nephrogenic Diabetes Insipidus

Jerry M. Bergstein

In nephrogenic diabetes insipidus the kidneys fail to respond to antidiuretic hormone (ADH) despite elevated blood levels of ADH.

ETIOLOGY.

Primary (congenital) nephrogenic diabetes insipidus is a rare inherited (usually X-linked recessive) disease characterized by complete tubular unresponsiveness to ADH in males and partial unresponsiveness in females. Partial or complete nephrogenic diabetes insipidus (secondary) may also be associated with disorders that (1) result in loss of the medullary concentrating gradient (acute or chronic renal failure, obstructive and postobstructive uropathy, vesicoureteral reflux, cystic diseases, interstitial nephritis, osmotic diuresis, nephrocalcinosis); or (2) diminish the effect of ADH on the tubules (hypokalemia, hypercalcemia, lithium, amphotericin B, and demeclocycline therapy).

PATHOGENESIS.

Concentration of the urine depends on the establishment of a hypertonic renal medulla and the permeability of the collecting ducts to water. The hypertonicity of the medulla is established by a countercurrent mechanism linked to reabsorption of sodium and urea. The permeability of the collecting ducts is regulated by ADH, release of which from the neurohypophysis is triggered primarily by osmosensitive neurons located in the hypothalamus and secondarily by monitors of intravascular volume that reside in the heart, large arteries, kidney, liver, and brain. In the kidneys, ADH acts to increase the permeability of the collecting ducts to water by means of a cyclic adenosine monophosphate-dependent mechanism. The activity of ADH is mediated by binding to a type 2 vasopressin (V_2) receptor on the cells of the collecting ducts. Type I receptors are found on platelets and on smooth muscle and liver cells; these receptors are intact in nephrogenic diabetes insipidus. Activation of the V_2 receptor promotes movement of preformed water channels (composed of aquaporin-2 protein) to the luminal membrane of the collecting ducts where it fuses to the membrane, thereby increasing the permeability of the membrane to water. This permits water to flow by passive diffusion from the duct into the hypertonic medullary interstitium of the kidney.

In primary nephrogenic diabetes insipidus, the collecting duct fails to respond normally to ADH, whether endogenous or exogenous, owing to one of several mutations in the V_2 receptor gene. Extrarenal responses (coagulation, fibrinolysis, vasodilatation) to V_2 receptors are also deficient. Rare patients with primary nephrogenic diabetes insipidus showing autosomal recessive inheritance and patients with certain forms of secondary nephrogenic diabetes insipidus (e.g., lithium intoxication) may have ADH resistance due to defective aquaporin-2 expression. Alternatively, secondary forms may result from loss of the hypertonic medullary gradient owing to a solute diuresis or inability of the tubules to reabsorb sodium chloride and urea.

CLINICAL MANIFESTATIONS.

Males with primary nephrogenic diabetes insipidus have a dramatic history of polyuria and polydipsia in infancy, often with episodes of hypernatremic dehydration.

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Females with the primary defect have milder symptoms that may not be detected until later in life. Patients having secondary forms of the disease present with hypernatremia during the course of their primary disorder.

DIAGNOSIS.

The diagnosis of primary nephrogenic diabetes insipidus is suspected on clinical history, often with a positive family history in males. Laboratory findings include hypernatremia and dilute urine. If the serum osmolality at initial study exceeds 295 mOsm/kg (mmol/kg) H₂O and concurrent urine osmolality is less than this value, then a dehydration test to establish the diagnosis is unnecessary. The diagnosis is confirmed by administering an intramuscular injection of 0.1-0.2 unit/kg of aqueous vasopressin and measuring the serum and urine osmolality each hour for 4 hr. If the ratio of urine-to-plasma osmolality remains less than 1.0, the patient has nephrogenic diabetes insipidus. If the ratio becomes greater than 1.0, central diabetes insipidus is suggested but psychogenic polydipsia must be precluded. Patients with initial serum osmolality levels less than 295 mOsm/kg (mmol/kg) H₂O should fast (during the day rather than overnight) until serum osmolality exceeds 295 mOsm/kg (mmol/kg) H₂O; vasopressin is then given as before. Withholding of fluids should be terminated if body weight declines by as much as 3%. In patients suspected of having primary nephrogenic diabetes insipidus, appropriate biochemical and cranial imaging studies should be done to preclude secondary causes.

COMPLICATIONS.

Primary nephrogenic diabetes insipidus was once thought to be associated with mental retardation. Retardation is more likely the result of repeated episodes of hypertonic dehydration than the consequence of the disease itself. Growth retardation is uniformly present in males with the primary disorder but is usually absent in females. Growth failure was originally thought to result from inadequate caloric intake due to excessive fluid intake, but it now seems that growth failure is intrinsic to the homozygous state. Dilatation of the urinary collecting system may result from excessive urine production. Accordingly, the anatomy of the urinary tract should be examined for evidence of hydronephrosis every few years by renal scan (intravenous pyelography may not visualize the collecting systems when there is rapid flow of large volumes of dilute urine).

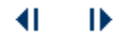
TREATMENT.

The keys to treatment include the provision of adequate fluid and caloric intake and reduction of the urinary solute load. These are accomplished by limiting the intake of a low-sodium formula (SMA, Wyeth Laboratories, Philadelphia, PA; Similac PM 60/40, Ross Laboratories, Columbus, OH) to only that which is necessary to supply optimal caloric intake for growth. The remainder of the daily fluid requirement (as determined by the maintenance of a normal serum sodium level) is administered as water or fruit juice. The parents should be cautioned that until their child can obtain free access to water, fluids should be offered every 1-2 hr during the day and three times during the night. Once a child becomes old enough to obtain free access to water, the intact thirst mechanism provides the appropriate stimulus for fluid intake. In patients with the primary disorder, the urinary volume can be dramatically reduced by diuretic therapy. This paradoxical response results because sodium depletion seems to enhance proximal tubular reabsorption of sodium and water. Less water, therefore, is presented to the defective portion of the tubules. Chlorothiazide (20-40 mg/kg/24 hr in divided doses) in conjunction with moderate salt restriction may significantly reduce the need for fluid intake and the frequency of voiding. Patients should be monitored for the development of hypokalemia. Patients who fail to respond to a low-solute diet and diuretics may be candidates for treatment with inhibitors of prostaglandin synthesis (e.g., indomethacin). This type of therapy is of no value for secondary forms of the disease.

PROGNOSIS.

Primary nephrogenic diabetes insipidus is a lifelong disease with a good prognosis if hypernatremic dehydration can be avoided. Genetic counseling should be provided for the family; studies to define the precise genetic defect and detect carriers are available. The prognosis for secondary forms of the disease depends on the nature of the primary disorder. The syndrome may resolve after correction of obstructive lesions.

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Chapter 539 - Bartter Syndrome

Jerry M. Bergstein

Bartter syndrome is a rare form of renal potassium wasting characterized by hypokalemia, normal blood pressure, vascular insensitivity to pressor agents, and elevated plasma concentrations of renin and aldosterone. In certain families, the disorder may be inherited as an autosomal recessive trait.

PATHOLOGY.

Generalized hyperplasia of the juxtaglomerular apparatus, the site of renin production, is observed in most patients. The renal parenchyma is otherwise normal in most patients; a few have shown nonspecific glomerular disease, interstitial disease, or both.

PATHOGENESIS.

The cause is unknown. Currently, the disorder is best explained as a primary defect in chloride reabsorption in the ascending limb of the loop of Henle. The resultant decrease in sodium chloride reabsorption in this portion of the loop reduces medullary hypertonicity, perhaps explaining the concentrating defect. The defect in chloride reabsorption presents extra sodium chloride to the distal tubule, where sodium is reabsorbed in exchange for potassium; the result is urinary potassium wasting. The induced hypokalemia stimulates the synthesis of prostaglandins (which may account for the vascular insensitivity to pressor agents and the defect in platelet aggregation); these, in turn, activate the renin-angiotensin-aldosterone system by increasing renin release and by stimulating aldosterone synthesis. The latter exacerbates renal potassium wasting.

CLINICAL MANIFESTATIONS.

A severe form of Bartter syndrome (sometimes called hyperprostaglandin E syndrome) may afflict newborns. It is characterized by polyhydramnios, prematurity, dehydration secondary to marked urinary sodium, potassium and water loss, and growth failure; hypercalciuria and nephrocalcinosis are common. Young children typically present with growth failure, muscle weakness, constipation, and polyuria. Older children have muscle weakness or cramps and carpopedal spasms.

DIAGNOSIS.

The diagnosis is suggested by the finding of hypokalemia; the serum potassium level is usually less than 2.5 mEq/L. Supportive findings include normal blood pressure;

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defective platelet aggregation; hypochloremia; metabolic alkalosis; elevated plasma levels of renin, aldosterone, and prostaglandin E₂; and high urinary levels of potassium and chloride. Some patients may also have hypercalciuria, hyperuricemia, hypomagnesemia, and urinary sodium wasting. The diagnosis may be confirmed by the histologic demonstration of hyperplasia of the juxtaglomerular apparatus, but this abnormality is not found in all patients and is frequently absent in young children.

Bartter syndrome must be differentiated from licorice abuse, laxative or diuretic use, persistent vomiting or diarrhea, pyelonephritis, and diabetes insipidus. Several of these (laxative use, vomiting, diarrhea, diabetes insipidus) are associated with hypovolemia, which results in a low urinary chloride level, whereas Bartter syndrome is associated with an elevated level.

Bartter syndrome may be confused with *Gitelman syndrome*. Both disorders are associated with hypokalemia, renal potassium wasting, activation of the renin-angiotensin-aldosterone axis, and normal blood pressure. Gitelman syndrome commonly presents in older children and young adults with muscle weakness, carpopedal spasms, or tetany. Patients with Bartter syndrome have normal to decreased serum magnesium levels, normal urinary magnesium excretion, and normal to increased calcium excretion; patients with Gitelman syndrome have hypomagnesemia, increased urinary magnesium, and decreased calcium excretion. Gitelman syndrome results from a mutation of the gene for the thiazide-sensitive sodium-chloride co-transporter of the distal tubule located on chromosome 16.

TREATMENT.

The goals of therapy are to supply adequate nutrition and to maintain the serum potassium level above 3.5 mEq/L. Therapy is initiated with oral potassium chloride supplementation, increasing the dose until the serum potassium level

reaches 3.5 mEq/L or the dosage reaches 250 mEq/24 hr. Reasonably well tolerated potassium preparations include K-Lyte/Cl (Mead Johnson Company, Evansville, IN), flavored effervescent tablets containing 25 or 50 mEq of potassium chloride, and Micro-K 10 Extencaps (A.H. Robins Company, Richmond, VA). Sodium chloride supplementation may also be required in small children. If the serum potassium level remains below 3.5 mEq/L (mmol/L) after reaching a dose of 250 mEq/24 hr of potassium chloride, then triamterene, 5-10 mg/kg/24 hr in divided doses, should be added. If this fails to resolve the hypokalemia, then indomethacin, 3-5 mg/kg/24 hr divided into three doses, should be given. Patients receiving indomethacin should be monitored for signs of gastrointestinal irritation.

PROGNOSIS.

The long-term prognosis of Bartter syndrome is uncertain. Many patients remain well, but some cases (especially those with glomerular or interstitial abnormalities) progress to renal insufficiency. Despite severe growth retardation in infancy, normal stature is ultimately obtained. The suggestion that mental retardation occurs in patients who have severe disease in the 1st yr of life remains to be confirmed.

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Chapter 540 - Interstitial Nephritis

Jerry M. Bergstein

Interstitial nephritis is a histopathologic term signifying inflammation between the glomeruli in the areas surrounding the tubules (the interstitium). Acute and chronic forms are recognized, depending on the nature of the inflammatory infiltrate

and the presence or absence of edema and fibrosis. Tubular damage is generally present; glomerular changes may be minimal. Common causes of acute or chronic interstitial nephritis in children are listed in [Table 540-1](#) .

ACUTE INTERSTITIAL NEPHRITIS

PATHOLOGY.

Whatever the cause of interstitial disease, the interstitial infiltrate is composed of lymphocytes, plasma cells, eosinophils, and occasional neutrophils ([Fig. 540-1](#)) . The tubules are separated by edema and may show degeneration or frank necrosis. Unless the interstitial nephritis is associated with glomerulonephritis, the glomeruli are normal.

PATHOGENESIS.

The genesis of acute interstitial nephritis is poorly understood. When it is due to drug ingestion, failure of the amount of drug administered to correlate with incidence of the syndrome suggests a hypersensitivity reaction. For methicillin, an immunologic mechanism has been suggested in several instances by the finding of anti-tubular basement membrane antibodies. Whether infections cause interstitial inflammation by direct invasion or by other mechanisms remains unclear. In certain forms of glomerulonephritis, tubular basement membrane deposition of immune complexes (lupus, membranoproliferative) or of anti-basement membrane antibodies (Goodpasture, membranous) may initiate the inflammatory

TABLE 540-1 -- Causes of Interstitial Nephritis

Acute	Chronic
<p>Drugs</p> <ul style="list-style-type: none"> Penicillin derivatives Cephalosporins Sulfonamides Co-trimoxazole Rifampin Phenytoin Thiazides Furosemide Allopurinol Cimetidine Amphotericin B Nonsteroidal anti-inflammatory drugs 	<p>Drugs</p> <ul style="list-style-type: none"> Analgesics Lithium
<p>Infections.</p> <ul style="list-style-type: none"> Streptococcal Pyelonephritis Toxoplasmosis Diphtheria Brucellosis Leptospirosis Mononucleosis Cytomegalovirus 	<p>Infections</p> <ul style="list-style-type: none"> Pyelonephritis

TABLE 540-1 -- Causes of Interstitial Nephritis	
Acute	Chronic
<p><i>Disease-Associated</i></p> <ul style="list-style-type: none"> Sarcoidosis Glomerulonephritis Transplant rejection 	<p><i>Disease-Associated</i></p> <ul style="list-style-type: none"> Vesicoureteral reflux Nephrocalcinosis Prolonged hypokalemia Oxalate nephropathy Heavy metals Radiation Obstructive uropathy Medullary cystic disease Sickle cell disease
<i>Idiopathic</i>	

reaction. In sarcoidosis and transplant rejection, cell-mediated mechanisms may have a role.

CLINICAL MANIFESTATIONS.

In hospitalized patients, drugs are the most common cause of acute interstitial nephritis. After a week or so of drug therapy, patients develop fever and at times maculopapular skin rash. Urine output may be normal or diminished. Increased numbers of eosinophils may be detected in the blood or urine or both. Acute renal failure or generalized tubular dysfunction or both may result. Other forms of acute interstitial nephritis present a clinical picture resembling acute glomerulonephritis or acute renal failure, along with manifestations of the initiating disorder. The onset may be preceded by anterior uveitis.

DIAGNOSIS.

The diagnosis is confirmed by renal biopsy, although acute interstitial nephritis may not be suspected before the biopsy. The differential diagnosis includes other causes of acute nephritis or renal failure.

PREVENTION.

The development of drug-related interstitial nephritis may be reduced by using alternative therapeutic agents when possible (substituting nafcillin for methicillin).

TREATMENT AND PROGNOSIS.

After appropriate management of the acute renal failure, withdrawal of possible inciting agents, and treatment of precipitating infection, the acute interstitial nephritis may resolve completely, but residual renal dysfunction is common. In

patients suffering severe histologic injury and renal failure, high-dose corticosteroid therapy may bring dramatic improvement.

CHRONIC INTERSTITIAL NEPHRITIS

PATHOLOGY.

In chronic interstitial nephritis, the inflammatory infiltrate consists of lymphocytes and plasma cells. The edema of the acute form is replaced by interstitial fibrosis. Tubular dilatation and atrophy are widespread. The glomeruli show partial or total sclerosis, presumably as a result of ischemia.

CLINICAL MANIFESTATIONS.

In children, chronic interstitial nephritis usually develops in association with an occult structural abnormality of the kidneys or lower urinary tract (cystic disease, obstruction, reflux). The presenting clinical manifestations may be those of chronic renal failure (nausea, vomiting, pallor, headache, fatigue, hypertension, growth failure) or

Figure 540-1 Biopsy from a patient having acute interstitial nephritis. The tubules are widely separated by edema and an intense inflammatory infiltrate containing lymphocytes, plasma cells, eosinophils, and neutrophils. The glomeruli are preserved ($\times 80$).

manifestations of the underlying disorder (urinary tract infection, flank mass).

DIAGNOSIS.

The diagnosis is suggested by the presence of chronic renal insufficiency in association with a known cause of the disorder; renal biopsy is not usually indicated.

TREATMENT AND PROGNOSIS.

The natural history of chronic interstitial nephritis is progression to end-stage renal failure. Whether elimination of infection or correction of reflux or obstruction will alter this progression is unclear. In adults, avoidance of analgesics (phenacetin) and lithium before the development of end-stage renal failure may result in improvement in renal function.

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Chapter 533 - Pathologic Proteinuria

The second category of proteinuria may result from glomerular or tubular disorders.

533.1 Tubular Proteinuria

Healthy individuals filter large amounts of proteins of lower molecular weight than albumin (lysozyme, light chains of immunoglobulin, beta₂-microglobulin, insulin, growth hormone); these are normally reabsorbed in the proximal tubule. Injury to the proximal tubules results in diminished reabsorptive capacity and the loss of these low molecular weight proteins in the urine; such proteinuria rarely exceeds 1 g/24 hr; it is not associated with edema. Tubular proteinuria (see [Table 532-1](#)) may be seen in acquired and inherited disorders and may be

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associated with other defects of proximal tubular function, such as glucosuria, phosphaturia, bicarbonate wasting, and aminoaciduria. Tubular proteinuria rarely presents a diagnostic dilemma because the underlying disease is usually detected before the proteinuria. Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by electrophoresis of the urine. In tubular proteinuria, the low molecular weight proteins migrate primarily in the alpha and beta regions and little or no albumin is detected, whereas in glomerular proteinuria the major protein is albumin.

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