

# CORE CURRICULUM IN NEPHROLOGY

## Tubulointerstitial Diseases

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### INTRODUCTION

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#### Definitions

Tubulointerstitial nephritis (TIN) may be either acute or chronic:

#### Acute TIN

- Associated with acute renal failure (ARF), which develops over period of days to several weeks due to either acute infection of kidneys or delayed hypersensitivity reaction to medication (reviewed in another section)

#### Chronic interstitial nephritis (CIN)

- Develops over months or years from causes in [Table 1](#)
- Is associated with progressive loss of glomerular filtration rate (GFR) over time and characterized by many syndromes of renal tubular dysfunction
- Primary CIN is associated with chronic renal tubular infection with Epstein-Barr virus
- Secondary CIN is due to renal tubular damage from wide variety of causes ([Table 1](#))

#### Composition of Normal Interstitium

##### Cortical interstitium

- Contains 2 types of cells:
  - Type 1 interstitial cells resemble fibroblasts and produce erythropoietin

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- Type 2 interstitial cells may act as dendritic cells, which are capable of antigen presentation
- Space between interstitial cells contains types 1 and 3 collagen

##### Medullary interstitium

- Contains 3 types of cells:
  - Type 1 cells do not produce erythropoietin, but may produce prostaglandins via cyclo-oxygenase 2 (COX-2)
  - Type 2 cells resemble lymphocytes; function unknown
  - Type 3 cells located near the vasa recti; function unknown
- Extracellular matrix of types 1 and 3 collagen lies between cells

##### Mechanisms of Tubular Interstitial Injury

- Tubulointerstitial response to injury from [Table 1](#) diseases is associated with tubular cell proliferation and tubular dilatation and cast formation followed by atrophy and/or apoptosis and fibrosis

##### Pathology of CIN

- Interstitial infiltration with lymphocytes, monocytes, macrophages; depending on the etiology, neutrophils, eosinophils, or plasma cells accumulate in renal interstitium
- Tubular atrophy, flattened epithelial cells, tubular dilation occur, also tubular basement membrane thickening
- Glomerulosclerosis: loss of glomeruli can occur indirectly from severe tubular damage in nephron segments of glomerulus or due to periglomerular fibrosis and segmental sclerosis eventually leading to global glomerular sclerosis
- Medullary microcysts from hypokalemia
- Cast formation (thyroidization) occurs, particularly in myeloma, but can be seen in idiopathic CIN
- Interstitial fibrosis
- Immunofluorescence microscopy is negative except in Sjögren syndrome, lupus, and myeloma

**Table 1. Secondary Causes of CIN (TIN)**

Category	Causes
Infections	Chronic pyelonephritis VUR
Drugs	Analgesic nephropathy Lithium Nucleoside inhibitors (cidofovir, tenofovir) Calcineurin inhibitors (cyclosporine, tacrolimus) Aristolochic acid (Chinese herbs) Chemotherapy (cisplatin, ifosfamide)
Toxins	Lead nephropathy Heavy metals (cadmium)
Hematologic/neoplastic diseases	Multiple myeloma Lymphoproliferative disorders Light-chain disease Sickle-cell disease
Immune-mediated disease	Sarcoidosis Sjögren syndrome Systemic lupus erythematosus TIN with uveitis TIN with hypocomplementemia
Metabolic disorders	Hypokalemia Hypercalcemia Urate nephropathy
Genetic disorders	Cystinosis Dent disease Primary hyperoxaluria Adenine phosphoribosyl transferase deficiency Primary hyperoxaluria Autosomal dominant hypoparathyroidism Karyomegalic interstitial nephropathy
Miscellaneous	Balkan endemic nephropathy Radiation nephritis Papillary necrosis Inflammatory bowel disease Post acute tubular necrosis

**Clinical Features and Course of CIN**

- Table 2 illustrates diverse abnormalities of renal tubular function
- Compared with chronic glomerulonephritis in CIN:
  - Hypertension is less common

- Daily protein excretion usually <1.5 g
- Urinary sediment is bland with a few white and red blood cells and, rarely, casts
- Anemia disproportionately severe at same GFR due to damage to erythropoietin-producing cells
- Sodium wasting occurs, but usually mild
- Non-anion gap metabolic acidosis results from proximal renal tubular acidosis (RTA) with or without Fanconi syndrome and from types 1 and 4 distal RTA
- Renal papillary necrosis is associated with analgesics or acute pyelonephritis
- Kidney stones are associated with metabolic or inherited disorders
- Nephrogenic diabetes insipidus (NDI) occurs from drugs, metabolic or genetic disorders

**PRIMARY (IDIOPATHIC) CIN****Pathogenesis**

- May be mediated by Epstein-Barr virus

**ADDITIONAL READING**

1. Becker JL, Miller F, Nuovo GJ, Josepovitz C, Schubach WH, Nord EP: Epstein-Barr virus infection of renal proximal tubule cells: Possible role in chronic interstitial nephritis. *J Clin Invest* 104:1673-1681, 1999

**SECONDARY CIN****Chronic Pyelonephritis and Reflux Nephropathy****Overview**

- Chronic pyelonephritis is term used for infection-related CIN without vesicoureteral reflux (VUR)
- Reflux nephropathy with secondary focal glomerulosclerosis associated with VUR accounts for overwhelming majority of cases of CIN associated with bacterial infections of urinary tract

**Pathogenesis of VUR**

- Occurs due to congenital anomalies in vesicoureteral junction leading to incompetent vesicoureteral valves upon bladder contraction

**Table 2. Clinical Features of Chronic Tubulointerstitial Disease**


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<b>Electrolyte/Acid-Base Disorders</b>
Proximal RTA or Fanconi syndrome
Multiple myeloma
Dent disease
Cystinosis
Sjögren syndrome
Distal RTA
Bacterial pyelonephritis
VUR
Lithium
Lead
Myeloma
Light-chain disease
Sjögren disease
Systemic lupus
Hypercalcemia
Hyperkalemic type IV RTA
VUR
Lead
Systemic lupus
Sickle-cell disease
Sodium wasting
Any disorder
<b>Clinical Syndromes</b>
Kidney stones
Hypercalcemia
Hyperoxaluria
Urate nephropathy
Dent disease
Sarcoidosis
Inflammatory bowel disease
Adenosine transferase deficiency
NDI
Lithium
Cisplatin
Hypokalemia
Hypercalcemia
Dent disease
ARF
Pyelonephritis
Analgesics
Lithium
Calcineurin inhibitors
Cisplatin
Nucleoside inhibitors
Myeloma
Lymphoma
Systemic lupus
Hypercalcemia
Uric acid
Radiation
Papillary necrosis
Acute pyelonephritis
Analgesic nephropathy

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- Staged 1 through 5 based on voiding cystourethrogram
- Diagnosed in 20% to 35% of infants and children after first urinary tract infection
- Up to 35% to 45% of asymptomatic siblings have VUR

**Unique pathologic features**

- Chronic inflammation can lead to xanthogranulomatous degeneration
- Reflux nephropathy is characterized by focal and segmental glomerulosclerosis leading to nephrotic-range proteinuria

**Clinical and laboratory features**

- Recurrent urinary tract infections and acute pyelonephritis are common
- Proteinuria can occasionally become nephrotic

**Treatment and outcome**

- Trials of surgical versus medical therapy show surgery reduces new episodes of acute pyelonephritis, but does not influence progressive renal insufficiency or new scar formation

**ADDITIONAL READING**

1. Dillon MJ, Goonasekera CD: Reflux nephropathy. *J Am Soc Nephrol* 9:2377-2383, 1998
2. Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC: Antibiotics and surgery for vesicoureteric reflux: A meta-analysis of randomized controlled trials. *Arch Dis Child* 88:688-694, 2003

**Drugs****Analgesic nephropathy****Epidemiology.**

- Strong association between analgesic nephropathy and long-term analgesic use with analgesic combination medications that contain aspirin, phenacetin, and caffeine
- Association between acetaminophen and the metabolite of phenacetin, either alone or in combination with aspirin and caffeine, is suggestive, but not definitive
- Aspirin alone is associated with acute GFR decreases, particularly in patients on low-sodium diet and elderly patients, but long-term use alone is not associated with analgesic nephropathy

- Long-term nonsteroidal anti-inflammatory drug (NSAID) use has been associated with CIN in smaller number of patients

#### **Pathogenesis.**

- Renal damage from analgesics predominantly affects renal medulla
- Acetaminophen undergoes oxidative metabolism via prostaglandin H synthase pathway, which utilizes glutathione; NSAIDs and aspirin deplete cortex and medulla of glutathione, allowing reactive acetaminophen metabolites to induce lipid peroxides and oxygen-free and hydroxyl radicals, which are toxic to renal tissue proteins
- NSAIDs and aspirin inhibit renal prostaglandin production, which induces medullary vasoconstriction with consequent ischemic injury and papillary necrosis

#### **Clinical and laboratory features.**

- More common in women, typically with a history of chronic pain and analgesic use
- Decreased urinary concentrating ability, acidification defects, papillary necrosis, sterile pyuria, low-grade proteinuria, hypertension, and anemia
- Characteristic findings on noncontrast computed tomography (CT) include papillary calcifications, decreased renal volume, and bumpy renal contours
- Papillary necrosis can be seen on intravenous pyelography
- Increased risk for transitional cell cancers of uroepithelium

#### **Treatment and outcome.**

- No specific treatment, but if drug stopped early, there may be renal function stabilization or even improvement

#### ADDITIONAL READING

1. Elseviers MM, DeSchepper A, Corthouts R, et al: High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure. *Kidney Int* 48:1316-1323, 1995
2. McLaughlin JK, Lipworth L, Chow WH, Blot WJ: Analgesic use and chronic renal failure: A critical review of the epidemiologic literature. *Kidney Int* 54:679-686, 1998
3. Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy: Relationship between nonphenacetin combined analgesics and nephropathy: A review. *Kidney Int* 58:2259-2264, 2000

#### ***Lithium-induced renal diseases***

Lithium is reabsorbed by the renal tubules, similar to sodium at nephron sites where sodium is reabsorbed.

#### **Pathogenesis.**

- NDI primarily is due to inhibition of adenylylate cyclase (ADH)-dependent aspects of water conservation
- Mechanism of CIN unknown

#### **Unique pathologic features.**

- Unique tubular lesion consisting of microcyst formation due to cystic dilation of distal tubules lined with columnar epithelium
- Lithium rarely causes nephrotic syndrome

#### **Clinical features.**

- NDI
  - Polydipsia in 40% and polyuria in up to 20% of patients
- RTA
  - Incomplete distal RTA in up to 50% of patients
- Chronic lithium nephropathy
  - CIN is the most common pathologic finding
  - Episodes of lithium intoxication and lithium-induced NDI may predispose to CIN development

#### **Treatment and outcome.**

- Withdrawal of lithium may be associated with gradual improvement in NDI and GFR
- May progress to end-stage renal failure, particularly if serum creatinine level  $\geq 2.5$  mg/dL ( $\geq 221 \mu\text{mol/L}$ ) at time of diagnosis
- While patients with focal segmental glomerulosclerosis and serum creatinine  $> 2.0$  mg/dL ( $> 177 \mu\text{mol/L}$ ) at diagnosis can progress to end-stage renal failure, patients with minimal change nephropathy experience complete remission upon drug withdrawal
- Amiloride blocks distal tubular reabsorption of lithium and attenuates NDI

#### ADDITIONAL READING

1. Braden GL: Lithium-induced renal disease, in Greenberg A (ed): *Primer on Kidney Diseases* (ed 2), chap 49. San Diego, CA, Academic Press, 1998, pp 332-334
2. Presne C, Fakhouri F, Noel LH, et al: Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney Int* 64:585-592, 2003

### ***Acyclic nucleoside inhibitors***

Cidofovir, adefovir, and tenofovir have been utilized to treat resistant cytomegalovirus infection, hepatitis B, and human immunodeficiency virus, respectively. All 3 drugs are cleared at rates greater than the GFR, indicating significant drug secretion by the proximal tubule.

#### **Pathogenesis.**

- Drugs are transported into proximal tubules by ornithine aminotransferase 1 transporter; cidofovir and adefovir induce proximal tubule cell (PTC) damage by causing mitochondrial damage
- Mechanism of tenofovir toxicity is due to a drug interaction with ritonavir; tenofovir is secreted into urine by multidrug resistance-associated protein 2 transporter, which is inhibited by ritonavir, leading to very high PTC concentrations of tenofovir

#### **Unique pathologic features.**

- Adefovir and cidofovir cause acute tubular necrosis with enlarged proximal tubule mitochondria, which are dysmorphic and have lost their cristae on electron microscopy
- Tenofovir induces PTC necrosis with enlarged dystrophic proximal epithelial cell nuclei

#### **Clinical and laboratory features.**

- Cidofovir
  - Probenecid, which inhibits ornithine aminotransferase 1 transporter, may minimize cidofovir nephrotoxicity
  - Proteinuria occurs in 12%, metabolic acidosis in 16%, and Fanconi syndrome may occur
- Adefovir
  - ARF and Fanconi syndrome occur with doses >60 mg/d
  - Up to 10% of patients have CIN
- Tenofovir
  - Fanconi syndrome and ARF due to acute tubular necrosis occur between 1.5 weeks and 2 years of therapy

#### **Treatment and outcome.**

- Cidofovir should be administered with concomitant oral probenecid
- Patients receiving adefovir should have frequent determinations of renal function

- Patients receiving both tenofovir and ritonavir should have frequent measurements of renal function, electrolytes, and phosphorus
- Incomplete recovery after drug withdrawal may occur from any of these agents

#### **ADDITIONAL READING**

1. Izzedine H, Launay-Vacher V, Isnard-Bagnis C, DeRay G: Drug-induced Fanconi's syndrome. *Am J Kidney Dis* 41:292-309, 2003

### ***Chronic calcineurin inhibitor toxicity***

Acute calcineurin inhibitor toxicity is associated with ARF, which is reversible upon dose reduction or cessation of therapy. Chronic calcineurin inhibitor use is associated with CIN in renal transplant recipients and in patients with autoimmune disorders treated with these drugs.

#### **Pathogenesis.**

- Chronic afferent arteriolar vasoconstriction causes glomerular ischemia and scarring
- Upregulation of renin angiotensin system, transforming growth factor  $\beta$ , and osteopontin stimulate interstitial fibrosis
- CIN occurs in 20% of patients with nonrenal transplants and can lead to end-stage renal disease (ESRD)
- Toxicity is more typically associated with chronic high-dose therapy, but can occur with low-dose therapy

#### **Unique pathologic features.**

- Characteristic findings include striped interstitial fibrosis in cortex and medulla, afferent arteriolar hyalinosis, vacuolization of tubular epithelium, and tubular atrophy
- Associated with glomerular thrombotic microangiopathy

#### **Clinical and laboratory features.**

- Toxicity manifests as insidious development of decrease in GFR and increased blood pressure
- Tubular abnormalities include metabolic acidosis, hyperkalemia, hypercalciuria, hypophosphatemia, hyperuricemia, and hypomagnesemia

#### **Treatment and outcome.**

- Reducing dose or stopping the drug altogether may be beneficial
- Replace calcineurin inhibitors with mycophenolate mofetil or sirolimus
- Angiotensin-converting enzyme (ACE) inhibitors may lessen interstitial fibrosis

- Fish oil, pentoxifylline, and calcium channel blockers have not been shown to slow progressive renal function loss

#### ADDITIONAL READING

1. Burdmann EA, Andoh TF, Yu L, Bennett WM: Cyclosporine nephrotoxicity. *Semin Nephrol* 23:465-476, 2003
2. Schlitt HF, Barkmann A, Boker H, et al: Replacement of calcineurin inhibitors with mycophenolate mofetil in liver transplant patients with renal dysfunction: A randomized controlled study. *Lancet* 357:587-591, 2001
3. Ojo AO, Held PF, Port FK, et al: Chronic renal failure after transplantation of a non-renal organ. *N Engl J Med* 349:931-940, 2003

#### *Aristolochic acid-associated nephropathy*

##### Pathogenesis.

- Substitution of *Aristolochia fangchi* for the Chinese herb *Stephania tetrandia* in pills used for weight reduction exposed patients to high doses of the nephrotoxic and carcinogenic aristolochic acids

##### Unique pathologic features.

- Extensive, hypocellular cortical interstitial fibrosis, and upper tract urothelial tumors in up to 50% of patients with ESRD from this cause

##### Clinical and laboratory features.

- Initial presentation of anemia, tubular proteinuria, and normotension in over half the patients

##### Treatment and outcome.

- Prednisolone therapy in patients with moderate renal insufficiency (serum creatinine, 1.8-3.9 mg/dL [159-345  $\mu$ mol/L]) may slow rate of renal failure progression
- Left untreated, aristolochic acid-associated nephropathy leads to rapid progression to ESRD in most patients

#### ADDITIONAL READING

1. Vanherweghem JL, Abramowicz D, Tielemans C, Depierreux M: Effects of steroids on the progression of renal failure in chronic interstitial renal fibrosis: A pilot study in Chinese herbs nephropathy. *Am J Kidney Dis* 27:209-215, 1996
2. Reginster F, Jadoul M, van Ypersele de Strihou C: Chinese herbs nephropathy presentation, natural history and fate after transplantation. *Nephrol Dial Transplant* 12:81-86, 1997

#### *Ifosfamide nephrotoxicity*

##### Pathogenesis.

- May be related to the ifosfamide metabolites chloroacetaldehyde or acrolein, which

have been shown to cause glutathione depletion and lipid peroxidation

##### Clinical and laboratory features.

- Associated with total ifosfamide dose, age, prior or concurrent treatment with cisplatin, and unilateral nephrectomy
- Proximal tubular dysfunction leads to metabolic acidosis, hypophosphatemia, aminoaciduria, and hypokalemia; severe renal failure also has been reported

##### Treatment and outcome.

- Nephrotoxicity may be mild, acute, and reversible or chronic and lead to long-term metabolic abnormalities and/or renal failure

#### ADDITIONAL READING

1. Skinner R, Cotterill SJ, Stevens MC: Risk factors for nephrotoxicity after ifosfamide treatment in children: A UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer* 82:1636-1645, 2000

#### Toxins

##### *Lead nephropathy*

##### Pathogenesis.

- Early accumulation of filtered lead, particularly by S<sub>3</sub> segment of proximal tubule, likely leads to direct tubulotoxic effects and subsequent interstitial fibrosis; subsequent hypertension and hyperuricemia also may contribute to further renal compromise

##### Unique pathologic findings.

- Acid-fast intranuclear inclusions of PTCs are characteristic of acute lead intoxication; in chronic nephropathy, focal tubular atrophy, interstitial fibrosis, and minimal cellular infiltrates predominate

##### Clinical and laboratory features.

- Decreased urate excretion, proximal tubular dysfunction, and hyporeninemic hypoaldosteronism are early renal manifestations of lead intoxication; late findings of progressive renal failure, hypertension, and recurrent episodes of gout (saturnine) are typical
- Diagnosis of lead nephropathy dependent on recognition of patients with an appropriate lead exposure history, chronic renal failure, hypertension, and gout (saturnine)
- Because >90% of total body lead resides in bone, serum lead levels generally are unhelpful in diagnosis of chronic lead exposure

- Ethylenediaminetetraacetic acid (EDTA) mobilization test with resultant urinary lead excretion (in patients with renal insufficiency, a 72-hour collection is necessary) greater than  $>600 \mu\text{g}$  is diagnostic of elevated total body lead burden

#### **Treatment and outcome.**

- Chelation therapy with EDTA leads to reversal of early tubular dysfunction, improves GFR in patients with mild to moderate renal failure, and decreases frequency of gouty flares; however, EDTA chelation is ineffective in reversing advanced renal failure secondary to lead nephropathy

#### ADDITIONAL READING

1. Lin JL, Lin-Tan DT, Hsu KH, Yu CC: Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. *N Engl J Med* 348:277-286, 2003
2. Brewster UC, Perazella MM: A review of chronic lead intoxication: An unrecognized cause of chronic kidney disease. *Am J Med Sci* 327:341-347, 2004

### ***Cadmium***

#### **Pathogenesis.**

- Renal toxicity is associated with prolonged low-level exposure, principally from contaminated food, cigarettes, and workplace exposure
- Cadmium is taken up by PTCs via pinocytosis; inside cell, complex is degraded by lysozymes and free cadmium causes cellular toxicity

#### **Clinical and laboratory features.**

- Risk for injury increases with age
- Irreversible proximal tubular dysfunction, hypercalciuria, and nephrolithiasis
- May be associated with bone disease, lung injury, and cancer

#### **Treatment and outcome.**

- Minimize exposure
- No role for chelating agents

#### ADDITIONAL READING

1. Hellstrom L, Elinder CG, Dahlberg B, et al: Cadmium exposure and end-stage disease. *Am J Kidney Dis* 38:1001-1008, 2001

### **Hematologic Neoplastic Diseases**

#### ***Multiple myeloma***

#### **Pathogenesis.**

- Renal dysfunction occurs in  $>50\%$  of patients

- Acute and chronic myeloma kidney results from light-chain toxicity; light chains are nephrotoxic due to either direct tubular toxicity or intrarenal obstruction from cast formation
- Multiple factors predispose patients with multiple myeloma to renal disease:
  - Volume depletion
  - Hypercalcemia
  - Hyperuricemia
  - Contrast media
  - Other nephrotoxins
- Characteristics thought to increase light-chain toxicity include:
  - Light-chain concentration and isoelectric point
  - Acidic intraluminal pH
  - Tubular flow rate
  - Presence of intact Tamm-Horsfall protein
  - Tubular concentration of calcium and sodium
- Acute myeloma kidney is ARF due to intratubular myeloma light-chain deposition as tubular casts; a more chronic process of tubular obstruction occurs over months and years in chronic myeloma kidney

#### **Unique pathologic features.**

- Tubular casts surrounded by multinucleated giant cells, interstitial infiltrates of plasma cells, and mononuclear cells; chronic myeloma kidney refers to aforementioned abnormalities, plus interstitial fibrosis and tubular atrophy
- Renal amyloidosis occurs in some patients with light-chain deposition in glomeruli leading to nephrotic-range proteinuria; characteristic fibrillary changes seen on electron microscopy and Congo red staining

#### **Clinical and laboratory features.**

- Monoclonal light chains in serum and urine are found as M spikes on protein electrophoresis or as  $\kappa$  or  $\lambda$  light chains on immunofixation studies
- Urinalysis shows a bland sediment, normal kidney size, and Fanconi syndrome, or low anion gap due to cationic immunoglobulin G (IgG) or IgM paraproteins, anemia, and hypercalcemia

#### **Treatment and outcome.**

- Volume repletion, correction of hypercalcemia/hyperuricemia, discontinuation of neph-

rotoxic medications, appropriate chemotherapy, and dialysis as needed

#### ADDITIONAL READING

1. Winearls CG: Acute myeloma kidney. *Kidney Int* 48:1347-1361, 1995
2. Pozzi C, D'Amico M, Fogazzi GB, et al: Light chain deposition disease with renal involvement: Clinical characteristics and prognostic factors. *Am J Kidney Dis* 42:1154-1163, 2003

### *Lymphoproliferative disorders*

Lymphomatous or leukemic cell infiltration of the kidneys is commonplace in non-Hodgkin lymphoma and lymphocytic leukemias. However, clinically identifiable renal disease is relatively rare.

#### Pathogenesis.

- ARF may develop as a result of rapid increases in interstitial pressure from cell infiltration; chronically, tubular atrophy and necrosis predominate

#### Unique pathologic features.

- Diffuse lymphocytic infiltration of the interstitium with dense monomorphic lymphoid cells with preserved glomerular architecture occurs

#### Clinical and laboratory features.

- ARF is associated with non-nephrotic-range proteinuria and bilateral enlarged, nodular kidneys noted on imaging

#### Treatment and outcomes.

- Treatment with systemic chemotherapy and/or radiation therapy leads to rapid renal function improvement and decrease in kidney size; prognosis dependent on response of malignancy to treatment

#### ADDITIONAL READING

1. Tornroth T, Heiro M, Marcussen N, Franssila K: Lymphomas diagnosed by percutaneous renal biopsy. *Am J Kidney Dis* 42:960-971, 2003

### **Immune Disorders**

#### *Sarcoidosis*

#### Pathogenesis.

- Increased production of 1- $\alpha$  hydroxylase from activated mononuclear cells leads to increased 1,25-dihydroxyvitamin D<sub>3</sub> levels and enhanced intestinal calcium absorption
- Tissue infiltration with activated CD4-T-lymphocytes of the T-helper 1 type produce

interleukin 2, interferon  $\gamma$ , and other cytokines

#### Unique pathologic features.

- Although noncaseating granulomatous interstitial nephritis is classic lesion in sarcoidosis, it is uncommon finding
- Renal lesions include mesangiocapillary and mesangial proliferative glomerulonephritis, IgA nephropathy, membranous glomerulonephritis, and crescentic glomerulonephritis

#### Clinical and laboratory features.

- Hypercalcemia occurs in up to 20% of cases of sarcoidosis, particularly in summer
- Calcium oxalate nephrolithiasis occurs in up to 14% of patients with sarcoidosis

#### Treatment and outcomes.

- Corticosteroid therapy inhibits macrophage activity and suppresses calcitriol synthesis
- Nephrocalcinosis may be responsible for CIN in up to 50% of patients
- Corticosteroid treatment for up to 6 months leads to improved renal function
- Incomplete renal recovery often occurs due to irreversible nephrosclerosis

#### ADDITIONAL READING

1. Gobel U, Kettritz R, Schneider W, Luft FC: The protean face of renal sarcoidosis. *J Am Soc Nephrol* 12:616-623, 2001

### *Primary Sjögren syndrome*

Sjögren syndrome is a disease with lymphocytic infiltration of the epithelial ducts of salivary and lacrimal glands. It accompanies B-cell hyperactivity with antinuclear antibodies and circulation immune complexes.

#### Pathogenesis.

- Unknown

#### Unique pathologic features.

- Most patients have CIN with predominance of T lymphocytes and, to a lesser degree, B cells, monocytes, and plasma cells
- Nephrotic syndrome can occur, with most common glomerular lesion being membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, and, rarely, membranous nephropathy

#### Clinical and laboratory features.

- Distal RTA is most common RTA and occurs in up to 5%
- NDI occurs in up to 13%

- Renal potassium wasting with severe hypokalemia

#### **Treatment and outcome.**

- CIN can improve with corticosteroids if started early; RTA rarely responds to corticosteroid therapy
- CIN occurs early within first 2 to 4 years
- Glomerulonephritis develops in patients after 8 to 10 years; value of immunosuppressive therapy for glomerular lesions is uncertain

#### ADDITIONAL READING

1. Bossini N, Savoldi S, Franceschini F, et al: Clinical and morphological features of kidney involvement in primary Sjogren's syndrome. *Nephrol Dial Transplant* 16:2328-2336, 2001

#### ***TIN with uveitis***

This disorder presents in adolescence and young adults, particularly females, often as ARF. The uveitis can develop prior to, concurrently, or after the TIN.

#### **Pathogenesis.**

- Peripheral blood shows increased numbers of B cells without abnormalities in T cells
- Associated with Epstein-Barr virus, antineutrophil cytoplasmic antibody, and chlamydia

#### **Unique pathologic features.**

- Renal tissue has a predominance of CD4 T lymphocytes, CD8 T lymphocytes, and monocytes and macrophages

#### **Clinical and laboratory features.**

- Often presents with signs of fever, anemia, and asthenia
- Uveitis of anterior chamber is most common
- Blood testing includes peripheral eosinophilia, anemia, and elevated erythrocyte sedimentation rate; serologic testing for systemic immunologic disease, such as sarcoidosis, Sjögren syndrome, Wegener granulomatosis, Behçet disease, as well as infectious diseases, are negative
- May be associated with Fanconi syndrome, distal RTA, and NDI
- In adolescents and young adults, renal disease spontaneously remits over 1 year without corticosteroid therapy

#### **Treatment and outcome.**

- In adults, corticosteroid therapy associated with improved renal function

- Uveitis often requires systemic corticosteroids and often has relapsing course

#### ADDITIONAL READING

1. Takemura T, Okada M, Hino S, et al: Course and outcome of tubulointerstitial nephritis and uveitis syndrome. *Am J Kidney Dis* 34:1016-1021, 1999

#### **Metabolic Disorders**

#### ***Hypokalemic nephropathy***

Hypokalemia can be associated with functional renal disturbances, particularly NDI, as well as renal cyst formation and irreversible CIN.

#### **Pathogenesis.**

- Major cause of NDI is tubular resistance to ADH due to impaired generation of cyclic adenosine monophosphate from adenylate cyclase, impaired ADH- and cyclic adenosine monophosphate-mediated water flow, and downregulation of aquaporin-2 water channels in cortex and medulla
- Increased ammoniagenesis from potassium depletion may induce renal tubular injury by interstitial complement activity
- Hypokalemia can stimulate insulin-like growth factor 1 and transforming growth factor  $\beta$ , leading to chemotaxis of inflammatory cells and fibrosis

#### **Unique pathologic features.**

- Any disorder producing chronic hypokalemia may be associated with proximal tubular lesion, interstitial fibrosis, tubular atrophy, and medullary cysts

#### **Clinical and laboratory features.**

- NDI occurs with serum potassium  $<3.0$  mEq/L (mmol/L)

#### **Treatment and outcome.**

- Morphological changes of chronic hypokalemia are reversible within first few months of potassium repletion, but irreversible CIN can occur
- Renal cysts can decrease after resection of adrenal adenoma or potassium therapy in primary hyperaldosteronism

#### ADDITIONAL READING

1. Torres VE, Young WF Jr, Offord KP, Hattery RR: Association of hypokalemia, aldosteronism and renal cysts. *N Engl J Med* 322:345-351, 1990

***Hypercalcemic nephropathy***

Hypercalcemia is associated with NDI, RTA, kidney stones, ARF, and CIN.

**Pathogenesis.**

- NDI is due to decreased medullary solute gradient and predominantly due to impaired hydro-osmotic effect of ADH

**Unique pathologic features.**

- Chronic hypercalcemia leads to interstitial calcification, tubular cell necrosis, tubular atrophy, and interstitial fibrosis, predominantly in the medulla
- Nephrocalcinosis often is present on plain film, but CT is more sensitive

**Clinical and laboratory features.**

- NDI occurs in up to 20% of patients with chronic hypercalcemia
- Large increases in serum calcium >12 mg/dL (>2.99 mmol/L) can cause ARF due to renal arterial vasoconstriction and volume contraction from natriuresis
- CIN is associated with polyuria, salt wasting, calcium oxalate stones, and distal RTA
- Most patients with CIN have chronic hypercalcemia

**Treatment and outcome.**

- Early correction of hypercalcemia may lead to recovery of renal function or slower progression of CIN

## ADDITIONAL READING

1. Braden GL, Singer I, Cox M: Nephrogenic diabetes insipidus, in Gonick HC, Buckalew VM (eds): *Renal Tubular Disorders*. New York, NY, Marcel Dekker, 1985, pp 431-494

***Urate nephropathy*****Pathogenesis.**

- Acute urate nephropathy is typically seen in setting of tumor lysis syndrome
- Although chronic toxicity from uric acid is controversial, mechanism is thought to involve deposition of urate crystals in medullary interstitium with consequent secondary chronic inflammatory response, leading to interstitial fibrosis

**Unique pathologic features.**

- Birefringent uric acid crystal deposition in tubules and interstitium
- Occasionally, medullary renal tophi are found on gross anatomic dissection

**Clinical and laboratory features.**

- Acute urate nephropathy presents with abrupt oliguria or anuria, and an elevated uric acid (typically >15 mg/dL [ $>892 \mu\text{mol/L}$ ]) and a urinary uric acid to creatinine ratio >1
- Chronic urate nephropathy presents with hypertension, mild renal dysfunction, mild proteinuria, decreased urinary concentrating ability, and bland urine sediment

**Treatment and outcome.**

- Allopurinol is used to lower serum uric acid to prevent acute urate nephropathy, but its efficacy in slowing progressive chronic urate nephropathy is unproven

## ADDITIONAL READING

1. Johnson RJ, Kivlighn SD, Kim YG, Suga S, Fogo AB: Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *Am J Kidney Dis* 33:225-234, 1999

2. Nicleleit V, Mihatsch MJ: Uric acid nephropathy and end-stage renal disease—review of a non-disease. *Nephrol Dial Transplant* 12:1832-1838, 1997

***Cystinosis*****Pathogenesis.**

- Autosomal recessive disorder, 1 per 100,000-200,000
- Caused by mutation of the *CTNS* gene on chromosome 17p13, which encodes protein cystinosin
- Abnormal cystinosin impairs cystine transport from lysosomes

**Unique pathologic features.**

- Hexagonal birefringent cystine crystals on polarized microscopy are present in urine, cornea, liver, spleen, lymph nodes, kidneys, thyroid, intestines, brain, and bone marrow
- Renal tubules have swan-neck deformity in proximal renal tubule and later develop CIN

**Clinical and laboratory features.**

- Diagnosis is made by measuring cystine content in peripheral blood leukocytes
- Fanconi syndrome develops between 6-12 months of age and is associated with hypophosphatemic rickets and polyuria due to obligate solute excretion

**Treatment and outcome.**

- Cysteamine binds to cystine in lysosomes and transports it through a lysine trans-

porter; 4 oral doses per day are given along with eye drops to prevent corneal blindness

- Renal transplantation is therapy of choice, but extrarenal manifestations of cystinosis require continued cysteamine therapy

#### ADDITIONAL READING

1. Gahl WA, Thoene JG, Schneider JA: Cystinosis. *N Engl J Med* 347:111-121, 2002

#### *Dent disease*

X-Linked recessive disorder of the proximal tubule characterized by Fanconi syndrome, kidney stones, nephrocalcinosis, rickets, and progressive renal insufficiency.

#### Pathogenesis.

- Originally named X-linked recessive nephrolithiasis
- Caused by mutations in *CLC5* channel protein gene at X<sub>p</sub>11.22
- Female carriers rarely develop manifestations of the disease
- Proximal tubular endosomal function is inhibited, leading to Fanconi syndrome

#### Unique pathologic features.

- Nephrocalcinosis occurs at young age in 75% of patients

#### Clinical and laboratory features.

- Diagnosis can be made by gene testing for defect on chromosome X<sub>p</sub>11.22
- Increased excretion of  $\beta_2$  microglobulin and retinal 2-binding protein in carriers and patients
- Hypophosphatemic rickets occurs in 25% of males
- Hypercalciuria occurs at early age with kidney stones and nephrocalcinosis
- CIN with nephrocalcinosis occurs in two thirds of affected males, leading to end-stage renal failure between ages 30-40 years

#### Treatment and outcome.

- Hypercalciuria can improve with low-sodium diet and thiazide diuretics
- Oral phosphate and carefully dosed vitamin D can improve bone disease
- Renal transplantation is definitive therapy

#### ADDITIONAL READING

1. Scheinman SJ: X-Linked hypercalciuric nephrolithiasis: Clinical syndromes and chloride channel mutations. *Kidney Int* 53:3-17, 1998

2. Hoopes RR, Hueber PA, Reid RJ, et al: *CLCN5* chloride-channel mutations in six new North American families with X-linked nephrolithiasis. *Kidney Int* 54:698-705, 1998

#### *Primary hyperoxaluria*

#### Pathogenesis.

- 2 forms: primary hyperoxaluria types 1 and 2 (PH1 and PH2)
- PH1 is more common and due to deficiency of the hepatic peroxisomal enzyme alanine glyoxylate aminotransferase (AGT), which leads to increased urinary oxalate and glyoxalate; mutations of the AGT genes on chromosome 2 Q36-37 lead to decreased function of AGT
- PH2 is due to deficiency of the liver cytosolic enzyme hydroxypyruvate reductase, which leads to increased urinary oxalate and glycerate excretion
- PH1 can be associated with severe calcium oxalate deposition in kidney interstitium with nephrocalcinosis and, once GFR <25 mL/min (<0.42 mL/s), there is diffuse systemic oxalate deposition

#### Unique pathologic features.

- Early medullary nephrocalcinosis progressing to diffuse nephrocalcinosis
- Extensive calcium oxalate deposition on tissue biopsy

#### Clinical and laboratory features.

- Nephrolithiasis usually occurs before age of 5 years, but adults can present with either stones or progressive renal insufficiency from nephrocalcinosis
- Once GFR <25 mL/min (<0.42 mL/s), cardiac conduction defects, distal gangrene, arthropathy, and retinal macular disease develop
- PH1 diagnosed by increased urinary oxalate and glyoxalate and by demonstration on liver biopsies of decreased AGT activity
- PH2 diagnosed by increased urinary oxalate and glycerate and decreased hydroxypyruvate reductase on liver biopsy

#### Treatment and outcome.

- General measures to decrease urinary supersaturation include increased fluid intake, pyridoxine (3-7 mg/kg/d), orthophosphate (30-40 mg/kd/d), and citrate (3-4 mEq/d) and magnesium (400-1600 mg/d)

- High-dose orthophosphate and pyridoxine have been shown to preserve renal function and decrease nephrolithiasis
- Combined liver and renal transplants are required once GFR <20 mL/min (<0.33 mL/s) to decrease systemic oxalate and renal oxalate deposition
- Orthophosphate, citrate, and magnesium needed in posttransplantation period to lessen systemic and renal oxalosis

#### ADDITIONAL READING

1. Milliner DS, Wilson DM, Smith LH: Phenotypic expression of primary hyperoxaluria: Comparative features of types I and II. *Kidney Int* 59:31-36, 2001
2. Millan MT, Berquist WE, So SK, et al: One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria: A single-center experience. *Transplantation* 78:1458-1463, 2003

#### *Balkan endemic nephropathy*

##### **Pathogenesis.**

- Although no specific causative agent has been identified, most data support environmental factors as leading cause of Balkan nephropathy

##### **Unique pathologic features.**

- No characteristic renal pathology has been identified

##### **Clinical and laboratory features.**

- Slowly progressive TIN
- Normotension predominates and anemia out of proportion to renal failure is commonplace
- Urothelial tumors occur up to 100 times more frequently in endemic areas and can be bilateral in up to 14% of affected patients

##### **Treatment and outcome.**

- Specific therapy is lacking
- Balkan endemic nephropathy accounts for up to 10% of all causes of ESRD in some Balkan regions

#### ADDITIONAL READING

1. Stefanovic V, Polenakovic MH: Balkan nephropathy. Kidney disease beyond the Balkans? *Am J Nephrol* 11:1-11, 1991
2. Petronic VJ, Bukurov NS, Djokic MR, et al: Balkan endemic nephropathy and papillary transitional cell tumors of the renal pelvis and ureters. *Kidney Int Suppl* 34:S77-S79, 1991

#### **Radiation Nephritis**

##### *Pathogenesis*

- In patients receiving >1,500-2,500 rads to kidney, there is endothelial cell injury and swelling, with eventual vascular occlusion and chronic ischemic injury
- Direct tubular epithelial cell injury occurs from the radiation
- Certain chemotherapy also may potentiate effects of radiation on kidney

##### *Unique pathologic features*

- Glomerular capillary endothelial injury with swelling and basement membrane splitting and occasionally thrombotic microangiopathy, especially in children

##### *Clinical and laboratory features*

- Acute radiation nephritis occurs 6-12 months after exposure, characterized by progressive renal insufficiency accompanied by proteinuria, accelerated renin-dependent hypertension, edema, and occasional intravascular hemolysis
- Onset of chronic radiation nephritis occurs more than 18 months after exposure and is characterized by proteinuria, progressive renal insufficiency, and hypertension
- Chronic radiation damage may present years later with significant proteinuria with preserved renal function or with just hypertension and mild proteinuria

##### *Treatment and outcome*

- Prevention is only specific measure, usually with kidney shielding and/or a fractionated radiation dose
- Aggressive treatment of hypertension and the use of ACE inhibition also may be helpful

#### ADDITIONAL READING

1. Cassady JR: Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys* 31:1249-1256, 1995

#### **Papillary Necrosis**

##### *Pathogenesis*

- Conditions that compromise papillary blood flow, either structurally or hormonally, can result in ischemic necrosis (eg, diabetes

mellitus, NSAIDs, urinary tract obstruction, and sickle cell disease)

- Nephrotoxic agents, such as analgesics, can be heavily concentrated in papilla, increasing their toxicity
- More than 1 clinical condition predisposing to papillary necrosis is present

#### *Unique pathologic features*

- Coagulative necrosis in inner medulla and papilla is characteristic
- Overlying cortical changes of CIN can coexist with papillary necrosis

#### *Clinical and laboratory features*

- Proteinuria and sterile pyuria are common; gross or microscopic hematuria can be seen, particularly with sloughing of papillae
- Polyuria and nocturia are early findings
- Sloughed papillae can cause ureteral colic or serve as a nidus for infection
- Diagnosis can be made by finding sloughed tissue in urine or radiographically with intravenous pyelography or retrograde studies; ultrasound and CT are less sensitive

#### *Treatment and outcome*

- Course can be variable, ranging from asymptomatic disease to recurrent episodes of urinary tract infection, renal colic, and progressive renal insufficiency
- Although no specific treatment exists, underlying condition or risk factor should be addressed; blood pressure control and ACE inhibition may be helpful

#### ADDITIONAL READING

1. Griffin MD, Bergstralhn EJ, Larson TS: Renal papillary necrosis—A sixteen-year clinical experience. *J Am Soc Nephrol* 6:248-256, 1995

#### **Inflammatory Bowel Disease**

Acute and chronic interstitial nephritis may occur in inflammatory bowel disease.

#### *Pathogenesis*

- Acute interstitial nephritis is associated with aminosalicyclic acid (ASA) therapy
- Enteric hyperoxaluria is possible cause of CIN, but rarely described
- CIN can occur in Crohn disease without prior exposure to salicylates
- ASA-induced CIN occurs at expected frequency of 1/500 patients

#### *Unique pathologic features*

- CIN without hypokalemic changes or calcium oxalate deposition

#### *Clinical and laboratory features*

- Most patients with CIN have recurrent episodes of ARF associated with volume depletion and prerenal azotemia and occasionally acute interstitial nephritis or acute tubular necrosis
- Proteinuria usually <2.0 g/mg and urinalyses are bland without casts

#### *Treatment and outcome*

- CIN from ASA may stabilize and improve upon ASA withdrawal
- Most cases with CIN are unrelated to ASA and progress to end-stage renal failure requiring dialysis and transplantation
- Variety of forms of glomerulonephritis, particularly membranoproliferative glomerulonephritis and amyloid, may occur in inflammatory bowel disease

#### ADDITIONAL READING

1. De Broe ME, Stolar JC, Nouwen EJ, Elseviers MM: 5-Aminosalicyclic acid (5-ASA) and chronic tubulointerstitial nephritis in patients with chronic inflammatory bowel disease: Is there a link? *Nephrol Dial Transplant* 12:1839-1841, 1997
2. Pardi DS, Tremaine WJ, Sandborn WJ, McCarthy JT: Renal and urologic complications of inflammatory bowel disease. *Am J Gastroenterol* 93:504-514, 1998