«Νεφρολογία»
Κατ΄επιλογήν Μάθημα
Ιατρική Σχολή ΕΚΠΑ

Διαμεσοσωληναριακές νεφρικές παθήσεις

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«Nephrology»
Medical School University of Athens
Tubulointerstitial renal diseases

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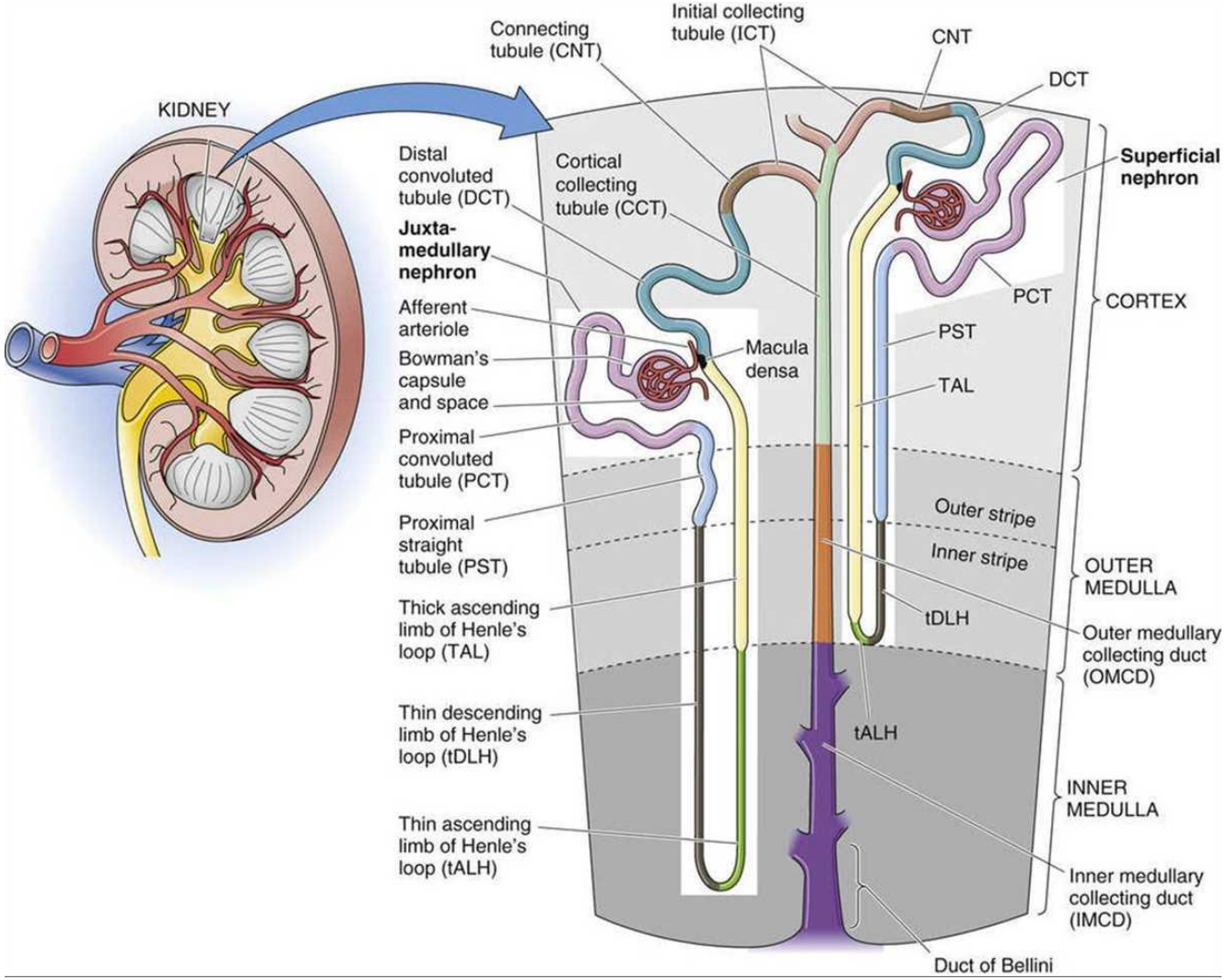
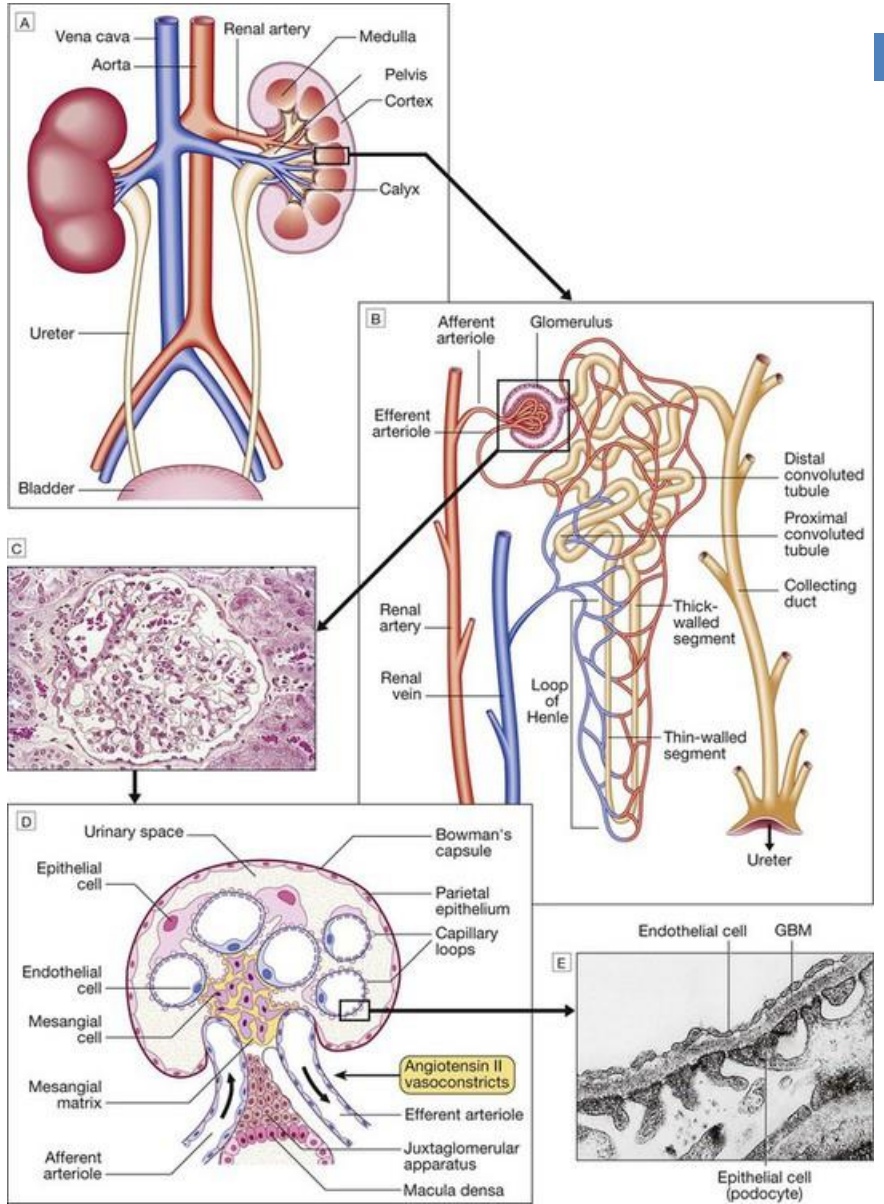
Tuesday 8 April 2025

1. Anatomy and physiology interstitial tissue and renal tubules
2. Acute Interstitial Nephritis
3. Chronic Interstitial Nephritis

Anatomy of the nephron



The renal glomerulus



- The glomerulus is the main filtering unit of the kidney.
- The blood supply to the glomerulus is provided via the afferent arteriole. The blood then flows through the capillary network, where it gets filtered, and then leaves the glomerulus via the efferent arteriole.
- The ultrafiltrate is collected in the Bowman's space and drains directly into the proximal tubule of the nephron.
- The glomerulus is composed mainly of three cell types:
  - Endothelial cells
  - Mesangial cells
  - Epithelial cells (parietal cells, podocytes)

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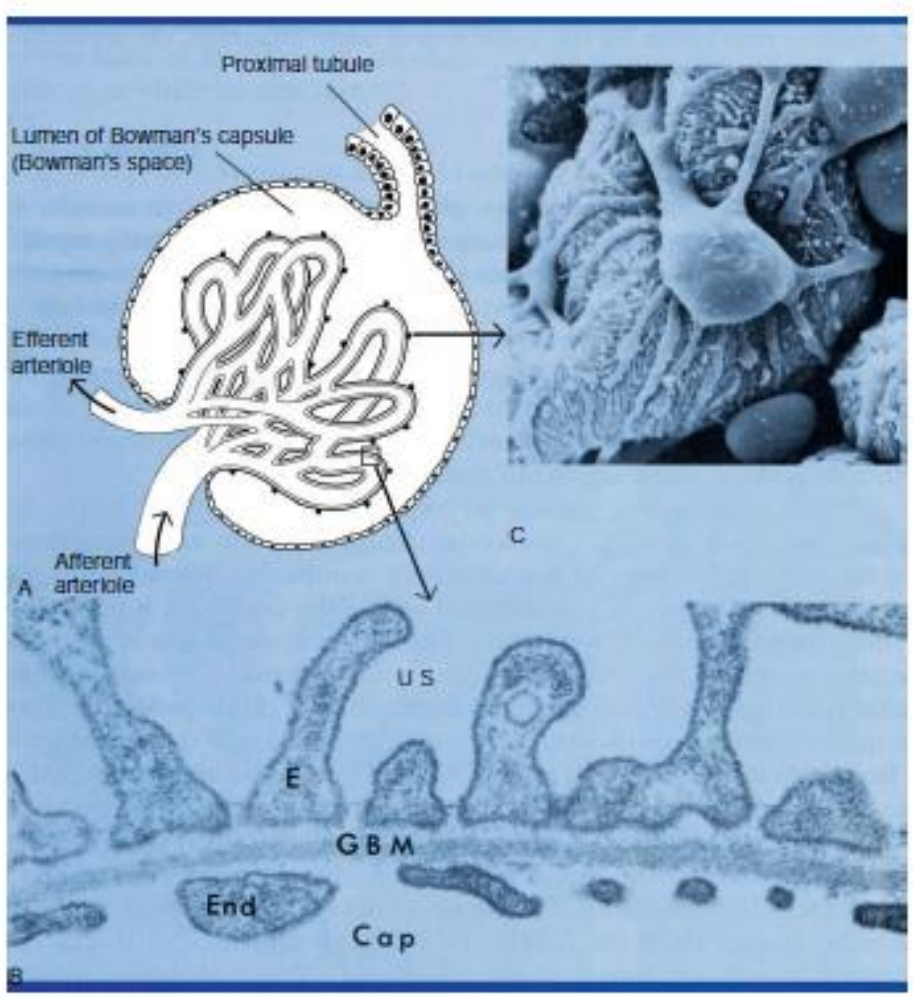
The renal glomerulus



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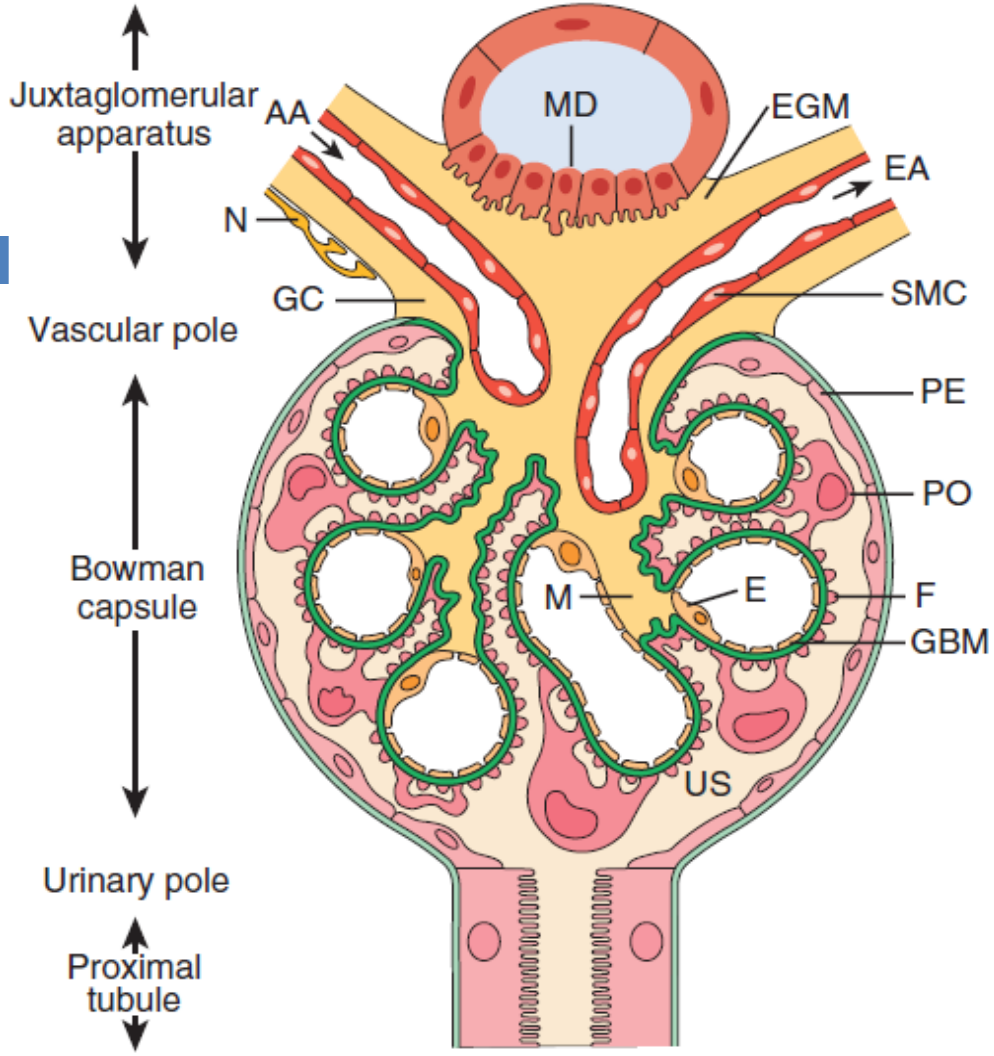
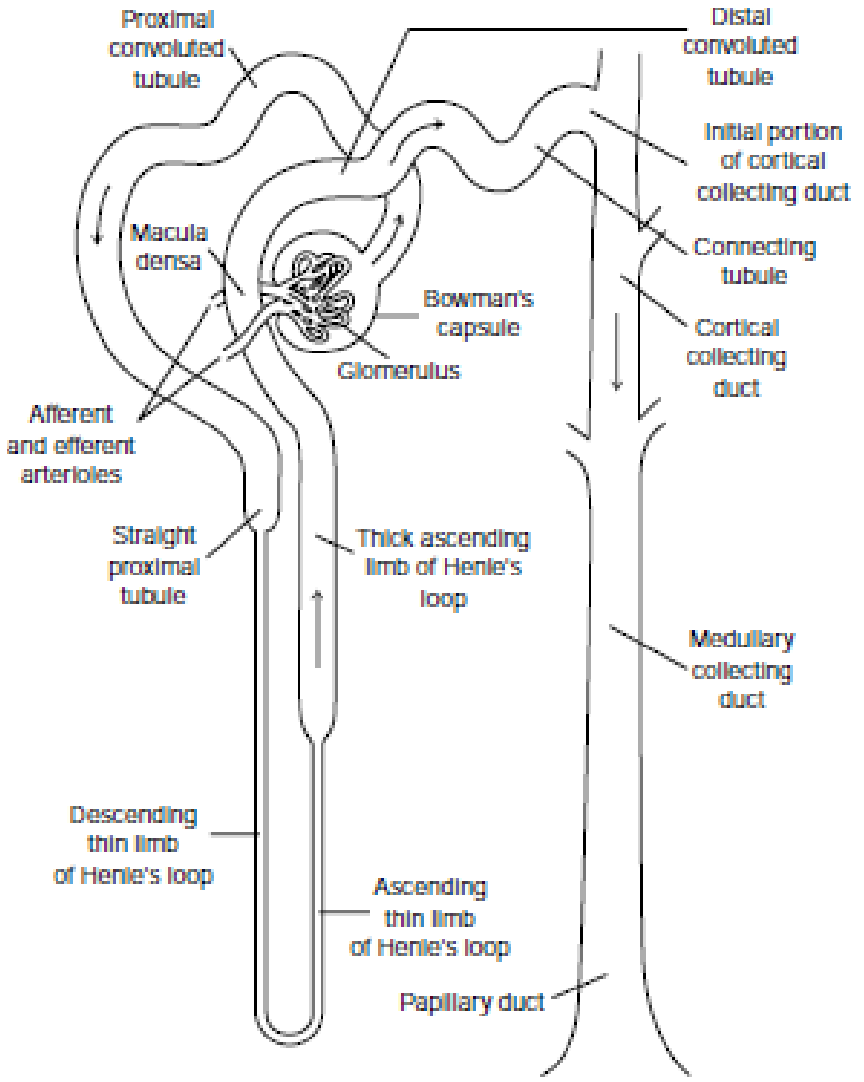


AA	Afferent arteriole
MD	Macula densa
EGM	Extraglomerular mesangium
EA	Efferent arteriole
N	Sympathetic nerve terminals
GC	Granular cells
SMC	Vascular smooth muscle cells
PE	Parietal epithelium
PO	Podocyte
M	Mesangium
E	Endothelium
F	Foot process
GBM	Glomerular basement membrane
US	Urinary space

Renal Tubules

- Proximal tubule
- Thin limb of Henle
- Thick ascending limb of Henle
- Distal tubule
- Connecting tubule
- Collecting duct



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Renal Tubules

- Renal tubules are outlined by a single-layer epithelium anchored to a basement membrane.
- Transporting epithelium consisting of flat or cuboid epithelial cells
- Transport across the epithelium
  - Transcellular pathway
  - Paracellular pathway

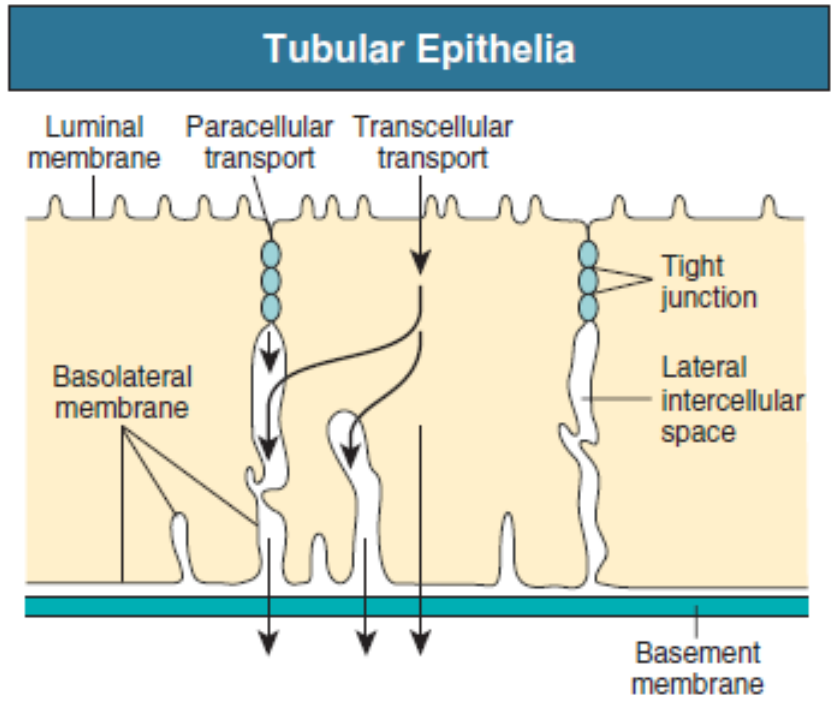
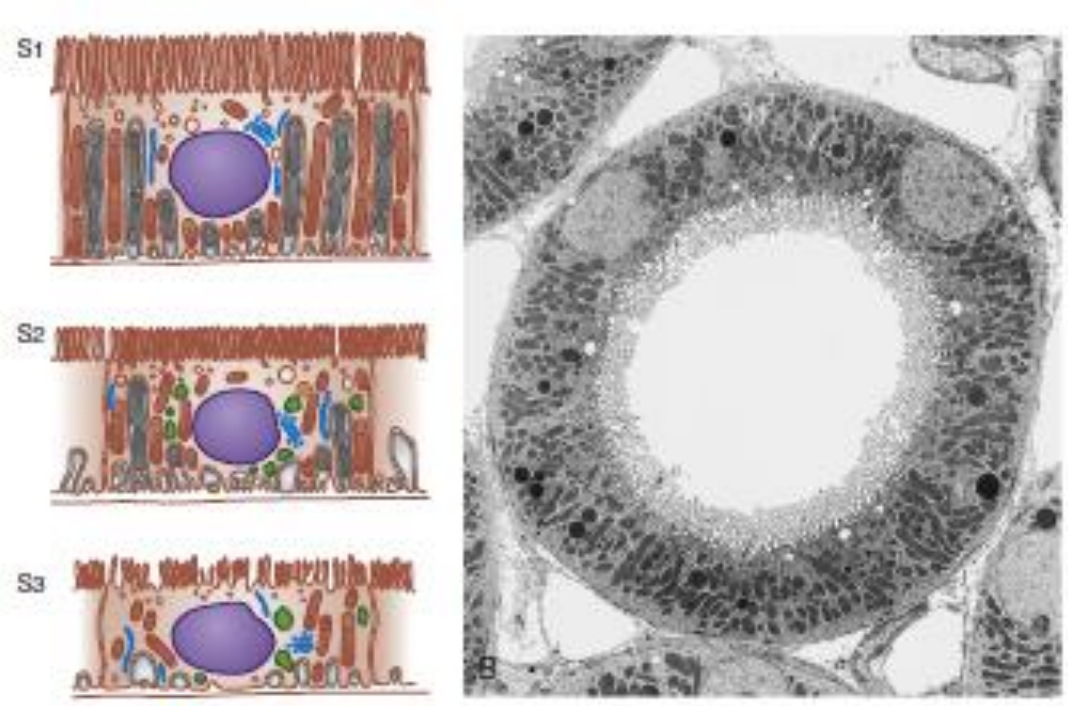


Figure 1-10 Tubular epithelia. Transport across the epithelium may follow two routes: transcellular, across luminal and basolateral membranes, and paracellular, through the tight junction and intercellular spaces.

The proximal convoluted tubule



The proximal tubule has been divided in two portions:
the proximal convoluted portion (pars convoluta)
and the straight portion (pars recta)
Another classification has divided proximal tubules in three portions:
S1, S2 and S3.
In the first portion the cells have abundant, acidophilic cytoplasm and have a very well developed brush border, with densely grouped microvilli. It contains numerous large and elongated mitochondries.

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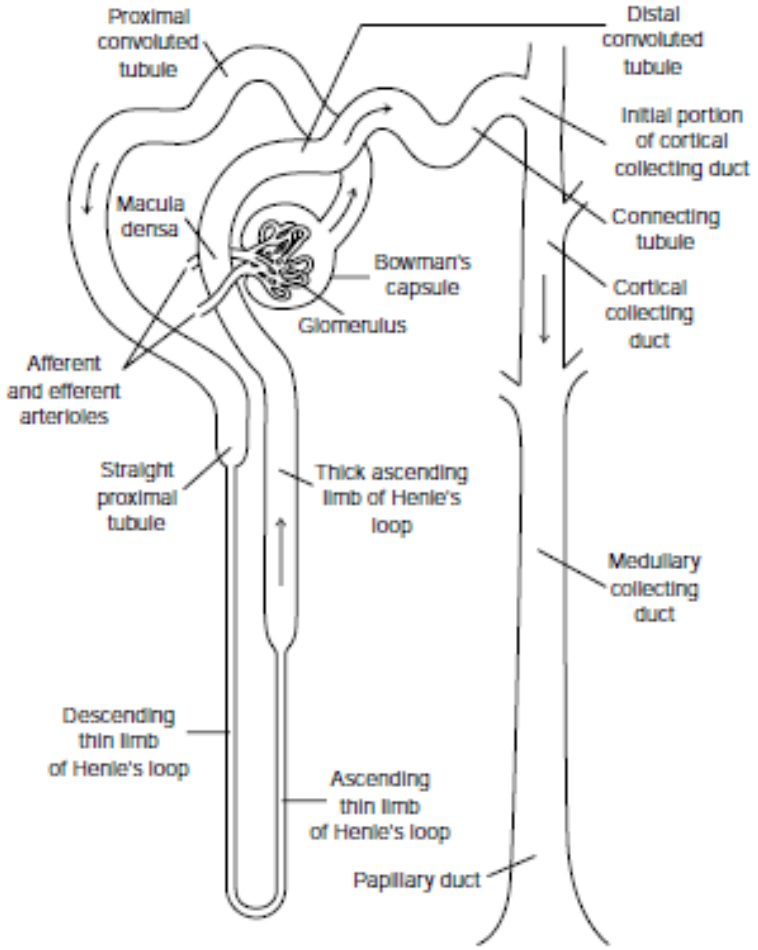
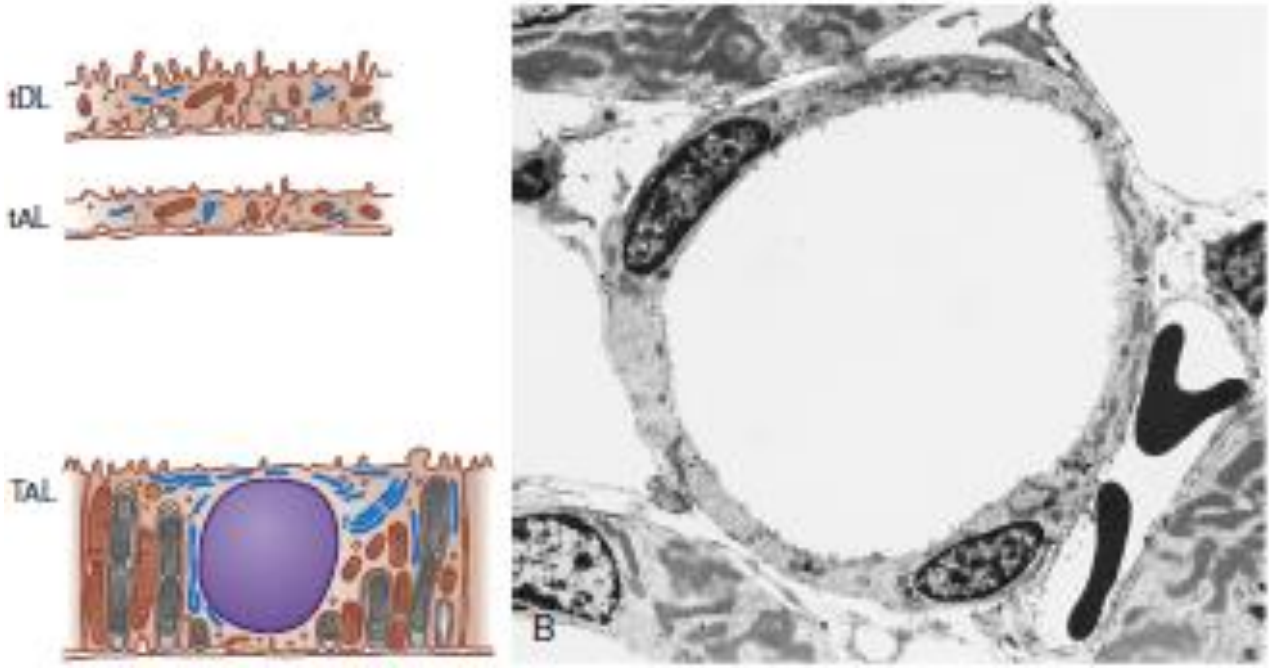
Loop of Henle





- **The pars recta of the proximal tubule,**
- **The thin descending limb**
- **The thin ascending limb**
- **The thick ascending limb**
- **Each part displays different permeability to water and sodium**

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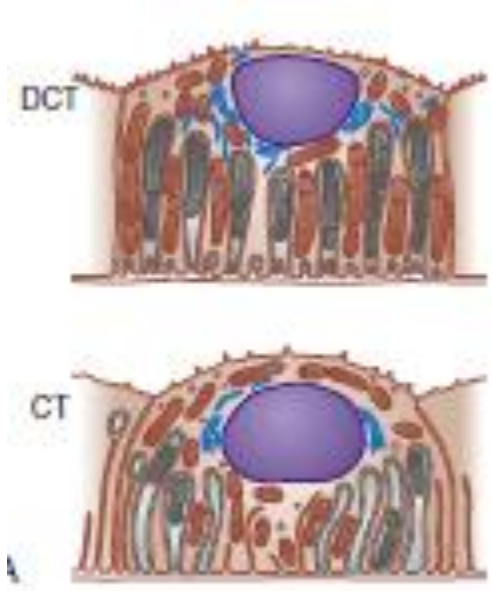
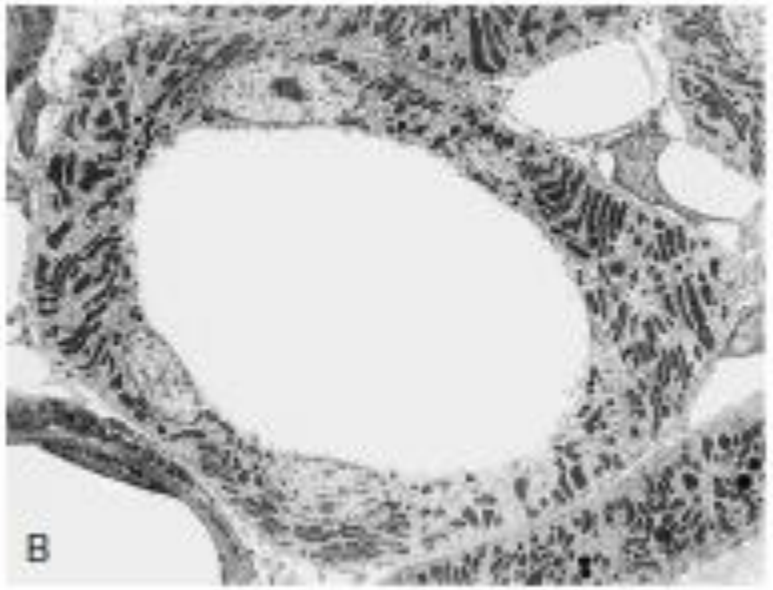
The distal convoluted tubule





The epithelium of pars straight have tall cells that interdigitate each other.

These cells are rich in mitochondries and Na-K-ATPase activity for Na reabsorption.

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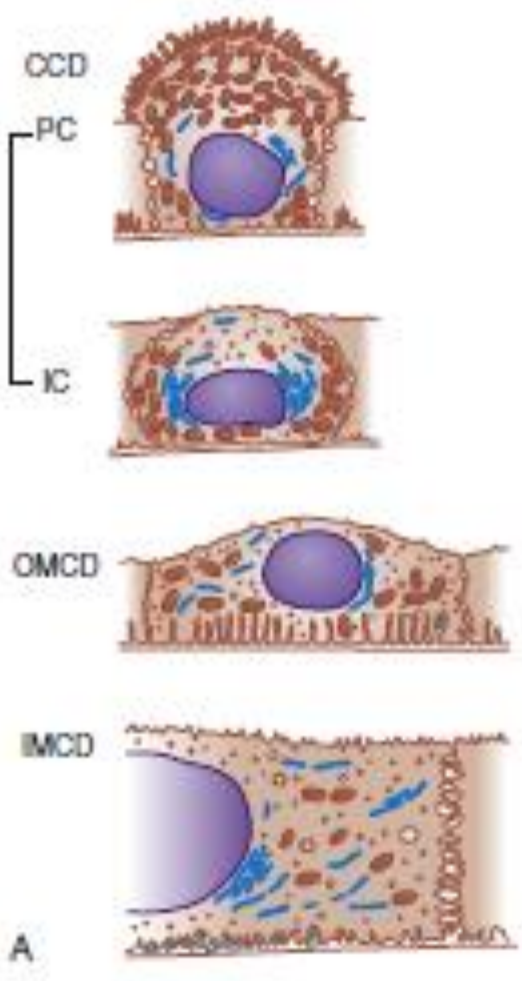
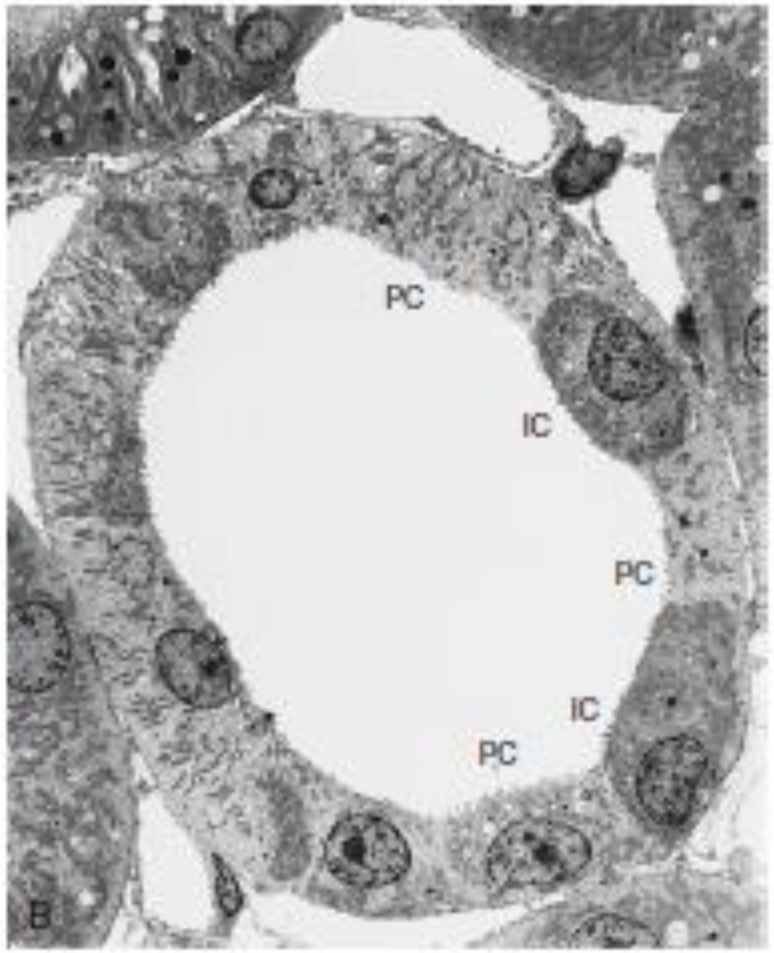
The collecting duct system of tubules

The collecting duct system of tubules has cortical and medullary portions and contains the connecting tubules and the collecting duct tubules.

There are two cell types:

- **principal cells (collecting duct cells) with an important function in water reabsorption and Na and K transport; these cells also have vasopressin receptors**
- **the intercalated cells, with darker cytoplasm that evidence high carbonic anhydrase activity, with an important role in acid-base balance.**





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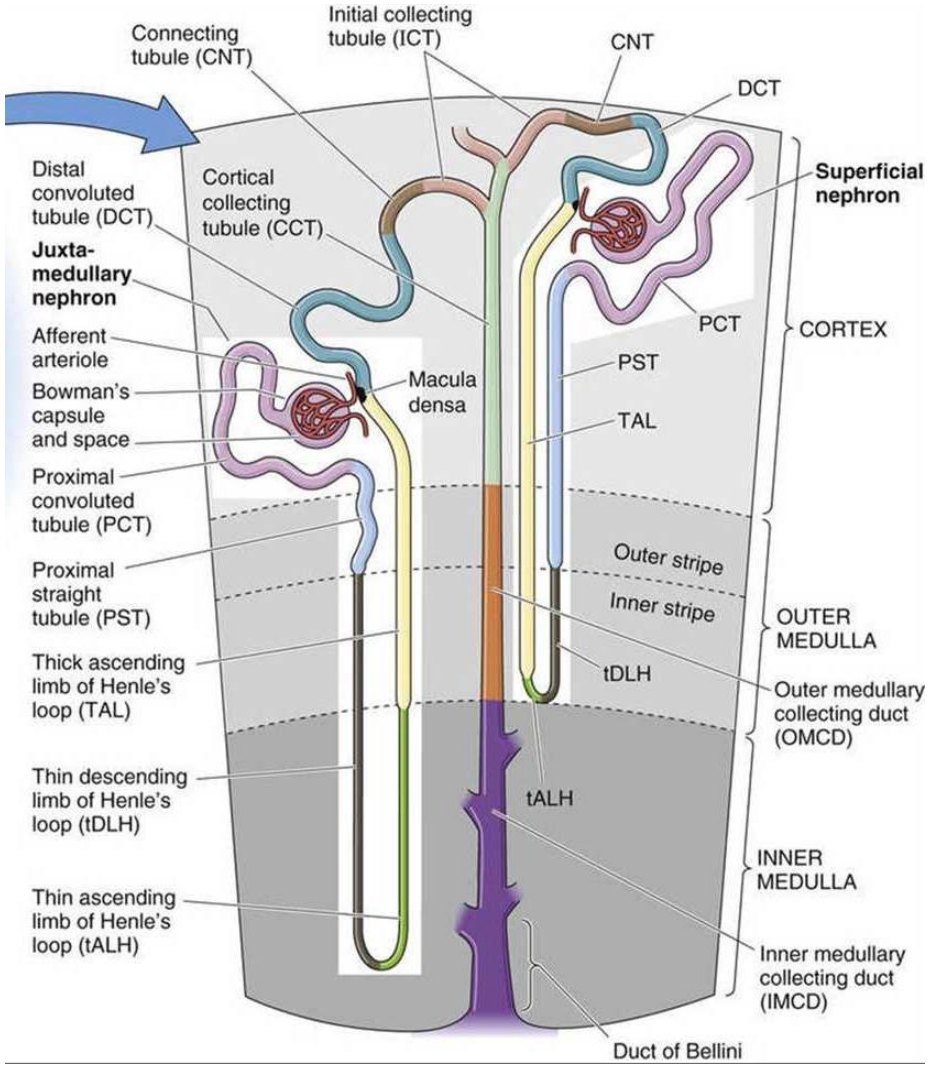
Renal Interstitium: Anatomy

- **The renal interstitium is defined as the intertubular, extraglomerular, extravascular space of the kidney.**
- **It is bounded on all sides by tubular and vascular basement membranes and is filled with cells, extracellular matrix, and interstitial fluid.**
- **It accounts for approximately 8% of the total parenchymal volume in the cortex and up to 40% in the inner medulla.**



Zeisberg M and Kalluri R. CJASN 2015, 10:1831–1840.

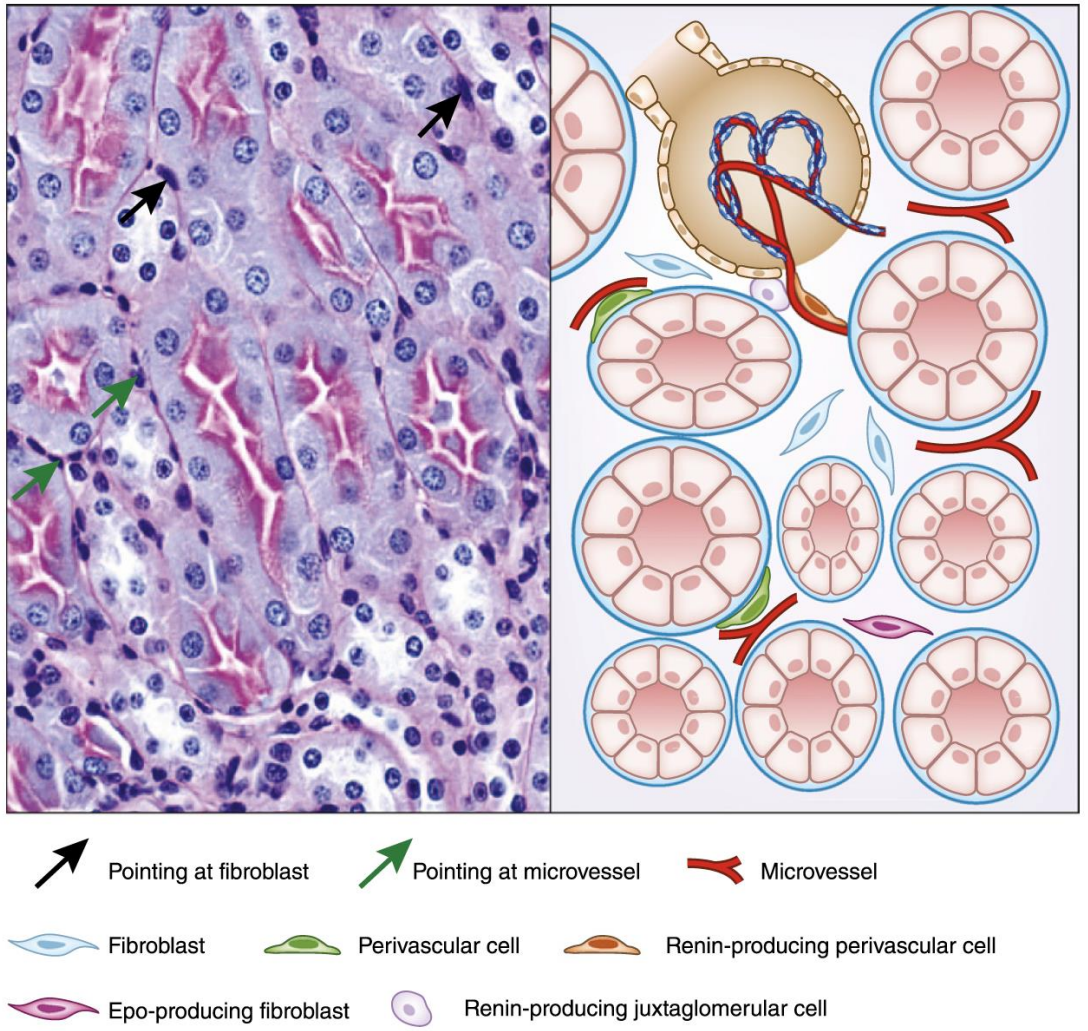
Renal Interstitium: Physiology

- **The physiologic role of the interstitium of the kidney has received comparatively little interest to date.**
- **It was long considered that the interstitium was mostly a passive tissue that structurally supported the tubular epithelium.**
- **The renal interstitium received increasing interest in the context of kidney abnormalities, when the role of interstitial fibrosis in progression of CKD became obvious.**

Zeisberg M and Kalluri R. CJASN 2015, 10:1831–1840.

Renal Interstitium

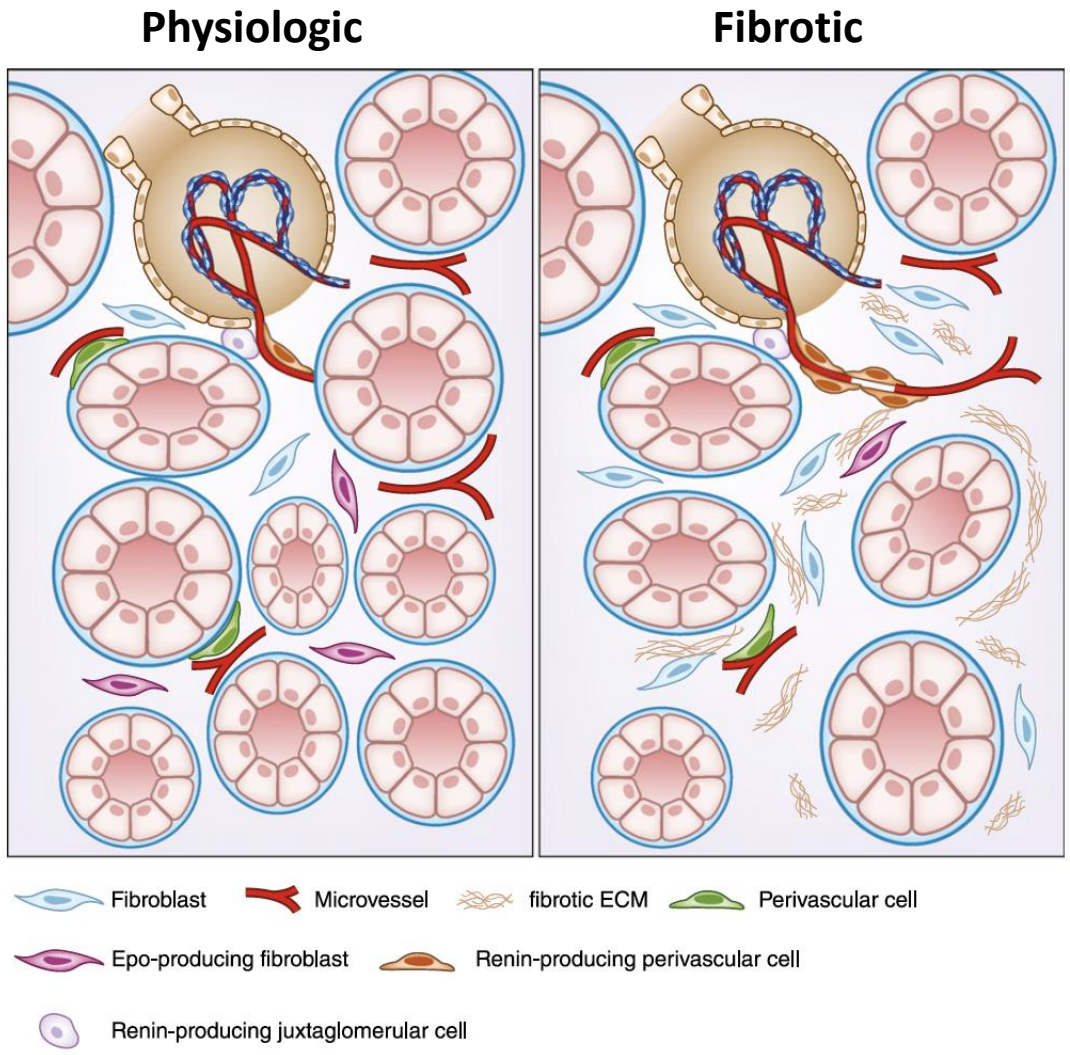
- Interstitium harbors dendritic cells, macrophages, lymphocytes, lymphatic endothelial cells and various types of fibroblasts, the hallmark cell type of connective tissues.
- The physiologic endocrine function of interstitial cells as sources of erythropoietin and renin.



Zeisberg M and Kalluri R. CJASN 2015, 10:1831–1840.

From physiology to pathophysiology of the renal interstitium

- Pathologic involvement of the interstitium, so-called fibrosis, determines progression of CKD.
- The interstitium increases in volume due to accumulation of fibrotic extracellular matrix and fibroblasts capable of producing collagen accumulate
- Epo-producing fibroblasts are diminished.
- Renin-producing perivascular cells accumulate within the interstitium.



Zeisberg M and Kalluri R. CJASN 2015, 10:1831–1840.

WHO Classification of Tubulointerstitial Diseases

Table 1. WHO classification of tubulointerstitial diseaes

- Infection
  - Acute infectious tubulointerstitial nephritis
  - Acute tubulointerstitial nephritis associated with systemic infection
  - Chronic infectious Tubulointerstitial nephritis (chronic pyelonephritis)
  - Specific renal infection
- Drug-induced tubulointerstitial nephritis
  - Acute drug-induced tubulotoxic injury
  - Drug-induced hypersensitivity tubulointerstitial nephritis
  - Chonic drug-induced tubulointerstitial nephritis
- Tubulointerstitial nephritis associated with immune disorders
  - Induced by antibodies reacting with tubular antigens
  - Induced by autologous or exogenous antigen-antibody complexes
  - Induced by, or associated with, cell-mediated hypersensitivity
  - Induced by immediate (IgE-type) hypersensitvity
- Obstructive uropathy
- Vesicoureteral reflux associated nephropathy (reflux nephropathy)
- Tubulointerstitial nephritis associated with papillary necrosis
- Heavy metal-induced tubular and tubulointerstitial lesions
- Acute tubular injury/necrosis
  - Toxic
  - Ischemic
- Tubular and tubulointerstitial nephropathy caused by metabolic disturbances
- Hereditary renal tubulointerstitial disorders
- Tubulointerstitial nephritis associated with neoplastic disorders
- Tubulointerstitial lesions in glomerular and vascular diseases
- Miscellaneous disorders
  - Balkan endemic nephropathy

Classification of Tubulointerstitial Nephritis

Table 2. Classification of tubulointerstitial nephritis (TIN)

I. Primary TIN
   1. Infection (bacterial pyelonephritis, Hantavirus, Leptospirosis)
   2. Immune-mediated (Sjögren syndrome, anti-tubular basement membrane disease)
   3. Drug-induced (AIN, analgesics-induced IN, lithium, cyclosporine, Chinese herbs)
   4. Toxins (lead)
   5. Metabolic disorders (gouty nephropathy, hypercalcemic IN, hypokalemoic)
   5. Hereditary TIN (Wilson disease, cystinosis, hyperoxaluria)
   6. Hematologic disorders (sickle cell disease, Light chain nephropathy, cast nephropathy, light chain deposit diseases, amyloidosis)
   7. Miscellaneous (Balkan nephropathy)

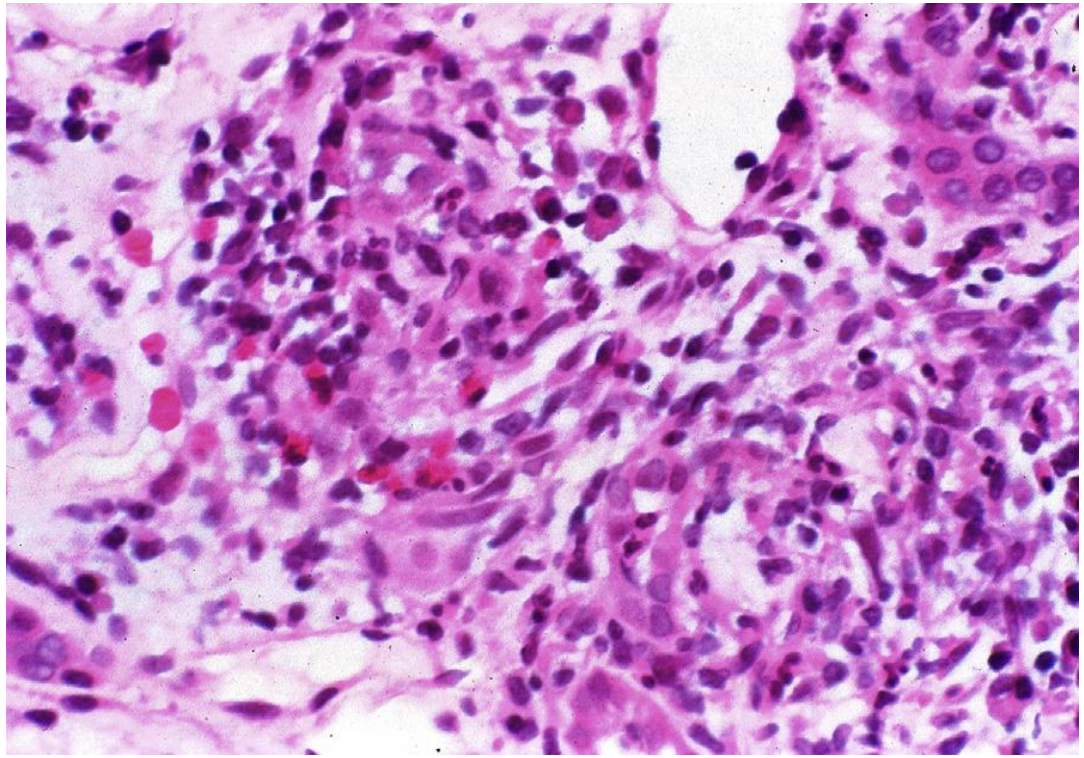
II. Secondary TIN
   1. Glomerular disease
   2. Vascular disease
   3. Structural disease
      a. Cystic diseases
      b. Obstructive disease
      c. Reflux

Acute Interstitial Nephritis

Acute interstitial nephritis

Definition

- Acute interstitial nephritis (AIN) is characterized by
  1. Presence of inflammatory infiltrates
  2. Oedema within the interstitium
  3. Acute deterioration in renal function



Acute interstitial nephritis with an interstitial lymphoplasmacytic infiltrate with eosinophils and associated interstitial edema (HE stain)

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961
Fogo A, et al. AJKD 2016;67(6):e35-e36

Acute interstitial nephritis (AIN)

Epidemiology

- 1–3% of all renal biopsies
- Renal Biopsy for acute kidney failure
  - AIN accounted for 15–27%
- Common cause of acute renal dysfunction, but its true incidence might even be underestimated by several reasons.
  - A significant number of patients in whom AIN is suspected on clinical grounds is not submitted to a confirmatory renal biopsy because empirical treatment is preferred, particularly in elderly and frail patients.
  - Mild forms of AIN can be underdetected, either because of the absence or vagueness of clinical symptoms or because acute renal failure is attributed to other causes of renal injury.

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Acute interstitial nephritis (AIN)

Aetiology

Table 1 | Etiology of biopsy-proven AIN

Drugs (>75% of AIN)	Antibiotics: ampicillin, cephalosporins, ciprofloxacin, cloxacillin, methicillin, penicillin, rifampicin, sulfonamides, vancomycin. NSAIDs Other: allopurinol, acyclovir, famotidine, furosemide, omeprazole, phenytoin
Infections (5–10%)	Bacteria: *Brucella*, *Campylobacter*, *Escherichia coli*, *Legionella*, *Salmonella*, *Streptococcus*, *Staphylococcus*, *Yersinia* Viruses: cytomegalovirus, Epstein–Barr, hantavirus, human immunodeficiency virus, polyomavirus Other: *Leptospira*, *Mycobacterium tuberculosis*, *Mycoplasma*, *Rickettsia*, *Schistosoma*, *Toxoplasma*
Idiopathic (5–10%)	Anti-TBM TINU
Associated with systemic diseases (10–15%)	Sarcoidosis, Sjögren, systemic lupus erythematosus

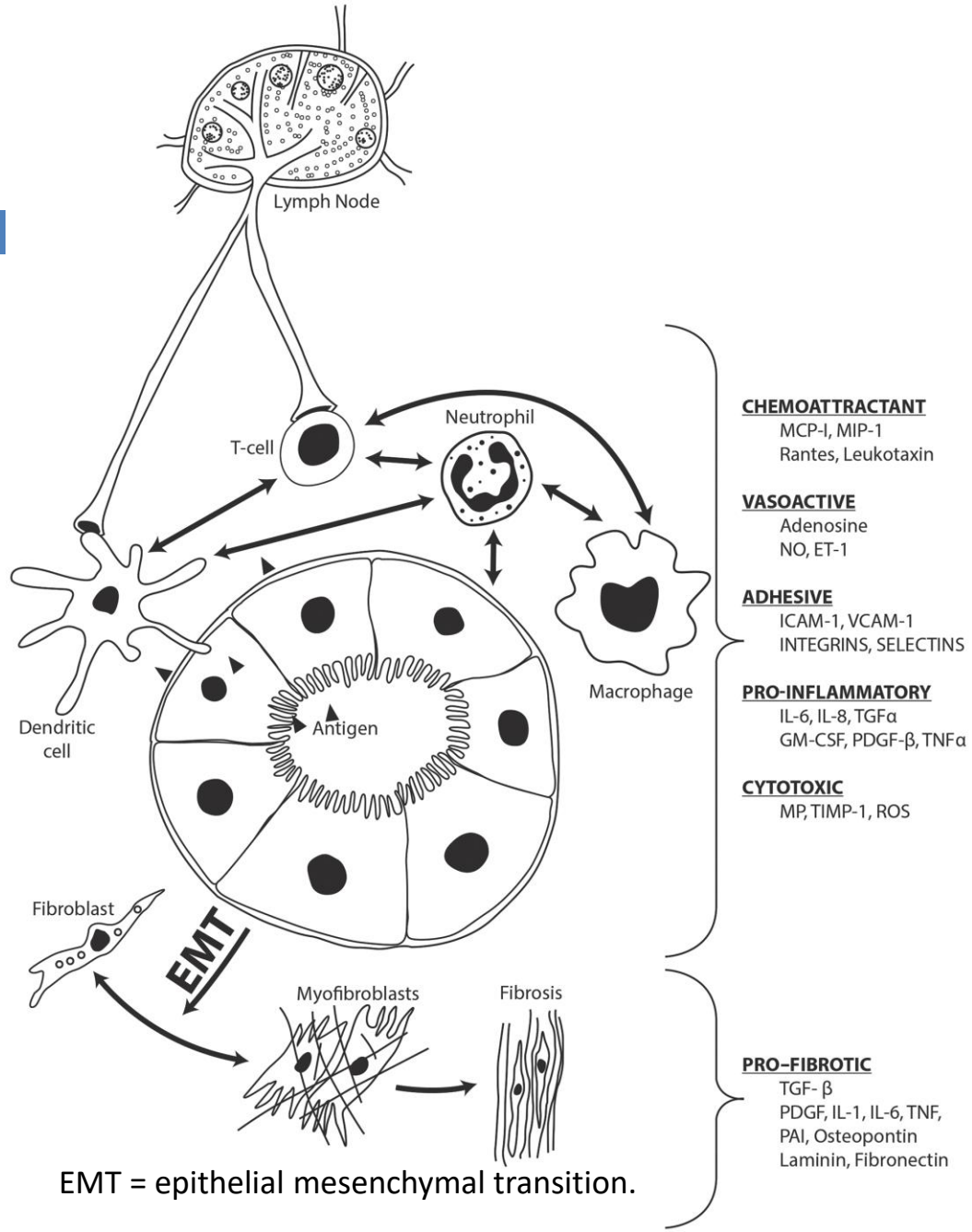
Abbreviations: AIN, acute interstitial nephritis; NSAID, nonsteroidal anti-inflammatory drug; TBM, tubular basement membrane; TINU, tubulointerstitial nephritis and uveitis syndrome.
Most commonly involved causative agents.

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Acute interstitial nephritis

Pathogenesis

- **Expression of endogenous nephritogenic antigens or exogenous antigens processed by tubular cells.**
- **The process begins with the recognition and subsequent processing of the putative antigen by dendritic cells that endocytose, process, and express the peptides on their surface MHC II molecules, which they then present to the naïve lymphocytes in the regional lymph nodes.**



EMT = epithelial mesenchymal transition.

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961, Raghavan A & Shawar S. Adv Chronic Kidney Dis. 2017;24(2):64-71

Acute interstitial nephritis

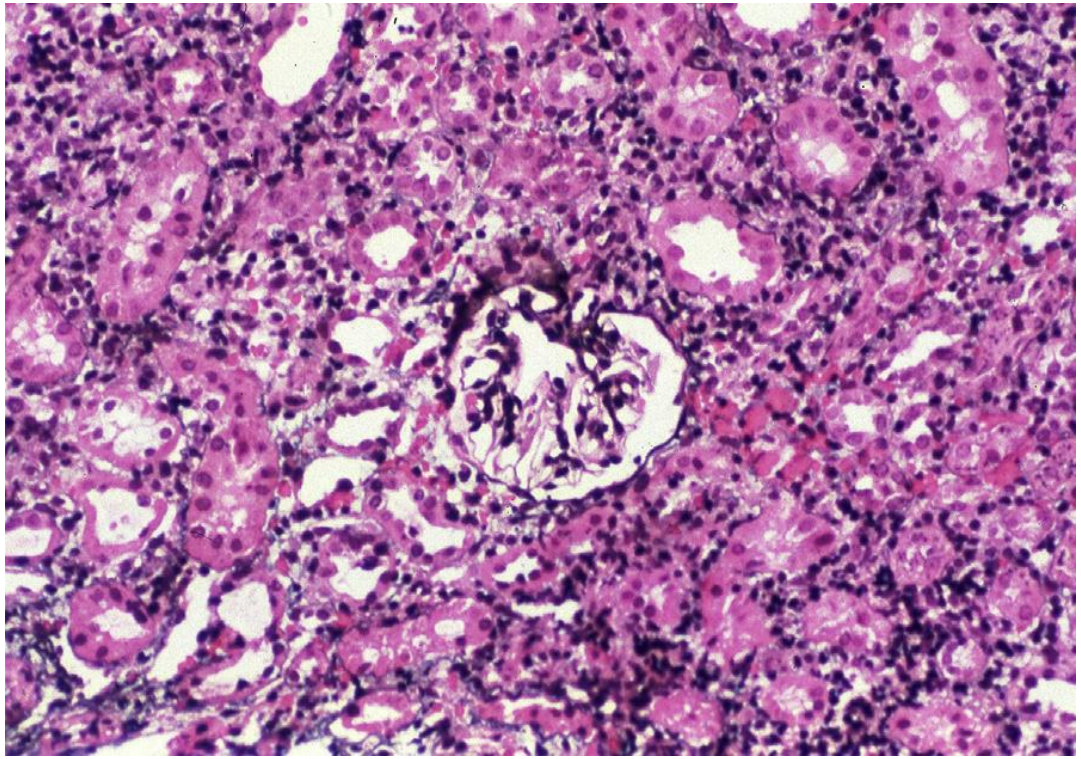
Clinical features

Acute renal failure	100%
Acute renal failure requiring dialysis	40%
Arthralgias[a]	45%
Fever	36%
Skin rash	22%
Eosinophilia (>500 eosinophils per mm^3)	35%
Microhematuria[b]	67%
Gross hematuria[b]	5%
Leukocyturia[b]	82%
Non-nephrotic proteinuria	93%
Nephrotic-range proteinuria	2.5%
Complete nephrotic syndrome	0.8%

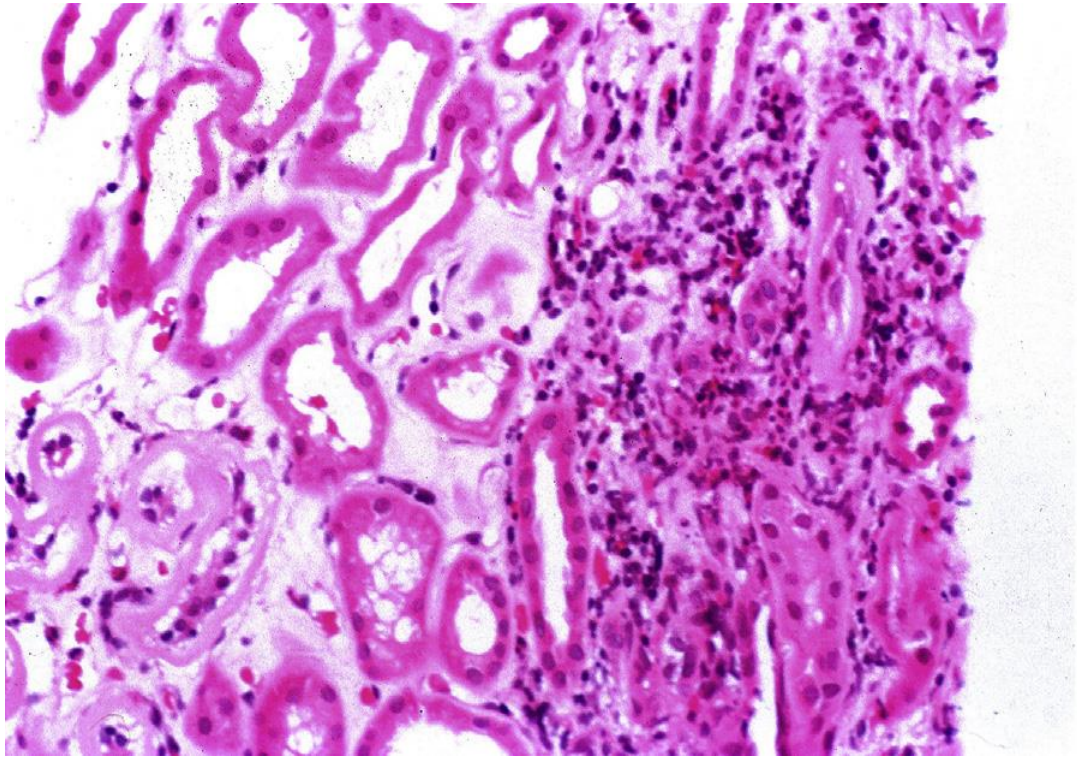
Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Acute interstitial nephritis

Histopathology



Acute interstitial nephritis with an interstitial lymphoplasmacytic infiltrate with associated rare lymphocytic tubulitis and mild interstitial edema (Jones stain).



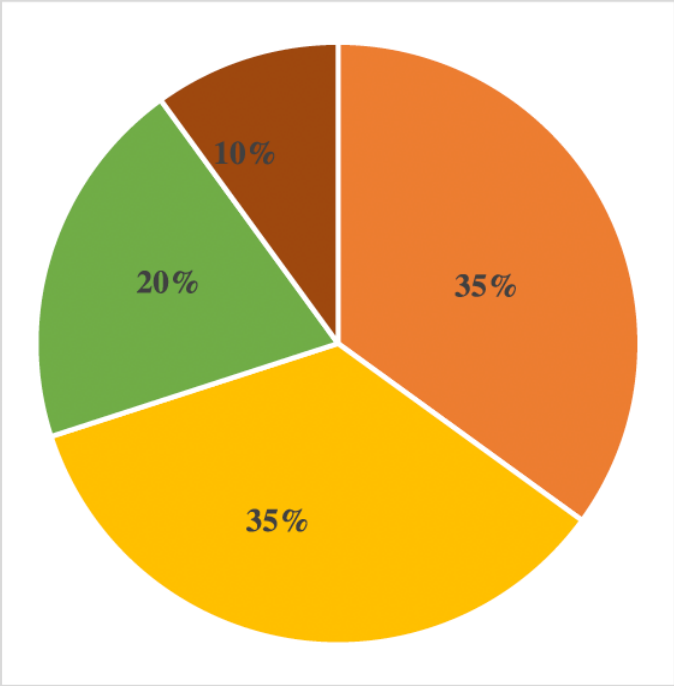
Acute interstitial nephritis with an interstitial lymphoplasmacytic infiltrate, edema, and prominent eosinophilic component (left), and preexisting mild tubulointerstitial fibrosis (right; HE stain).

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961
Fogo A, et al. AJKD 2016;67(6):e35-e36

Drug-induced Acute interstitial nephritis

Aetiology

The classification of drugs on the basis of their involvement as a causal factor.	
Antibiotics	35%
Proton pump inhibitors (PPIs)	35%
NSAIDs	20%
Others	10%



Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961
Muhammad A, et al. Clinical Kidney Journal 2024

Antibiotics	β-lactam drugs*
	Fluoroquinolones*
	Rifampin*
	Sulfa-based drugs*
	Vancomycin
	Minocycline
	Ethambutol
	Erythromycin
	Chloramphenicol
Antiviral medications	Acyclovir
	Abacavir
	Indinavir
	Atazanavir
GI medications	Proton pump inhibitors*
	Histamine-2 receptor blockers
Analgesics	Nonsteroidal anti-inflammatory drugs*
	Selective COX-2 inhibitors
Anti-seizure drugs	Phenobarbital
	Phenytoin*
	Carbamazepine
Other drugs	Allopurinol*
	5-Aminosalicylates*
	Captopril
	Interferon
	Cyclosporine
	Anti-angiogenesis drugs (tyrosine kinase inhibitors)
	Diuretics

Table 1. Medications Associated With Interstitial Nephritis

Antibiotics

Penicillins: Amoxicillin, Ampicillin, Aztreonam, Benzylpenicillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Methicillin, Mecloxcilin, Nafcillin, Oxacillin, Piperacillin/Tazobactam

Fluroquinolones: Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

Cephalosporins: Cefaclor, Cedamandole, Cefazolin, Cefoperazone, Cefotaxime, Cefotetan, Cefoxitin, Cefuroxime, Ceftriaxone, Cephalexin, Cephaloridine, Cephalothin, Cephradine

Sulfonamides: Trimethoprim-Sulfamethoxazole

Macrolides: Azithromycin, Clarithromycin, Erythromycin, Telithromycin

Other: Cefepime, Chloramphenicol, Clindamycin, Colistin, Doxycyclin, Ethambutol, Flurithromycin, Genatmicin, Griseofulvin, Imipenem, Isoniazid, Lincomycin, Linezolid, Minocycline, Nitrofurantoin, Piromidic acid, Polymyxin B, Quinine, Rifampin, Teicoplanin, Vancomycin

Anti-Retrovirals

Abacavir, Acyclovir, Atazanavir, Azythromycin, Foscarnet, Indinavir, Interferon-alpha

NSAIDs

COX2 inhibitors: Celecoxib, Rofecoxib

Other: Aceclofenac, Benoxaprofen, Diclofenac, Diflusinol, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamate, Meloxicam, Namubetone, Naproxen, Noramidopyrine, Nimesulide, Oxapropzin, Phenazone, Phenylbutazone, Prioxicam, Sulindac, Tolmetin, Zomepirac,

5-Aminosalicylates

Balsalazide, Mesalazine, Olsalazine, Sulfasalazine

GI Protective (Antacids)

Proton pump inhibitors: Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole

H2 blockers: Cimetidine, Famotidine, Ranitidine

Chemotherapeutic Agents

Immune checkpoint inhibitors: Atezolizumab, Ipilimumab, Nivolumab, Pembrolizumab

Tyrosine kinase inhibitors: Cediranib, Sorafenib, Sunitinib

Other: Adriamycin, Alendronate, Azathioprine, BCG, Bevacizumab, Bortezomib, Carboplatin, Gemcitabine, Interleukin-2, Interferon, Ifosfamide, Lenalidomide, Methotrexate, Pemetrexed, Vemurafenib

Diuretics

Thiazide: Chlorothiazide, Hydrochlorothiazide, Indapamide, Metolazone

Chlorthalidone (thiazide like)

Loop: Bumetanide, Furosemide, Tienilic acid, Torsemide

Potassium sparing: Amiloride, Triamterene

Antihypertensives

ACE inhibitors: Captopril, Lisinopril

Angiotensin receptor blockers: Candesartan, Losartan

Calcium channel blockers: Amlodipine, Nifedipine

Anticonvulsants

Carbamazepine, Diazepam, Lamotrigine, Levetiracetam, Phenobarbital, Phenytoin, Valproic acid

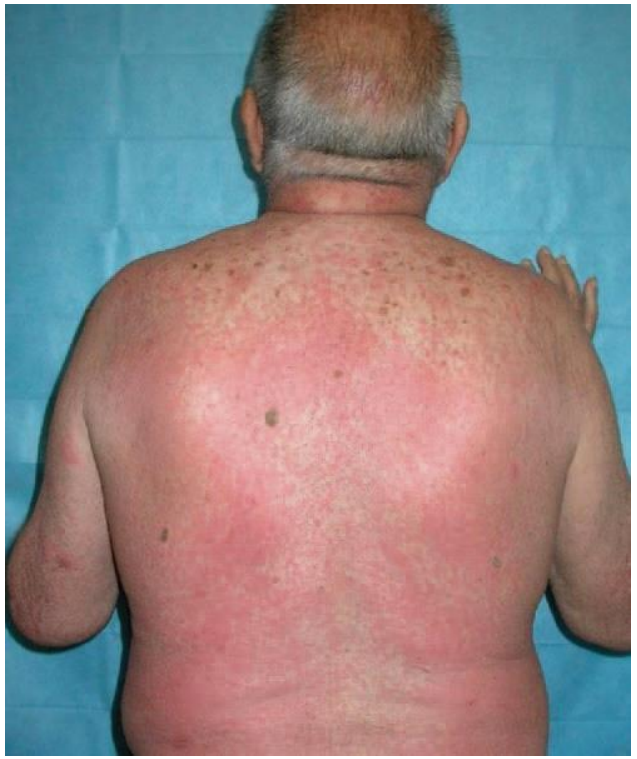
Other:

Allopurinol, Andvarenicline Atorvastatin, Carbimazole, Chlorporpamide, Cysteamine, Deferasirox, Exenatide, Febuxostat, Flecainide, Fluindone, Gemfibrozil, Leflunomide, Metamizole, Propranolol, Propylthiouracil, Risedronate, Sildenafil

Drug-induced Acute interstitial nephritis

Clinical features

- Allergic-type reaction
- Low-grade fever
- Maculopapular skin rash
- Arthralgias
- Eosinophilia and Eosinophiluria

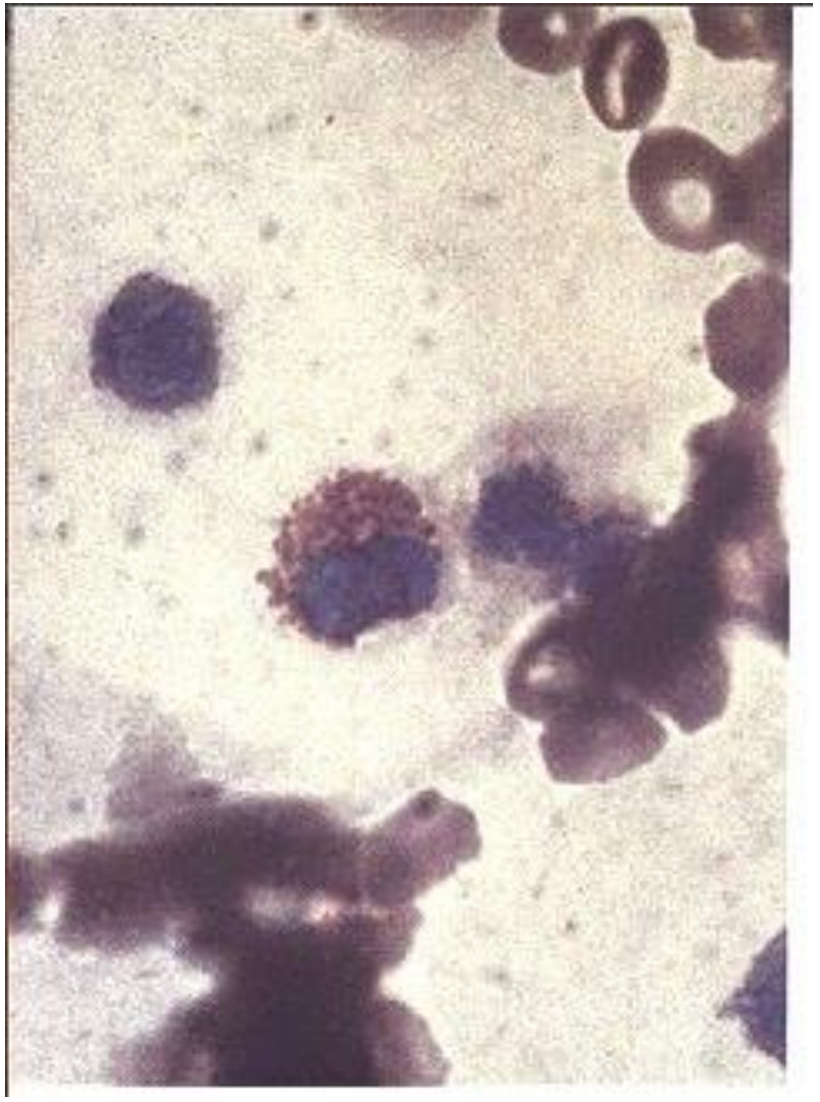


Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Drug-induced Acute interstitial nephritis

Eosinophilia and Eosinophiluria

Hansel's stain
Urinary eosinophil identified
by the presence of brilliant red granules



Nolan C, et al. N Engl J Med 1986;315:1516-1519

Antibiotics associated Acute Interstitial Nephritis

- 35% of drug induced AIN is due to antibiotics
- More common
  - Beta-lactams: methicillin
  - non-β-lactam antibiotics: rifampicin
  - Sulfonamide
  - Ciprofloxacin
- Clinical presentation days or weeks after the onset of treatment

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961, Nast CC. Adv Chronic Kidney Dis. 2017;24(2):72-79
Perazella, M. Nat. Rev. Nephrol. 2010; 6: 461–470

Proton Pump Inhibitors associated AIN

- **Incidence: 2-20/100.000 patients (depending on the age)**
  - **Patients >60 years old => 10fold relative risk**
- **Clinical presentation: 10-13 weeks of treatment (1 week – 18 months)**
- **~50% do not show full recovery**
- **Long term use is correlated with chronic kidney disease**

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961,
Nast CC. Adv Chronic Kidney Dis. 2017;24(2):72-79
Perazella, M. Nat. Rev. Nephrol. 2010; 6: 461–470

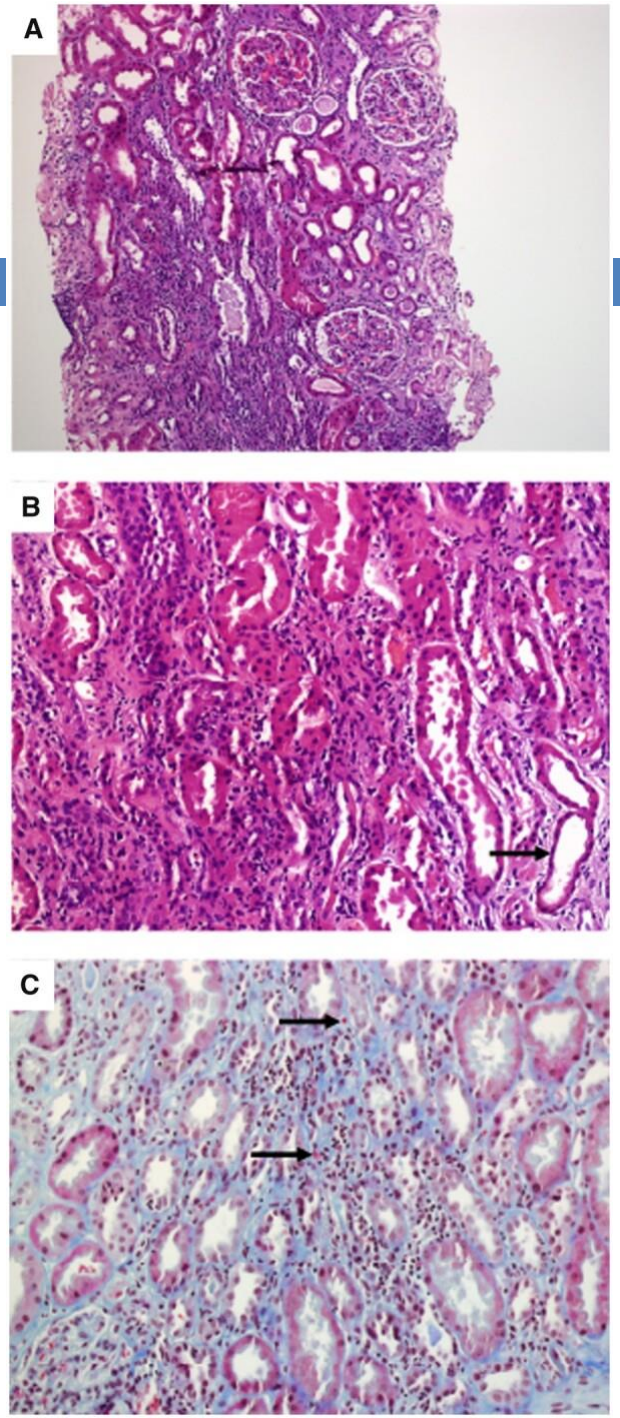
Non Steroidal Anti-Inflammatory Drugs associated AIN

- Non Steroidal Anti-Inflammatory Drugs (NSAIDs) including selective cyclo-oxygenase (CoX-2) inhibitors
- The duration of therapy prior to the development of AIN is long, typically in the range of 6–18 months.
- Frequent in patients > 60 years old with regular use of NSAIDs.
- Histopathology: interstitial inflammation and tubulitis, usually less intense than in other forms of drug-induced AIN and are not accompanied by a predominance of eosinophils.
  - Rare presentation Nephrotic syndrome – Minimal change disease
- Improvement of renal function after withdrawal of medication

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961, Nast CC. Adv Chronic Kidney Dis. 2017;24(2):72-79, Perazella, M. Nat. Rev. Nephrol. 2010; 6: 461–470

Acute interstitial nephritis associated with immune checkpoint inhibitor

- Immune checkpoint inhibitors are used to treat solid organ metastatic malignancies. They act by triggering a vigorous immune response against tumoural cells, preventing their proliferation and metastasis. However, this is not a selective response and can cause immune-related adverse events.
- The most frequent type of toxicity described is acute interstitial nephritis
- (A) Tubulo-interstitial inflammatory infiltrates and no structural abnormalities in the glomeruli are observed (HE stain).
- (B) Predominantly monocytic inflammatory infiltrates in the interstitial compartment. Tubular epithelium simplification suggesting acute tubular injury (arrow) (HE stain).
- (C) Inflammatory cells in the basolateral aspect of the tubular epithelium (arrow), scattered eosinophils in the interstitium (Masson's trichrome).



Oleas D et al. CKJ 2020;14(5):1364–1370.

Infection associated AIN

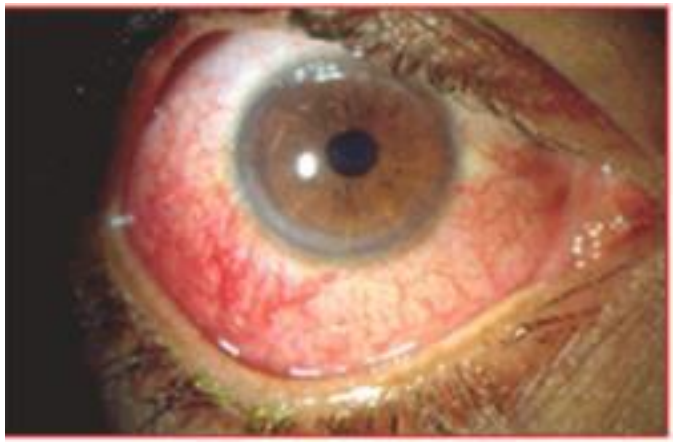
- **4-6%: Developed Countries**
- **40-50%: Developing Countries**

Infectious causes	**Bacteria** acute pyelonephritis streptococci, corynebacteria (diphtheria), streptococcus pneumoniae, brucella, legionella, salmonella, yersinia, mycobacterium tuberculosis…
	Virus cytomegalovirus (CMV), Ebstein-Barr virus (EBV), Hanta, measles, Coxsackie, Echovirus, Hepatitis A and C, influenza, herpes simplex, BK (kidney transplant), Human immunodeficiency virus (HIV)...
	Spirochetes Treponema (syphilis), leptospira...
	Other toxoplasma, chlamydia, mycoplasma, rickettsia, Candida...

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961, Nast CC. Adv Chronic Kidney Dis. 2017;24(2):72-79, Perazella, M. Nat. Rev. Nephrol. 2010; 6: 461–470

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU)

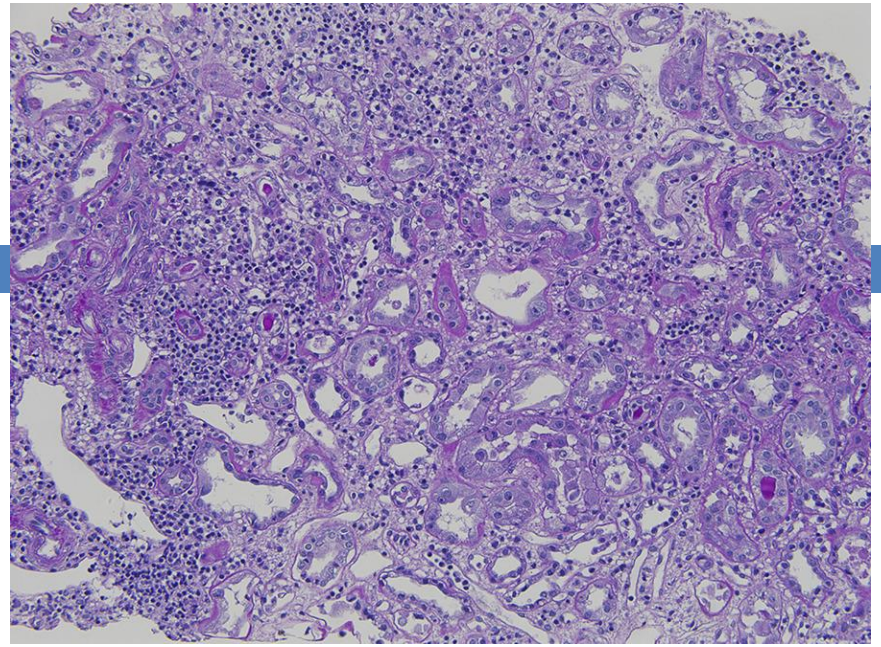
- Rare oculorenal inflammatory condition
- First described in 1975
- >592 cases reported worldwide
- Prevalence of TINU is higher in younger age groups
- Female preponderance (65%)
- Clinical Presentation: bilateral sudden-onset anterior uveitis with typical symptoms of redness, pain and photophobia.
- Posterior or panuveitis as well as adult age are associated with an increased risk of developing CKD.
- Treatment: Steroids (second line: immunosuppression eg. Methotrexate, mycophenolate, cyclosporine)

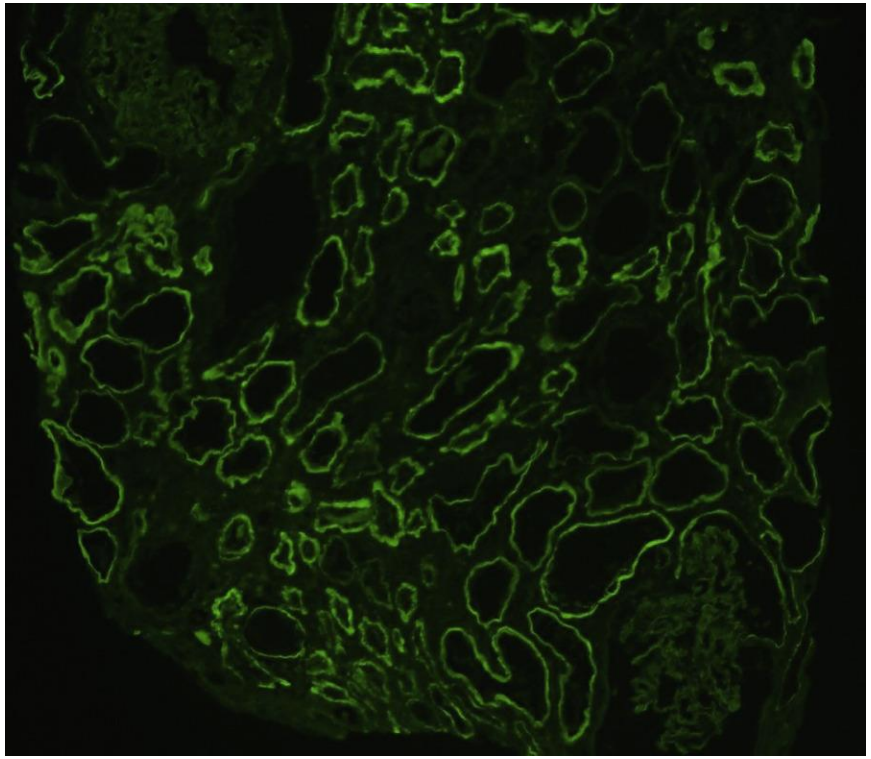


Regusci A et al. NDT 2022;37(5):876-886.

Anti–Tubular Basement Membrane Antibody Nephritis

- Very rare
- Clinical Presentation:
  - polyuria and polydipsia
  - acute or chronic kidney injury
  - microhematuria
  - proteinuria (sometimes nephrotic-range).
- Histopathology:
  - Interstitial mononuclear infiltrate with tubulitis and tubular injury
  - Strong linear IgG staining along TBMs by immunofluorescence
- Anti-TBM antibodies detected in serum





Lusco et al. Am J Kidney Dis. 2017;70(1):e3-e4.

Systemic diseases and Acute interstitial nephritis

- Sarcoidosis
- Sjogren's Syndrome
- Systemic lupus erythematosus
- IgG4 related disease

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Acute interstitial nephritis

Diagnosis

- Clinical
  - Hypersensitivity reaction (skin rash, low grade fever)
- Laboratory
  - ↑ Creatinine
  - Acute kidney injury
  - Proteinuria <1 gr/day
  - ↑ Eosinophils
- Urine dipstick:
  - Aseptic pyuria
  - Leukocyturia
  - Hansel's stain: Sensitivity 40-63%, Specificity 72-93%
- Imaging: Ultrasound, Gallium-67 scintigraphy

Clinical Suspicion – Medical History

Gold standard: Renal biopsy

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961

Prognosis of Acute Interstitial Nephritis

- 30% require hemodialysis during the episode of acute kidney injury
- 60-65% complete renal recovery
- 10-20% partial renal recovery
- 5-10% progress to chronic kidney disease requiring renal replacement therapy
- Risk factors
  - Prolonged AKI > 3 weeks
  - NSAIDS
  - Biopsy findings: Granuloma, Interstitial Fibrosis and tubular atrophy

Raghavan R & Eknoyan G. Clinical Nephrology 2014; 82: 149-162.

Treatment of Acute Interstitial Nephritis

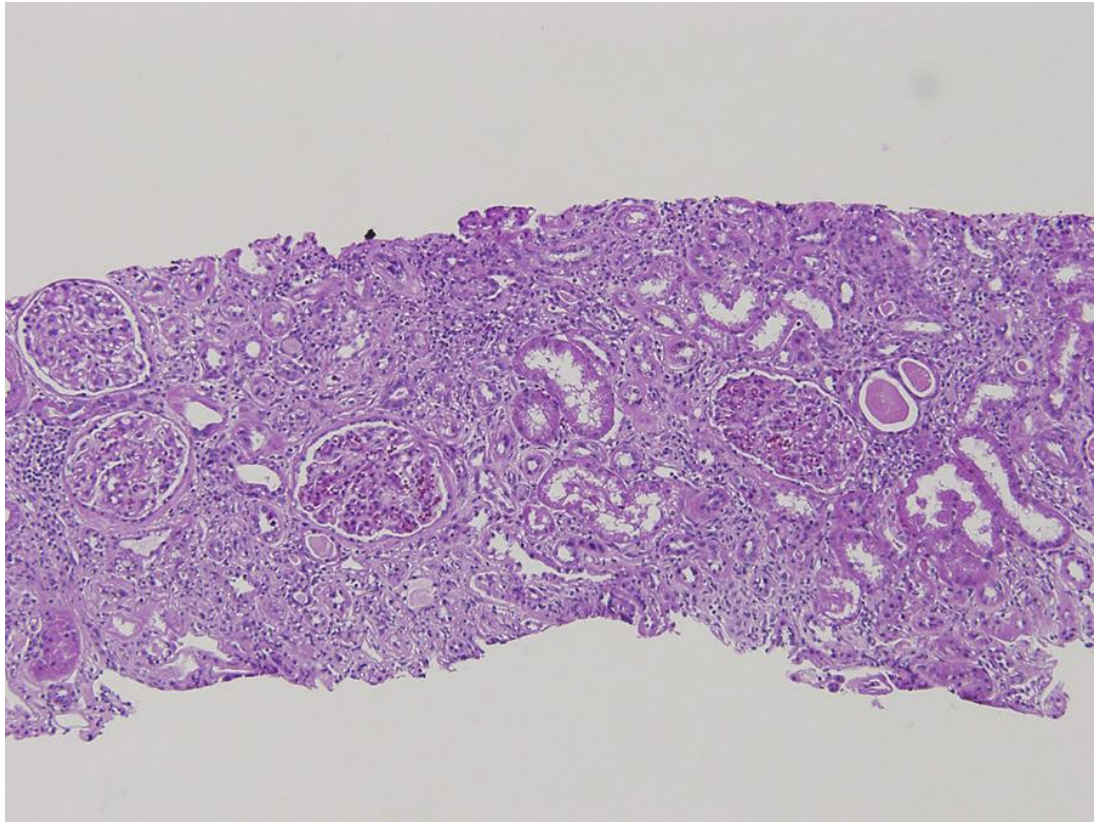
- **Withdrawal of the causative agent**
- **The role of steroids remains controversial**
  - **Randomized trials have not been conducted**
  - **Acute interstitial nephritis associated with systemic diseases**
  - **In cases without improvement of renal function despite discontinuation of offending agent for 3-7 days**
  - **Therapeutic dose: 1 mg/kg/d (max 40-60 mg/d) prednisolone for 2 weeks and then tapering for 4-6 weeks.**

Praga M, Gonzalez E. Kidney int 2010;77(1): 956-961
Raghavan R & Eknoyan G. Clinical Nephrology 2014; 82: 149-162.

Chronic Interstitial Nephritis

Chronic interstitial nephritis (CIN)

- **Chronic interstitial nephritis is a histologic entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, macrophage and lymphocytic infiltration, and interstitial fibrosis.**
- **Nonspecific diagnosis of a pattern of kidney injury, which may occur due to any of many conditions that initially cause an acute interstitial nephritis.**
- **Patients may present at any age, usually with low-grade proteinuria and slowly progressive decline in glomerular filtration rate, and may reach end-stage kidney disease.**

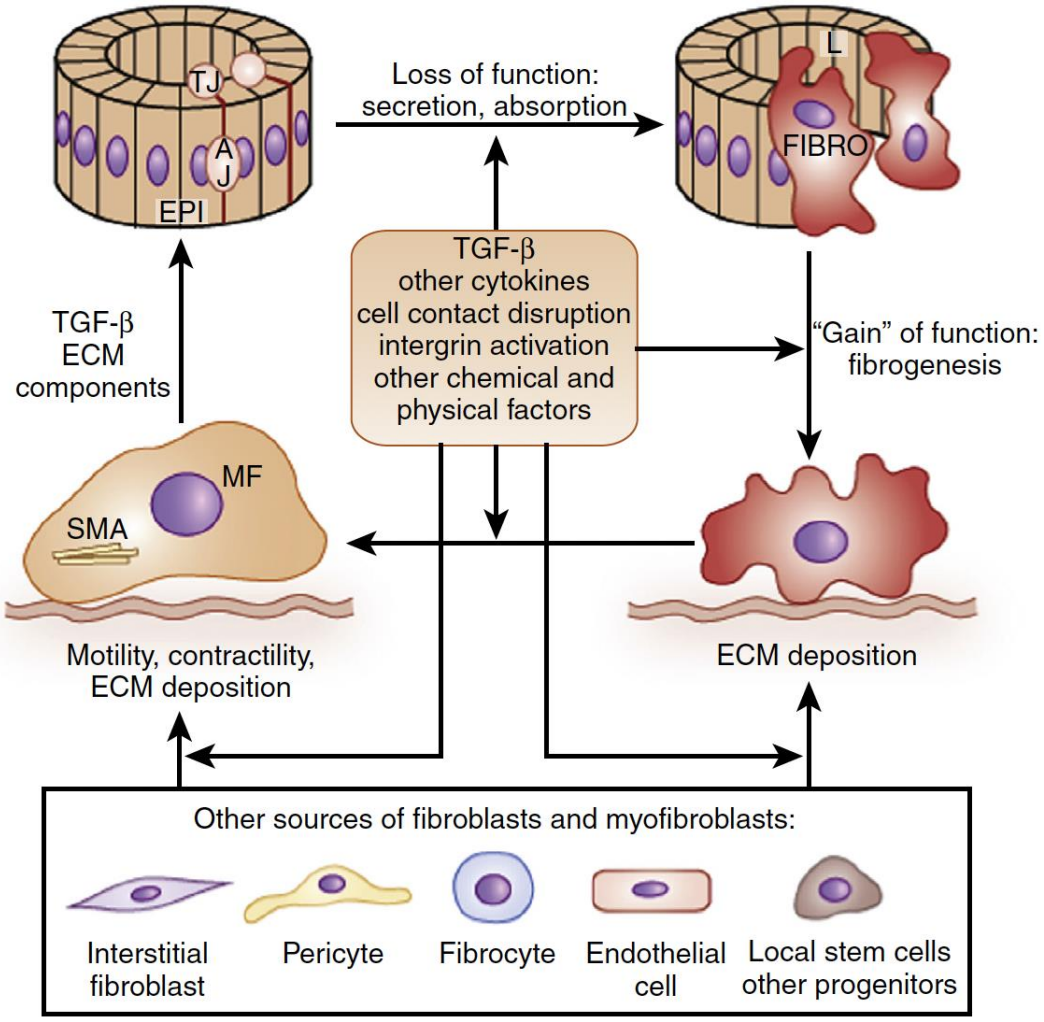


Chronic interstitial nephritis with diffuse interstitial lymphocytic infiltrate with occasional eosinophils associated with interstitial fibrosis, tubular atrophy, and occasional tubulitis. Glomeruli are unremarkable (HE stain).

Fogo A, et al. Am J Kidney Dis. 2017;70(1):e1-e2

Pathogenesis of Chronic Interstitial Nephritis

- **Fibroblasts and myofibroblasts (MF) originate from other cell types and play a significant role in the process of renal fibrosis.**
- **Tubular epithelium undergoes profound phenotypic changes after exposure to fibrogenic stimuli. This results in loss of epithelial characteristics and gain of mesenchymal characteristics. The transitioning cells might remain in the tubular wall or migrate into the interstitium.**
- **Epithelial-derived fibroblasts contribute to the deposition of extracellular matrix (ECM), and a subpopulation may begin expressing α-smooth muscle actin (SMA).**
- **Activated fibroblasts and MF secrete elevated amounts of transforming growth factor-β (TGF-β)**

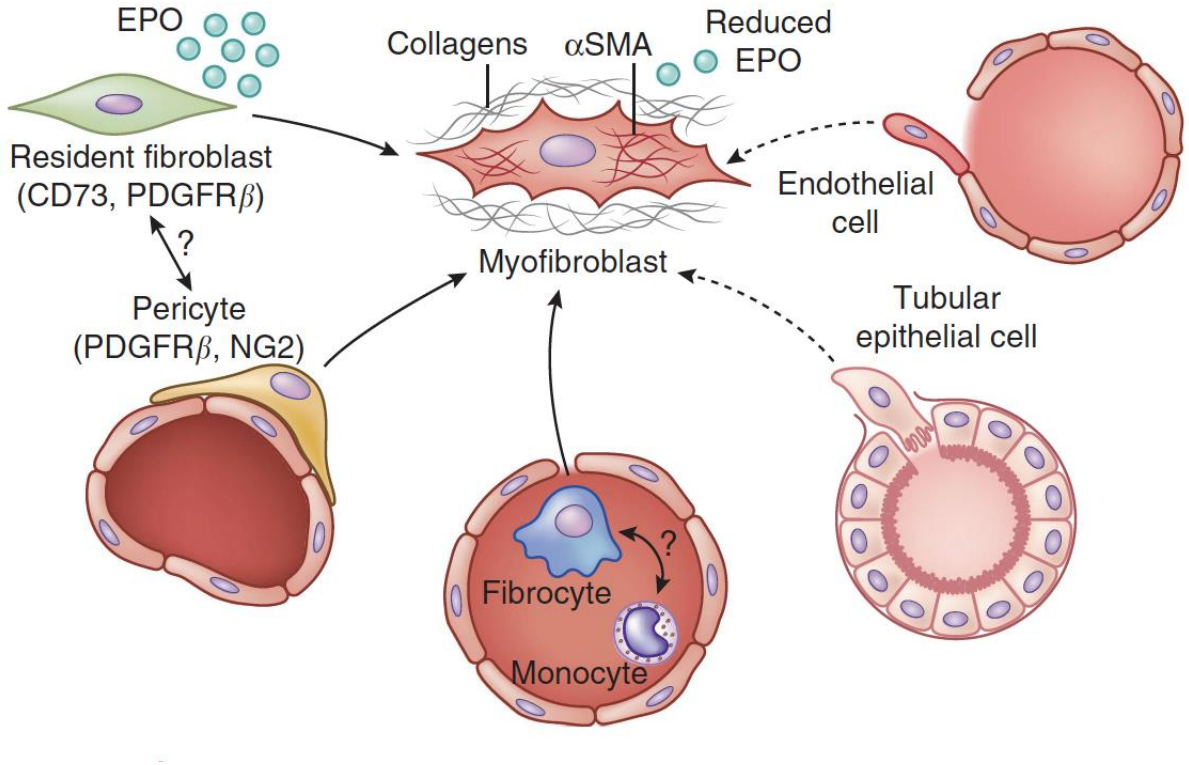


Quaggin SE, Kapus A. Kidney Int 80:41-50, 2011.

Chronic Interstitial Nephritis (CIN)

Pathogenesis

- Collagen producing myofibroblasts in the kidney can be derived from various cellular sources.
- Resident renal fibroblasts and cells of hematopoietic origin migrating into the kidney seem to be the most important ancestors of myofibroblasts.
- It is likely that both cell types communicate with each other and also with other cell types in the kidney.

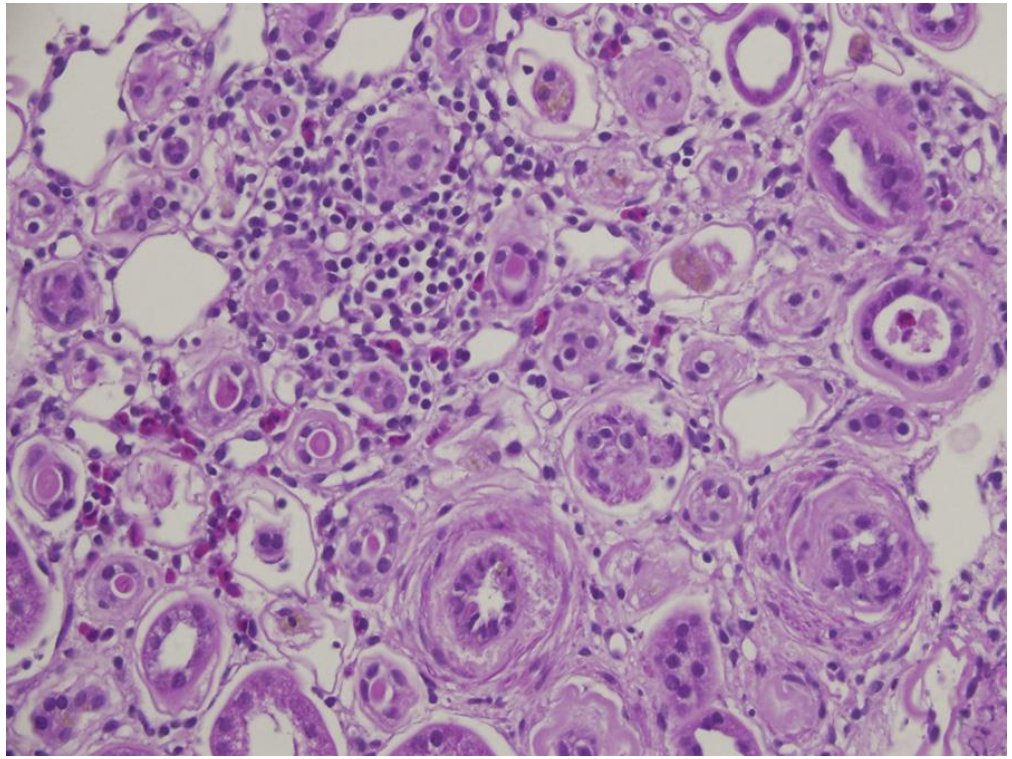


Mack & Yanagita. Kidney International (2015) 87, 297–307

Chronic Interstitial Nephritis (CIN)

Histopathology

- The pathologic features of CIN are nonspecific.
- They include
  - tubular cell atrophy or dilation
  - interstitial fibrosis that is composed of interstitial (types I and II) collagens and
  - mononuclear cell infiltration with macrophages, T cells, and occasionally other cell types (neutrophils, eosinophils, and plasma cells).
  - Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts producing a thyroid-like appearance, thyroidization.

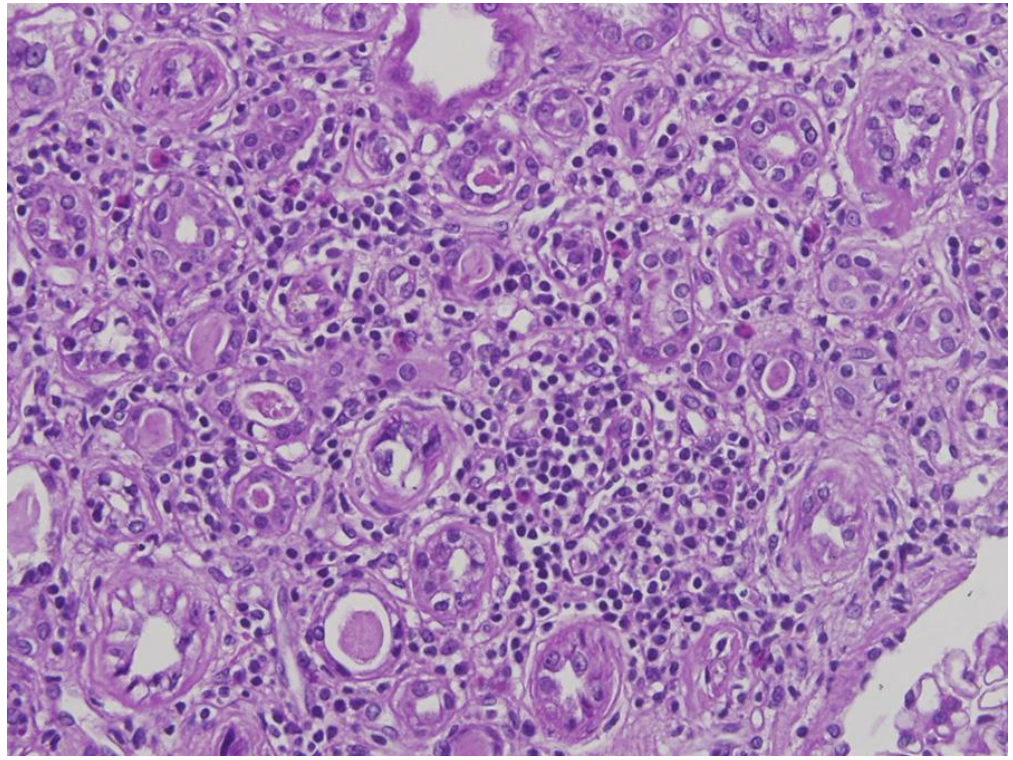


Chronic interstitial nephritis with interstitial lymphocytic infiltrate with eosinophils associated with tubulitis, interstitial fibrosis, and tubular atrophy (hematoxylin and eosin stain).

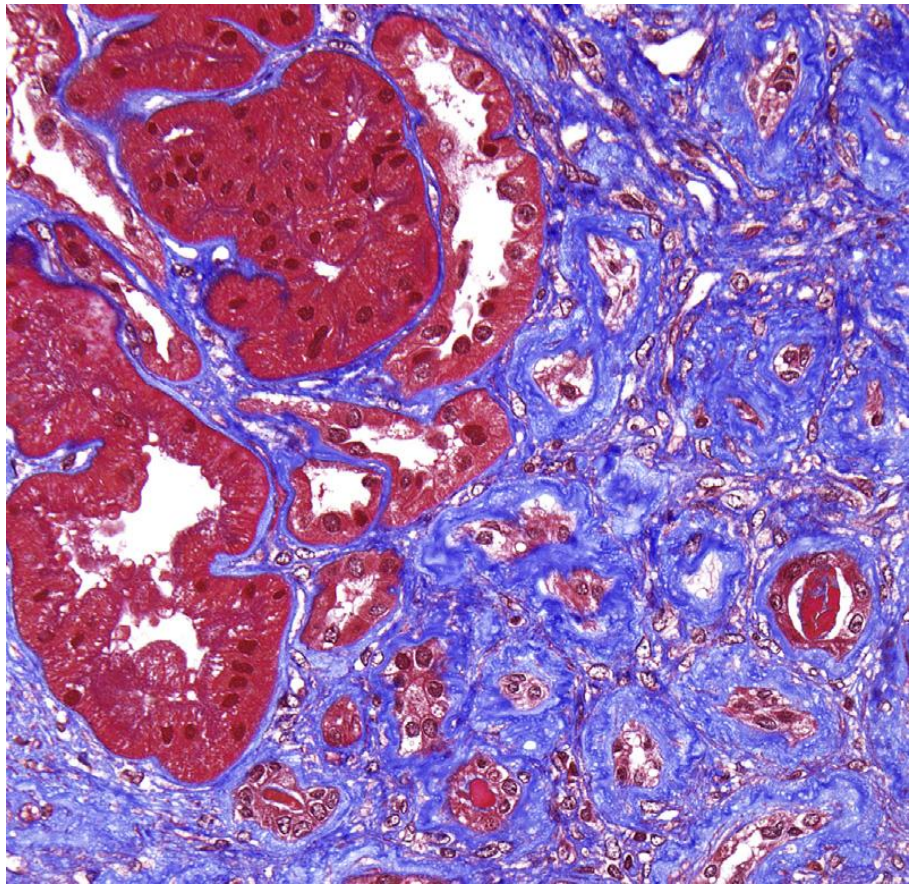
Fogo A, et al. Am J Kidney Dis. 2017;70(1):e1-e2

Chronic interstitial nephritis (CIN)

Histopathology



Chronic interstitial nephritis with interstitial lymphocytic infiltrate with occasional plasma cells and eosinophils associated with tubulitis, interstitial fibrosis, and tubular atrophy (hematoxylin and eosin stain).



Kidney biopsy from a patient with chronic kidney disease of unknown etiology demonstrating tubulointerstitial fibrosis and tubular atrophy (Masson's trichrome).

Fogo A, et al. Am J Kidney Dis. 2017;70(1):e1-e2

Chronic interstitial nephritis (CIN)

Aetiology

Medications/toxins

NSAIDs, analgesic combinations, lithium, PPIs, calcineurin inhibitors, chemotherapeutic agents, lead, cadmium, aristolochic acid, chronic radiation nephritis

Infection

Chronic pyelonephritis, malakoplakia, xanthogranulomatous pyelonephritis

Autoimmune diseases

Sjogren's syndrome, sarcoidosis, SLE, TINU, IgG4 TIN, hypocomplementemic TIN, vasculitis

Systemic diseases

Lymphoproliferative diseases, sickle cell disease, paraproteinemias, inflammatory bowel disease, cystinosis, Dent disease, atheroembolic disease, DRESS

Metabolic disorders

Chronic oxalate nephropathy, chronic uric acid nephropathy, nephrocalcinosis, hypokalemic nephropathy

Progression of ATIN

Perazella MA. Adv Chronic Kidney Dis. 2017;24(2):57-63

Laboratory Findings in Chronic interstitial nephritis (CIN)

Table 45.1 Laboratory Findings in Interstitial Nephritis

Parameter	Finding
Urinary sediment	Erythrocytes, leukocytes (eosinophils), leukocyte casts
Fractional excretion of sodium	Usually >1%
Proximal tubular defects	Glucosuria, bicarbonaturia, phosphaturia, aminoaciduria, proximal RTA
Distal tubular defects	Hyperkalemia, sodium wasting, distal RTA
Medullary defects	Sodium wasting, urine-concentrating defects

RTA, Renal tubular acidosis.

Primer on kidney diseases- 6th Edition

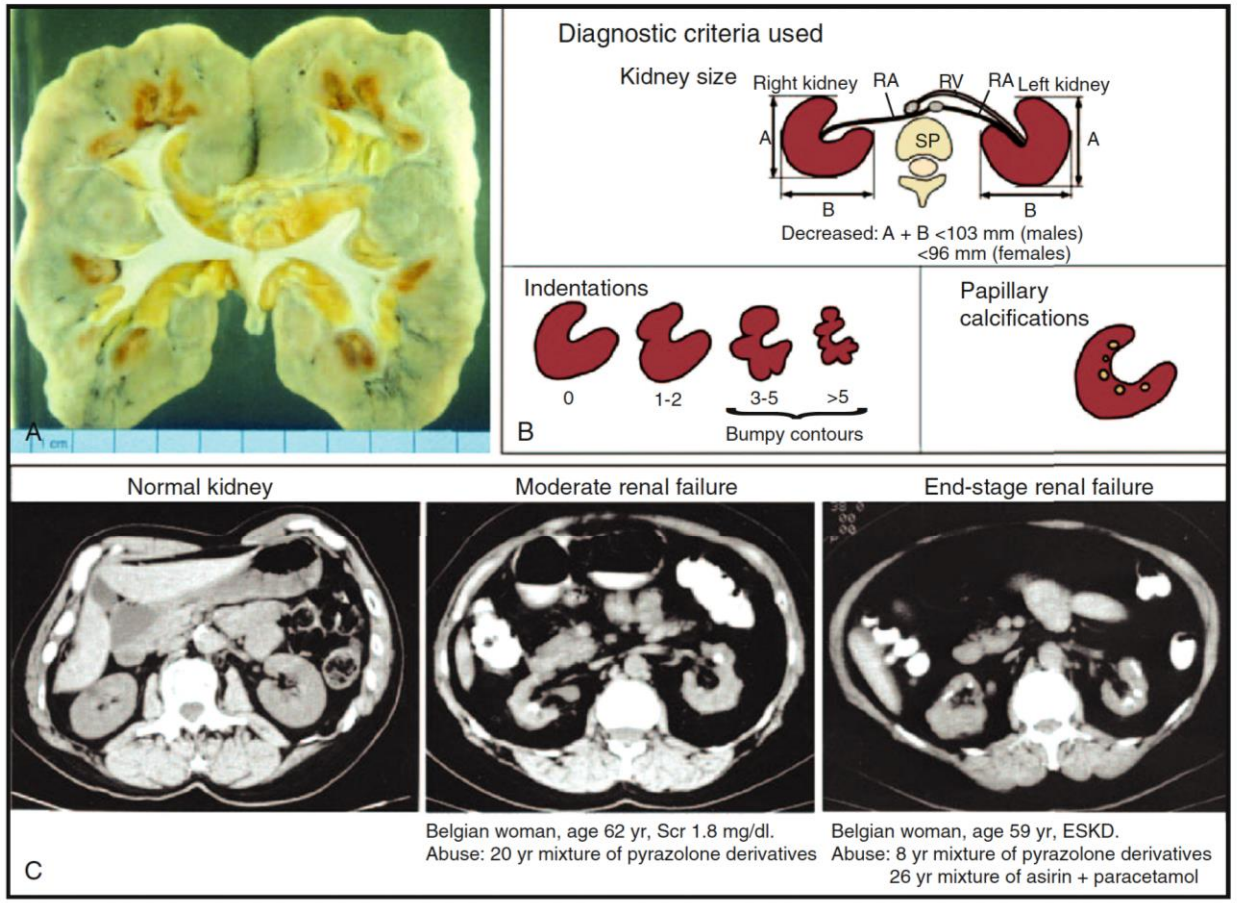
Clinical Course and Treatment of CIN

- Slowly progressive loss of kidney function observed in most cases of CIN.
- Treatment of an underlying systemic disorder
- Avoidance of drug or toxin exposure
- Therapy for interstitial fibrosis and scarring, along with the resultant impairment in kidney function, in CIN is largely supportive (except for interstitial lesions associated with lead exposure, sarcoidosis, IgG4)

Primer on kidney diseases- 6th Edition

Analgesic Nephropathy

- Chronic excessive consumption of combined analgesic preparations over many years.
- Affected patients typically have regularly ingested combination analgesic products (e.g., aspirin, phenacetin, paracetamol) that also contain codeine or caffeine
- Dose-dependent
- Medullary lesions most prominent early in the disease course.
- Early medullary capillary and tubular changes then extend to interstitial injury and fibrosis, as well as renal papillary necrosis (RPN) with calcification.



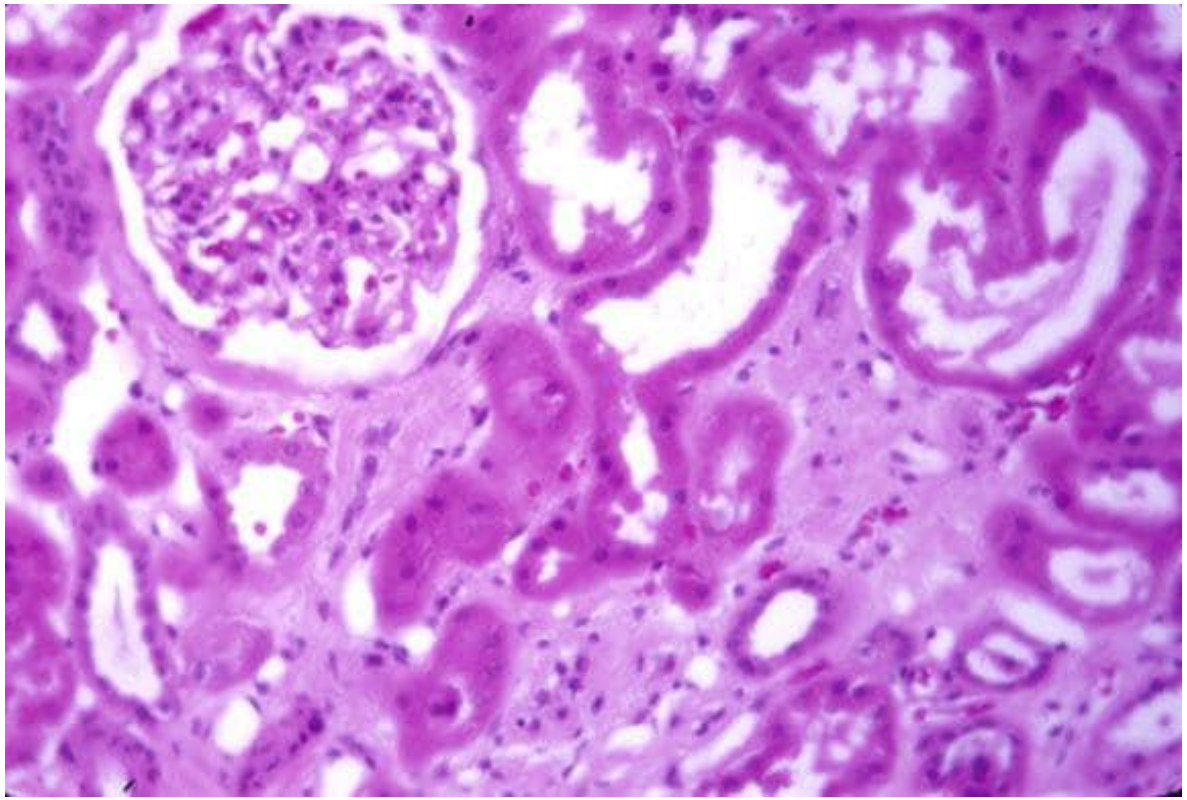
De Broe ME. J Am Soc Nephr 20:2098-2103, 2009.

Lead Nephropathy

- Environmental levels of lead have increased, including the Industrial Revolution, leaded gasoline, lead-based paint, mining operations, plumbing.
- Acute lead poisoning (blood lead levels > 80–100 µg/dL) disrupts both proximal tubular structure and function.
  - Clinically development of glucosuria, aminoaciduria, phosphaturia, or Fanconi syndrome.
  - Usually reversible after cessation of lead exposure and, if indicated, chelation therapy.
- Chronic lead poisoning may also result in lead nephropathy
  - Tubulointerstitial fibrosis, tubular atrophy, glomerular sclerosis, low-level inflammatory cell infiltrates, hypertrophic arteriolar changes.
  - Chronic lead exposure has also been shown to cause hypertension
- Chelation therapy with calcium disodium ethylenediaminetetraacetic acid (EDTA) has been advocated as a means of decreasing the progression of chronic kidney disease in patients with measurable body lead burdens.

Primer on kidney diseases- 6th Edition

Chronic Lead Nephropathy



Kidney biopsy results from a patient with chronic lead nephropathy show nonspecific tubular atrophy and interstitial fibrosis. Note the absence of an interstitial infiltrate. The one glomerulus included in the section is normal.

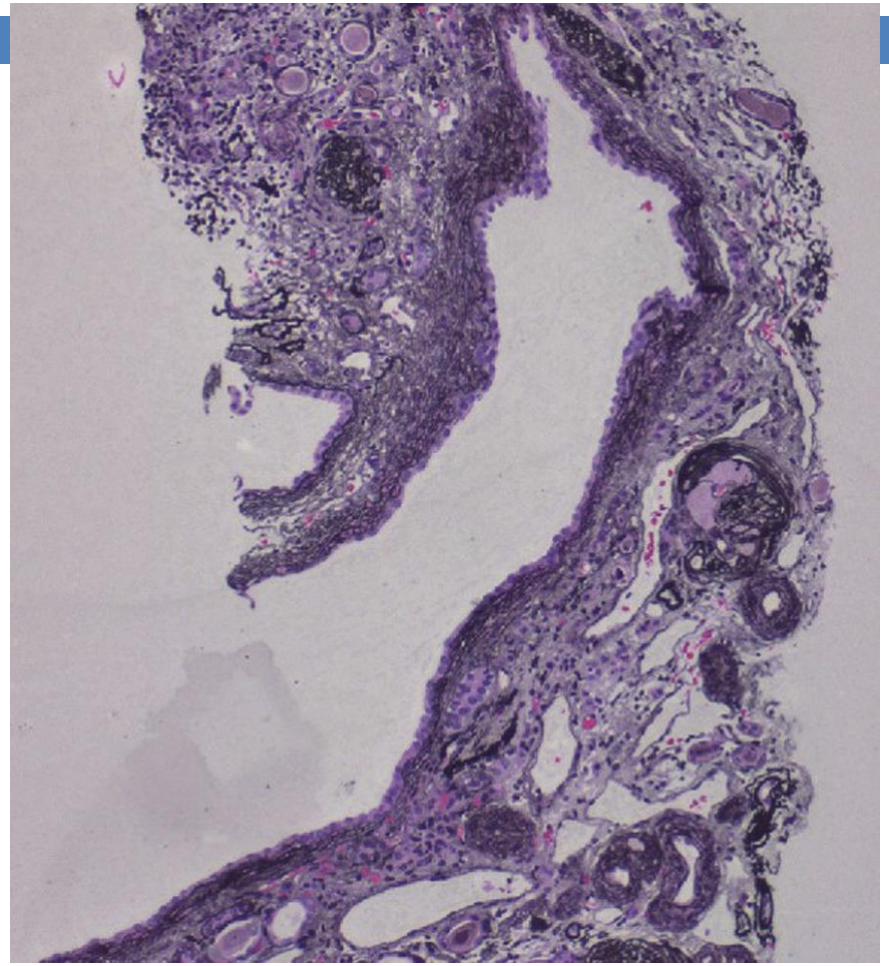
Primer on kidney diseases- 6th Edition

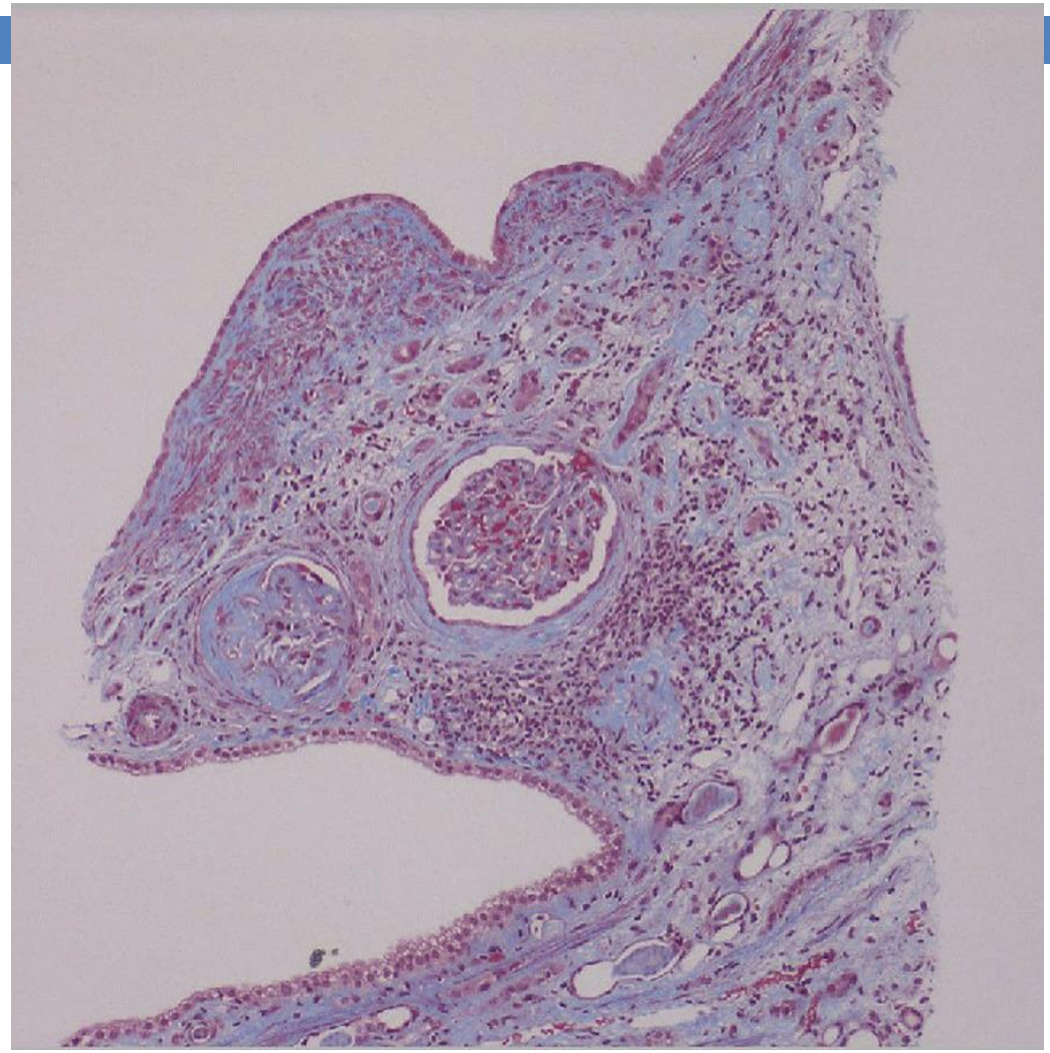
Lithium-induced nephropathy

- Chronic lithium ingestion in patients with bipolar illness has been associated with several different forms of kidney injury.
- The predominant form of chronic kidney disease associated with lithium therapy is a chronic tubulointerstitial nephropathy
- Mild kidney function impairment attributable to lithium therapy,
- End-stage kidney disease (ESKD) secondary to lithium-associated chronic tubulointerstitial nephropathy => in a small percentage of patients.
- Other renal diseases associated with lithium
  - Arginine vasopressin resistance (previously called nephrogenic diabetes insipidus)
  - Renal tubular acidosis
  - Hypercalcemia

https://www.uptodate.com/contents/renal-toxicity-of-lithium

Lithium-induced nephropathy

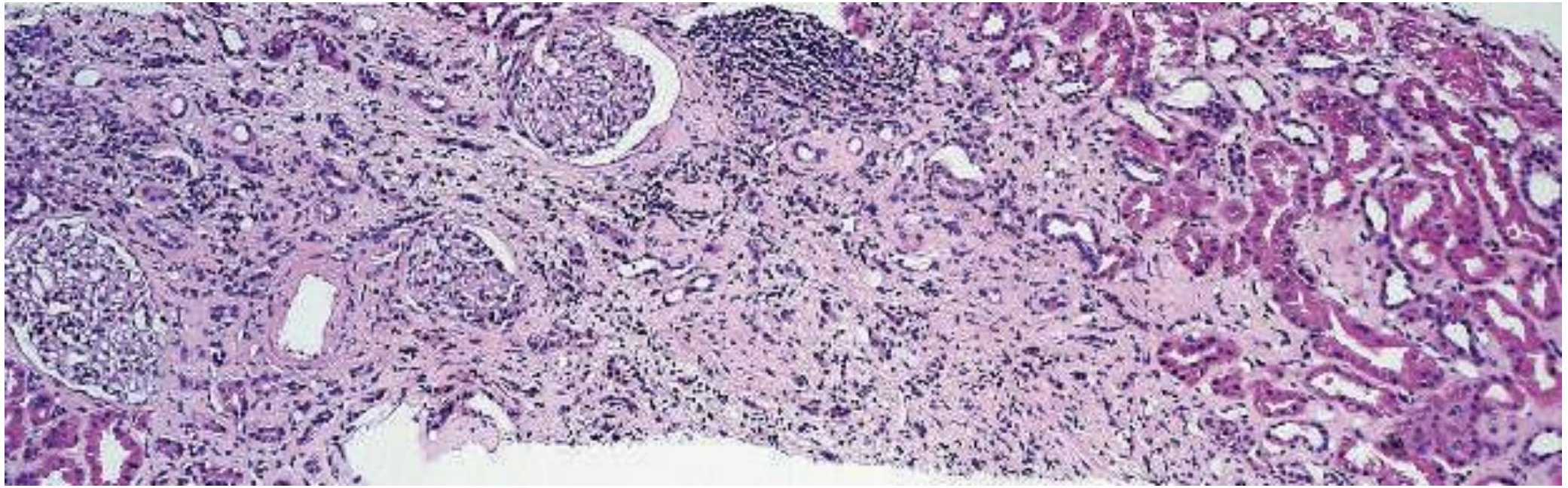




Lithium nephrotoxicity with microcystic tubular dilatation and interstitial lymphocytic infiltrate associated with tubulointerstitial fibrosis and segmental glomerulosclerosis.

Fogo A, et al. Am J Kidney Dis. 2017;69(1):e1-e2

Calcineurin Inhibitor (CNI) induced nephropathy

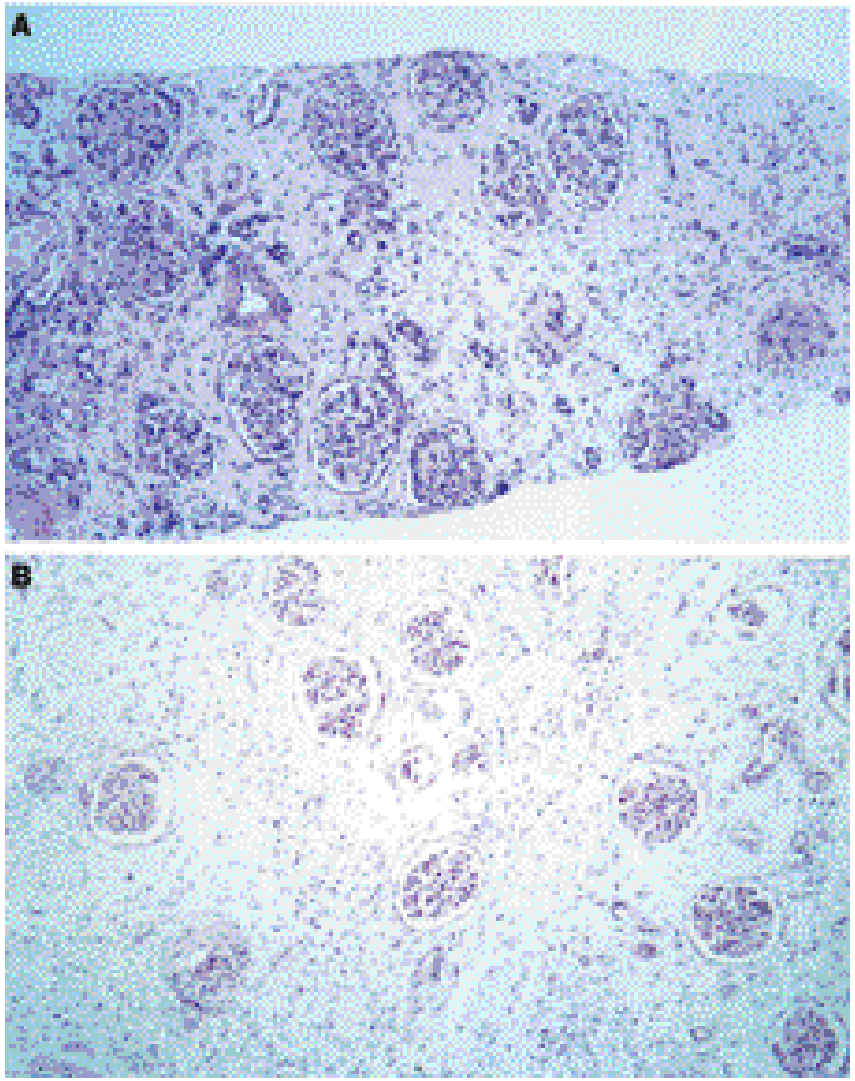


- **CNI: cyclosporine – tacrolimus**
- **May occur any time after initiation of therapy, and can affect transplant or native kidneys and present as acute or chronic reductions in kidney function**
- **Chronic CNI toxicity shows a striped pattern interstitial fibrosis with proportional tubular atrophy.**

Liptak P and Ivanyi B. Nat Clin Pract Nephrol 2006;2(7):398-404

Aristolochic Acid associated Nephropathy (Chinese Herb Nephropathy)

- Rapidly progressive interstitial nephropathy reported after the introduction of Chinese herbs in a slimming regimen.
- It is characterised by early, severe anaemia, mild tubular proteinuria and initially normal arterial blood pressure in half of the patients.
- Renal histology shows unusual extensive, virtually hypocellular cortical interstitial fibrosis associated with tubular atrophy and global sclerosis of glomeruli decreasing from the outer to the inner cortex.
- Urothelial malignancy of the upper urinary tract develops subsequently in almost half of the patients.



Lord GM et al. Lancet 1999;354:481-2, Cosyns JP. Drug Saf. 2003;26(1):33-48.

Balkan Endemic Nephropathy

- Chronic tubulointerstitial disease associated with a high frequency of urothelial atypia, occasionally culminating in tumors of the renal pelvis and urethra.
- Affected patients most commonly reside in Southeastern Europe - the Balkans: Serbia, Bosnia and Herzegovina, Croatia, Romania, and Bulgaria.
- BEN is most likely to occur among those living along the confluence of the Danube River, a region in which the plains and low hills generally have high humidity and rainfall.
- The currently accepted cause of BEN is exposure to aristolochic acid.
- In contrast to the classic presentation of AA nephropathy, which is characterized by a rapid decline in kidney function (six months to two years), BEN is slowly progressive (10 to 20 years), however, likely related to low-level exposure.

https://www.uptodate.com/contents/balkan-endemic-nephropathy

Chronic Interstitial Nephritis due to Metabolic Disorders

- **Chronic urate nephropathy**
- **Hypokalemic nephropathy**
- **Hypercalcemic nephropathy**
- **Hyperoxaluria**

Chronic Interstitial Nephritis caused by Hereditary Diseases of the Kidney

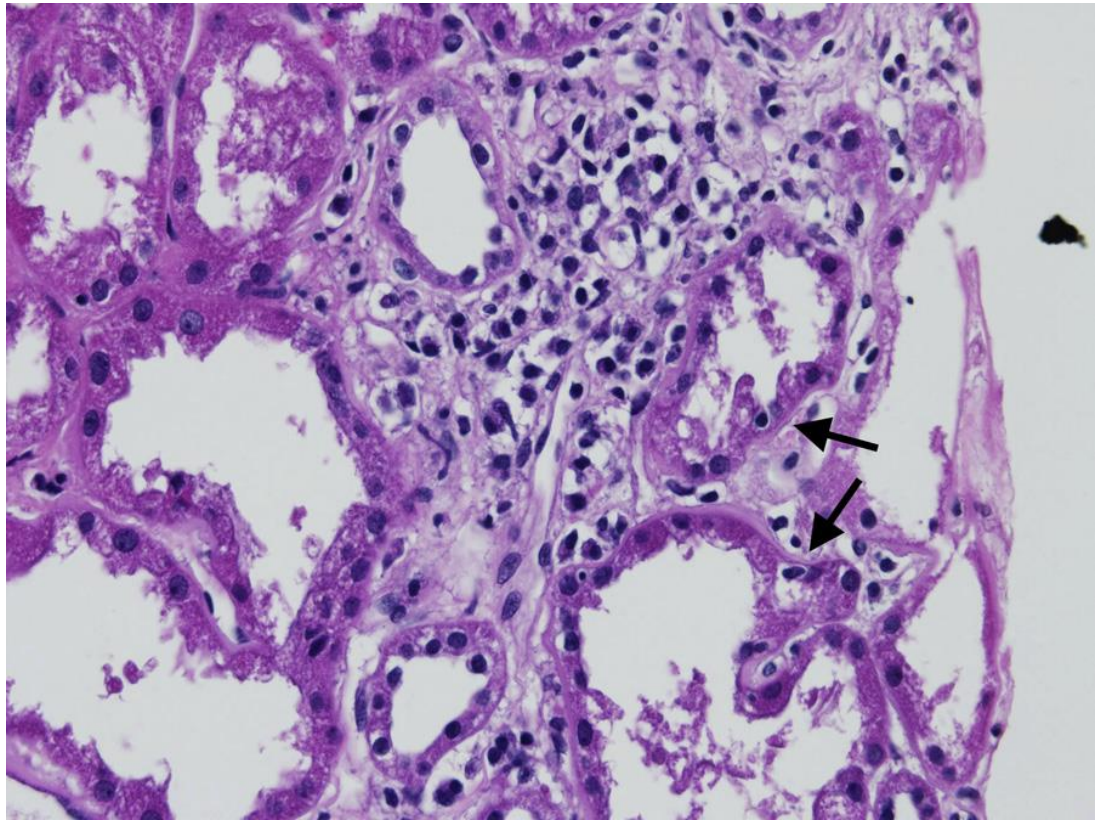
- **Nephronophthisis (NPHP)**
  - Autosomal recessive cystic kidney disease and is one of the most frequent genetic causes for kidney failure (KF) in children and adolescents.
  - It is caused by variants in a large number of genes that encode proteins involved in the function of primary cilia, basal bodies, and centrosomes, resulting in kidney disease and extra-renal manifestations including retinal degeneration, cerebellar ataxia, and liver fibrosis.
- **Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)**
  - Characterized by tubular damage and interstitial fibrosis in the absence of glomerular lesions, with inescapable progression to end-stage renal disease.
  - ADTKD is caused by mutations in at least five different genes, including UMOD, MUC1, REN, HNF1B and, more rarely, SEC61A1.
- **Cystinosis**
  - Rare autosomal recessive lysosomal storage disorder caused by a malfunctioning of the protein cystinosin, encoded by the CTNS gene. It is characterized by the accumulation of cystine within cellular lysosomes

Autoimmune and systemic diseases associated with Chronic interstitial nephritis

- Sjogren's Syndrome
- Sarcoidosis
- Systemic lupus erythematosus
- IgG4 related disease

Chronic Interstitial Nephritis in Sjogren's Syndrome

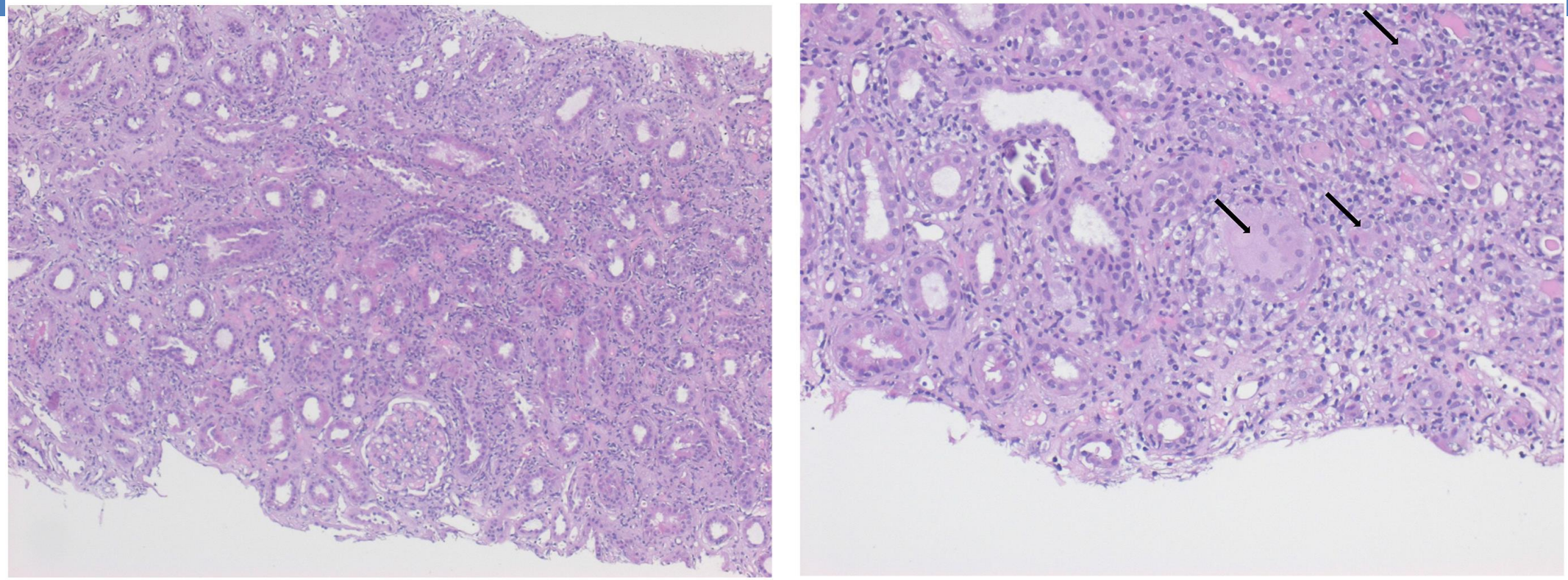
- **Kidney disease manifests typically 2-3 years after onset of exocrine gland manifestations as insidious low-grade proteinuria and slowly decreasing kidney function, due to acute or chronic interstitial nephritis, in about two-thirds of those who undergo kidney biopsy.**
- **Patients may show distal renal tubular acidosis, and less frequently proximal renal tubular acidosis with full-blown Fanconi syndrome, with glycosuria, aminoaciduria, and low-level tubular proteinuria.**



Sjogren syndrome with interstitial lymphoplasmacytic infiltrate with tubulitis (arrows) involving areas of interstitial fibrosis (hematoxylin and eosin stain).

Fogo A, et al. Am J Kidney Dis. 2017;69(6):e29-e30

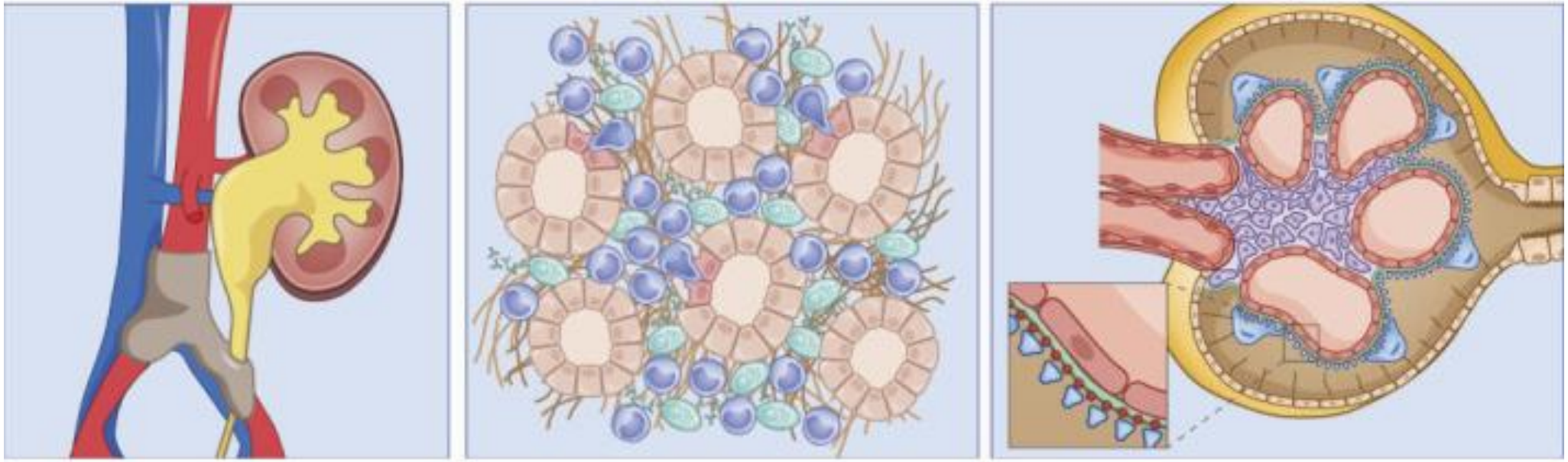
Chronic Interstitial Nephritis in Sarcoidosis



- **Kidney manifestations include interstitial nephritis with or without granuloma formation, and nephrocalcinosis and/or nephrolithiasis resulting from abnormal calcium homeostasis. The classic kidney lesion is noncaseating granulomatous interstitial nephritis. However, hypercalciuria and hypercalcemia are most often responsible for clinically significant kidney disease.**

Bonella F, et al. J Autoimmun. 2024 Dec;149:103207, https://www.uptodate.com/contents/kidney-disease-in-sarcoidosis

IgG4 related disease

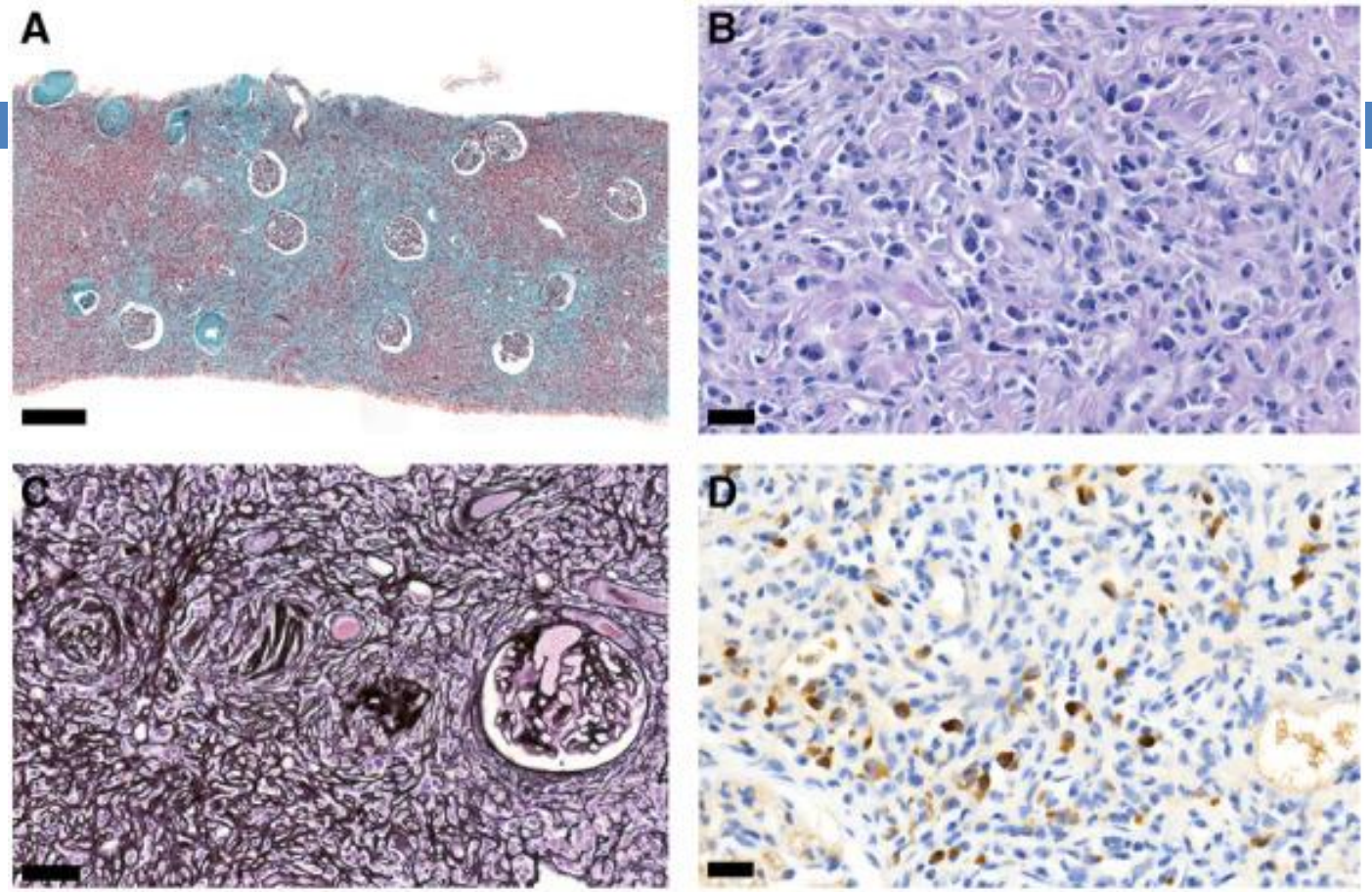


Retroperitoneal fibrosis	Tubulointerstitial nephritis	Membranous nephropathy
• AKI or CKD • No proteinuria • Usually normal C3 and C4	• AKI or CKD • Tubular proteinuria • Frequently reduced C3 and/or C4	• AKI or CKD • Nephrotic-range proteinuria • Usually normal C3 and C4

IgG4-related tubulo-interstitial nephritis is the commonest form of parenchymal IgG4-related kidney disease. It is typically characterized by proteinuria of mild entity and a variable degree of kidney failure, which may be acute or chronic.

Peyronel F, Vaglio A. Clin J Am Soc Nephrol. 2023;18(8):994-996.

IgG4 related disease



(A) Light microscopic kidney biopsy findings in an IgG4-TIN patient with extensive interstitial fibrosis, tubular atrophy, and interstitial inflammation (trichrome stain). (B) High-power view of lymphoplasmacytic infiltrate within the kidney interstitium with interlacing fibrils of storiform fibrosis (Periodic acid–Schiff stain). (C) Typical storiform fibrosis in IgG4-TIN (periodic acid-methenamine silver stain). Lymphocytes and plasma cells are encircled by collagenous tissue and diffuse fibrosis. (D) Immunohistochemistry for IgG4 showing numerous interstitial IgG4-positive plasma cells.

Chaba A, et al. Clin J Am Soc Nephrol. 2023;18(8):1031–1040.

Take home message

The renal interstitium has gained increased interest due to the involvement in fibrosis and the progression of chronic kidney disease. The interstitium increases in volume due to accumulation of fibrotic extracellular matrix.

Acute interstitial nephritis is a common cause of acute kidney injury usually due to medications like antibiotics, PPIs and NSAIDs.
Good renal prognosis in 65% of cases with withdrawal of causative agent.

There are many primary and secondary causes of chronic interstitial nephritis.

Slowly progressive loss of kidney function observed in most cases.

Therapy for interstitial fibrosis and scarring is mainly supportive.