Goal: to examine tubular and interstitial pathology

Objectives:
1. Examine the epidemiology, clinical and laboratory features of acute infectious interstitial nephritis and the role of predisposing factors
2. Contrast and compare acute versus chronic pyelonephritis
3. Examine the clinical and laboratory features of acute drug-induced interstitial nephritis associated with infection versus drug reaction
4. Contrast and compare acute NSAIDs-induced interstitial nephritis with minimal change-like disease versus idiopathic minimal change disease
5. Describe examples of metabolic tubulointerstitial nephritis
6. Contrast and compare chronic pyelonephritis with idiopathic minimal change disease
7. Describe the relationship between tubular injury and interstitial nephritis
8. Describe the 2 main mechanisms of tubular injury
9. Identify the main causes of the urinary tract obstruction

Robbins pp 564-569

Tubulo-interstitial nephritis = inflammatory involvement primary - primarily involving the renal tubules and interstitium

(I) Infectious, the most common diseases of the kidney
(II) Non-infectious:
• Drug and toxin-induced, the second most common
  • metabolic (urate, oxalate, hypercalcemia)
  • neoplasm (multiple myeloma)

secondary - associated with other diseases such as glomerulonephritis, vascular, cystic...
TIN: tubulo-interstitial nephritis

- In general, tubules and interstitium are frequently involved together, either from the beginning or subsequently, with disease progression.
- In metabolic diseases in particular, initially, mainly tubules are affected (acute uric acid nephropathy, light chain cast nephropathy).
- With progression of the disease process there is also involvement of the interstitium.

Infectious tubulo-interstitial nephritis

Pyelonephritis: inflammation affecting the tubules, interstitium, and renal pelvis

Acute and chronic

Acute pyelonephritis, mostly bacterial infection

Pathways of infection
- Hematogenous
  - Obstruction, immunosuppression, diabetes, sepsis, septicemia, endocarditis, non-enteric streptococci, fungi
- Ascending
  - Reflux, obstruction, other abnormality of the urinary tract

Colonization of distal urethra/introitus, urinary bladder: multiplication of bacteria in the bladder, urine retention, vesicoureteral reflux

VESICO-URETERAL REFUX = INCOMPETENCE OF THE VESICOURETERAL VALVE

A. Competent valve = one way valve
   No retrograde flow of urine
B. Incompetent valve = reflux of urine into ureters, i.e. vesicoureteral reflux (reflux = flowing back)
Grades of vesicoureteric reflux

Voiding cystogram with bilateral grade III reflux (widened ureters & distorted calyces)

ACUTE PYELONEPHRISIS – 1

1. Clinical: acute versus chronic
   - acute: sudden onset, costovertebral angle pain, fever, malaise, frequency/urgency, urosepsis in severe infection
   - chronic - insidious

2. Epidemiology:
   - age and sex

3. Etiology/pathogenesis:
   - bacterial infections:
     - Gram (-) rods: E.coli, Proteus, Klebsiella, Enterobacter, 85%;
     - Gram (+): Streptococcus faecalis (Strap D, enteric in origin)
   - Fungi, viruses - immunocompromised
   - predisposing factors: instrumentation/catheterization, urinary tract obstruction, congenital abnormalities, stones, tumors, enlarged prostate, prolapsed uterus, pregnancy, neurogenic bladder, vesicoureteral reflux
   - Other: diabetes mellitus, immunosuppression, immunodeficiency

ACUTE PYELONEPHRISIS – pathology

Acute ~ reversible

Patchy interstitial suppurative inflammation, tubular necrosis medulla → cortex, focal abscesses perinephric abscess, papillary necrosis (sac of pus)

Fungal infection – different treatments!
ACUTE PYELONEPHRITIS – 2

4. Pathology:
   - acute inflammation with PMNs in tubules & interstitium

5. Laboratory:
   - CBC
   - urinalysis and culture

6. Prognosis:
   - good for acute onset
   - renal failure for chronic

7. Treatment:
   - anti-bacterials/causative agent
   - predisposing factors
Chronic pyelonephritis - gross

- chronic tubulo-interstitial renal disorder
- many cases (but not all) bacterial in origin
- onset insidious, scarring
- gradual renal insufficiency
- routine u/a: pyuria/proteinuria
- loss of concentrating ability: polyuria & nocturia
- X-ray – contracted kidneys/deformed calyceal system
- chronic obstructive pyelonephritis
- reflux nephropathy – hypertension in children

Chronic pyelonephritis ~ irreversible microscopic

Intestinal lymphocytes
Glomerular/periglomerular fibrosis & sclerosis
Dilated tubules "thyroidization"
Vascular changes = "benign" hypertension

Xanthogranulomatous pyelonephritis = chronic pyelonephritis mimicking malignancy

Proteus, obstruction
Tubulointerstitial nephritis

noninfectious tubulointerstitial nephritis
drug and toxin-induced, the second most common

Acute drug-induced interstitial nephritis

1. Clinical presentation;
   - rash – 25%
   - acute renal failure – 50%, older patients

1. Epidemiology:
   - all ages

2. Etiology/pathogenesis: adverse reaction to drugs
   - IgE and T cell mediated immune reaction to drug
   - synthetic antibiotics, diuretics, NSAIDs

Acute drug-induced interstitial nephritis - pathogenesis:

Immune mechanism:
- idiosyncratic and not dose-related
- hypersensitivity: latent period, eosinophilia, rash, recurrence after re-exposure
- IgE-mediated (type I hypersensitivity reaction)
- positive skin test to drug hapten – T-cell mediated
- delayed hypersensitivity reaction (type IV)

Drugs act as haptens, which covalently bind to cells and become immunogenic
IgE and/or cell-mediated immune reactions to tubular cells/their basement membrane

Drug-induced acute interstitial nephritis is a common cause of acute kidney injury

Biopsy-proven acute interstitial nephritis - drug-induced >70%
Acute drug-induced interstitial nephritis – pathology

Kidney biopsy:
• interstitial inflammation
• often abundant eosinophils
• edema

Skin rash

Acute drug-induced interstitial nephritis

4. Pathology:
- interstitial inflammation
- often abundant eosinophils and edema

5. Laboratory tests:
- renal failure
- blood/urine eosinophilia

6. Prognosis:
- good in acute
- renal failure in chronic

7. Treatment
- drug withdrawal !!!
- steroids

Drug-induced interstitial nephritis
– typical presentation:

A 29 yo man has developed a fever and skin rash over the past 3 days. Five days later he had increasing malaise and sought medical attention. PE: maculopapular erythematous rash on his trunk was nearly faded away. His temperature was 37.1 °C, his BP = 135/85 mm Hg. Serum creatinine: 2.8 mg/dL. UA: 2+ proteinuria, 1+ hematuria, glucose (-), ketones (-), nitrite (-). Urine sediment showed RBCs and WBCs, some of which were eosinophils...

Clinical diagnosis: suspect acute drug-induced interstitial nephritis

Immune mechanism
Latent period, eosinophilia & rash
Idiosyncratic nature of the drug reaction (i.e. the lack of dose dependency)
Recurrence of hypersensitivity after re-exposure to the same/similar drug
NSAIDS: nonsteroidal antiinflammatory drugs

• Acute hemodynamic (inhibition of prostaglandin synthesis) – see a separate lecture
• Acute hypersensitivity interstitial nephritis

**Clinical: renal failure + nephrotic syndrome**
Renal failure is due to interstitial nephritis

• Pathology:
  • interstitial nephritis
  • minimal-change disease-like glomeruli

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Question 14

A 32 yo computer programmer presents with generalized edema and unintentional weight gain. In general he has been healthy. Only recently he complained of a lower back pain during a period requiring long hours at the computer… However, the pain was relieved with some over the counter meds. His urinalysis shows 3+ protein. His serum creatinine is 5.0 MG/DL [n=0.7-1.5]. You are suspecting that…

a. His biopsy will show crescents
b. His biopsy will look normal by light microscopy
c. His biopsy will show subepithelial deposits
d. He most likely has interstitial nephritis and minimal change disease
e. He has postinfectious glomerulonephritis

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Several “over the counter” preparations can lead to tubulo-interstitial nephritis!!!

**Chinese herb nephropathy:**
Aristolochic acid = potent nephrotoxin
- rapidly progressive interstitial fibrosis and end-stage renal disease (ESRD)

*ESRD in young women using a Chinese herb as part of a slimming regimen*
A 26 yo female is discovered to have elevated serum creatinine level. She has been healthy, well nourished. In fact she has been trying to shed some weight but with no great success...

- You suspect cancer as a cause of her renal failure
- You ask her about all her prescription medications
- She probably has reflux nephropathy
- She has acute pyelonephritis
- You ask her about her about herbal preparations

Other causes of non-infectious tubulointerstitial nephritis:

- metabolic (urate, oxalate, hypercalcemia)
- neoplasm (multiple myeloma)

TIN: tubulo-interstitial nephritis

- in general, tubules and interstitium are frequently involved together, either from the beginning or subsequently, with disease progression
- in metabolic diseases in particular, initially, mainly tubules are affected (acute uric acid nephropathy, light chain cast nephropathy)
- with progression of the disease process there is also involvement of the interstitium
**Urate nephropathy:**
- acute, predominantly tubular component, chronic – also interstitial...

**Acute uric acid nephropathy:**
- leukemia/lymphoma on chemotherapy (tumor lysis syndrome)

**Chronic urate (gouty) nephropathy**
- tophi: urate crystals + inflammatory reaction

**Frozen section – polarized light**

**Nephrolithiasis - stones**

**Outline of urate crystal**

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**Oxalate nephropathy:**
- acute, predominantly tubular component, chronic – also interstitial...

**Oxalate nephropathy:**
- primary (hereditary) hyperoxaluria
- ethylene glycol (antifreeze) intoxication (acute)
- enteric hyperoxaluria
- exposure to the anesthetic agent methoxyflurane
- pyridoxine (vitamin B6) deficiency
- excessive ingestion of vitamin C, diet rich in oxalic acid (rhubarb, cocoa, parsley, nuts)

**Chronic oxalate nephropathy after bariatric surgery**
(slimming surgery causing malabsorption)

**Calcium oxalate crystals:**
- translucent crystals of different shapes, predominantly intraluminal,
  under polarized light strongly birefringent, fan-like, strap-like, or irregular shapes

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**Multiple myeloma - plasma cell malignancy**

- Uric acid (therapy)
- Hypercalcemia — bone resorption
- Light chain casts: monoclonal

Light chains produced by malignant plasma cells are circulating in blood and filtered into urine, subsequently precipitate in distal tubules as intratubular light chain casts

**RENAL FAILURE!!!**
TIN: tubulo-interstitial nephritis - summary

Inflammatory disease primarily involving the renal tubules and interstitium

1. infectious: acute or chronic pyelonephritis (UTI, reflux nephropathy, etc)
2. drugs induced interstitial nephritis – IgE and T-cell mediated immune reaction to drug (antibiotics, NSAIDs)
3. metabolic diseases (urate, oxalate, hypercalcemia)
4. multiple myeloma (light chain cast nephropathy)

Acute tubular injury (ATI)

ischemic, toxic, combined

1. Typical clinical presentation
   - rapid reduction of renal function and urinary output (oliguria)
   - uremia and signs of fluid overload, electrolyte abnormalities, acidosis
   - "non-oliguric" ATI (up to 50% of ATI)
2. Epidemiology
   - most common cause of acute renal failure
3. Etiology/pathogenesis
   - ischemic tubular injury
   - toxic injury

see also separate lecture
Acute Tubular Injury (ATI)

- necrosis of segments of the tubules (typically proximal tubules)
- FOCAL
- proteinaceous casts in distal tubules
- interstitial edema
- disturbances in blood flow (intra-renal vasoconstriction)
- reduced GFR (glomerular filtration rate)
- diminished delivery of oxygen/nutrients to tubular epithelial cells

**Acute Tubular Injury (ATI) pathology**

Normal tubules (left) versus ischemic tubules (right)

**ATI**

- see also a separate lecture

4. Pathology
   - tubular necrosis, exfoliation...regeneration

5. Laboratory tests
   - renal failure
   - diagnosis is usually based on clinical grounds

6. Prognosis
   - reversible
   - initiation, maintenance, recovery

7. Treatment
   - supportive
ATI – typical presentation:

A 20 yo college student was involved in a motorcycle accident with acute loss of blood. Upon arrival of paramedics, his BP was low and after stabilization of acute bleeding he was transported to a hospital, where he received a transfusion of 3 units of packed RBCs. Over the next week his serum creatinine increased to 4 mg/dL and his urinary output decreased.

Clinical diagnosis:
- acute tubular injury (ATI), primarily ischemic.
- He underwent hemodialysis for the next 2 weeks and subsequently developed marked polyuria with urinary output close to 3 L/day.
- His renal function gradually returned to normal.

ATI

- **Ischemic**: BP drop, severe trauma, acute pancreatitis
- **Toxic**: drugs (antibiotics), contrast dyes, poisons (heavy metal), organic solvents
- **Combined** (ischemic + nephrotoxic):
  - mismatched blood transfusion/other hemolytic crises (hemoglobinuria)
  - skeletal muscle injury (myoglobinuria)
  - intratubular casts, crystals
  - frequently also interstitial component as well

ATI – combined - typical presentation - 1

College student involved in a motorcycle accident severe blunt trauma to the abdomen and extremities oliguria and dark brown urine over 3 days...

Urine dipstick analysis positive for blood
Urine microscopic urinalysis negative for RBCs
BUN increased to 38 mg/dL...

Clinical diagnosis:
- acute tubular injury (ATI) toxic and ischemic
- dialysis for the next 3 weeks improvement
- Urinary output >3 L/24 hrs for 1 week before BUN normalized
This patient sustained muscle crash injury that resulted in myoglobinemia and myoglobinuria.

The large amount of excreted myoglobin was toxic to tubules and this patient developed acute tubular injury (ATI).

With supportive care, the tubular epithelium can regenerate, and renal function can be restored.

During the recovery phase there is polyuria because the glomerular filtrate cannot be adequately reabsorbed by the damaged tubular epithelium.

Acute antifreeze poisoning: calcium oxalate in tubules (polarized light)

Chronic: bariatric surgery (slimming surgery causing malabsorption) primary hyperoxaluria (see also #27-29)

Ethylene glycol is a colorless, odorless, sweet liquid, found in antifreeze. It may be drunk accidentally or purposefully. When broken down by the body it results in glycolic and oxalic acid. Calcium oxalate crystals may be seen in the urine and can be visualized under polarized light.

Acute uric acid nephropathy: leukemia/lymphoma on chemotherapy (tumor lysis syndrome)

Uric acid crystals in tubules (frozen section, polarized light)

Chronic urate (gouty) nephropathy - tophi: urate crystals + inflammatory reaction (see also #27-29)

Urinary tract obstruction

- Infection, tumors
- Stones – chemical analysis! dietary changes....
- Hydronephrosis (other lectures)

Staghorn calculus and 2nd hydronephrosis
A retired dentist developed a sudden onset of a severe flank pain radiating to the back with nausea and vomiting. Urinalysis showed 10–15 red blood cells per high power field.

His past medical history includes type 2 diabetes and hypertension.

What should be considered in the differential diagnosis?

a. Nephrolithiasis
b. Acute tubulointerstitial nephritis
c. Acute tubular injury
d. Chronic pyelonephritis
e. Acute cystitis
Renal calculi - typical case:
- sudden onset of severe flank pain
- radiating to the back with nausea and vomiting
- urinalysis: 10–15 red blood cells per high power field

Patient described in a previous case passed spontaneously a stone. What would be the best choice?

a. Send stone to pathology for chemical analysis
b. Send stone to pathology for photographic analysis
c. Most likely atheromatous stone
d. Give back stone to patient for safe keeping
e. Discard the stone if patient is not interested in keeping it

questions?
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