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
4. Contrast and compare the clinico-pathologic picture of tubulointerstitial nephritis associated with infection versus drug reaction
5. Contrast and compare acute NSAIDs-induced interstitial nephritis with minimal change-like disease versus idiopathic minimal change disease
6. Describe examples of metabolic tubulointerstitial nephritis
7. Explain 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

Outline:

Tubulointerstitial nephritis:
(i) infectious, acute, chronic, reflux nephropathy
(ii) Drug induced (antibiotics, analgesic nephropathy, NSAIDs, Aristolochic acid)
(iii) Other: urate, oxalate, hypercalcemia, “myeloma kidney”

Acute Tubular Injury (ATI):
(i) ischemic,
(ii) toxic,
(iii) combined

Tubulointerstitial nephritis:
- primary tubulointerstitial nephritis (in inflammatory diseases primarily involving the renal tubules and interstitium)
  o infections, acute and chronic
  o drugs and toxins
  o metabolic diseases (urate, oxalate, hypercalcemia)
  o neoplasms (multiple myeloma)
- secondary tubulo-interstitial nephritis – associated with other diseases (glomerulonephritis, autoimmune…)

UTI (urinary tract infection): see also separate lecture

ACUTE PYELONEPHRITIS: bacterial infection
Acute pyelonephritis can be caused either by ascending infection or by hematogenous spread of bacteria, at times with formation of abscess in the kidney and even with a papillary necrosis. Pathways of infection – please see Fig.20-26

- hematogenous pathway, associated with reflux, obstruction, immunosuppression, diabetes, septicemia, endocarditis; can be caused by non-enteric bacteria (streptococci), fungi

- ascending pathway may occur following colonization of distal urethra/introitus, with subsequent involvement of the urinary bladder, multiplication of bacteria in the bladder, and ascending progression of the bacterial spread.

REFLUX = a flowing back due to incompetence of a valve

L. miction/mingere = to make water

ACUTE PYELONEPHRITIS – 1
1. Clinical: acute versus chronic
   a. acute: sudden onset, costovertebral angle pain, fever, malaise, frequency/urgency, urosepsis in severe infection
2. chronic: insidious
2. Epidemiology: age and sex

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

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

5. Laboratory:
   a. CBC
   b. urinalysis and culture

6. Prognosis:
   a. good for acute onset
   b. renal failure for chronic

7. Treatment:
a. anti-bacterials/causeative agent
b. predisposing factors

Clinical diagnosis: UA (urinalysis) with PMNs, blood cultures, urosepsis in severe infection. *Beware of fungal infection which requires different treatments*

Epidemiology of acute pyelonephritis (age & sex predilection, etc) will be discussed in a separate lecture.

Papillary necrosis may be due to:
- analgesics
- diabetes
- sickle cell anemia
- obstruction
- TB (tuberculosis)

Analgesic nephropathy is the result of consumption of large amounts of certain analgesics; may result in papillary necrosis and progressive renal dysfunction

Polyoma virus nephropathy = interstitial nephritis caused by polyoma virus in immunocompromised patients. It occurs in 5% of renal transplant patients. Diagnosis by immune stain

Chronic pyelonephritis = chronic tubulo-interstitial renal disorder
- many cases, but not all, are bacterial in origin
- onset may be insidious, with scarring of the involved kidney and gradual progression of renal insufficiency
- routine UA: pyuria/proteinuria
- loss of concentrating ability: polyuria & nocturia
- X-ray – contracted kidneys/deformed calyceal system

Chronic obstructive pyelonephritis due to reflux nephropathy in children is frequently associated with HTN

Pathology:
- grossly scarred and contracted kidney
- microscopic: interstitial lymphocytes, periglomerular fibrosis and glomerular sclerosis, dilated tubules “thyroidization”, vascular changes similar to those seen in “benign” HTN

Xanthogranulomatous pyelonephritis: a distinct form of pyelonephritis typically associated with infection by *Proteus*, obstruction and stones. Clinically and radiologically may mimic cancer!

**Acute drug-induced interstitial nephritis:**

1. Clinical presentation;
   a. rash – 25%
   b. acute renal failure – 50%, older patients
2. Epidemiology:
   a. all ages
3. Etiology/pathogenesis
   a. IgE and T cell mediated immune reaction to drug, synthetic antibiotics, diuretics, NSAIDs
4. Pathology:
   a. interstitial inflammation
   b. often abundant eosinophils and edema
5. Laboratory tests:
   a. renal failure
   b. blood/urine eosinophilia
6. Prognosis:
   a. good in acute
   b. renal failure in chronic
7. treatment
   a. drug withdrawal !!!

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…
Hx: recent hx of treatment with antibiotic (ampicillin) for a sore throat…

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:
   • acute hemodynamic effects (inhibition of prostaglandin synthesis) see separate lecture
   • acute hypersensitivity interstitial nephritis
   • in some patients: interstitial nephritis + minimal change disease with nephrotic syndrome. Development of interstitial nephritis is typically associated with renal function impairment.

Chinese herb nephropathy:
   • due to aristolochic acid
   • microscopic picture: interstitial fibrosis with relative paucity of leukocytes
   • associated with increased incidence of urothelial carcinoma
• several “over the counter” preparations can lead to tubulo-interstitial nephritis!

Urate nephropathy:
1. acute in patients with leukemia/lymphoma on chemotherapy (rapid cell turnover, “tumor lysis syndrome”)
2. chronic urate nephropathy, aka gouty nephropathy: tophi consisting of aggregates of urate crystals surrounded by inflammatory reaction
3. nephrolithiasis – stones

Oxalate nephropathy:
- primary (hereditary) hyperoxaluria
- ethylene glycol (antifreeze) intoxication (acute)
- enteric hyperoxaluria (Crohn’s disease)
- 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)

Kidney in multiple myeloma (plasma cell malignancy):
• Uric acid (increased cell turnover)
• Hypercalcemia – bone resorption
• Light chain casts nephropathy with renal failure. Monoclonal immunoglobulin light chain which are produced by the abnormal plasma cell clone circulate with blood and are filtered into tubules where they precipitate as intra-tubular casts with obstruction and acute or subacute renal failure
• light chain amyloidosis – monoclonal light chain is deposited in various tissues, including kidney, as fibrillar deposits (amyloid) or non-fibrillar deposits (light chain deposition disease).

TIN: tubulo-interstitial nephritis – summary
• Inflammatory disease primarily involving the renal tubules and interstitium
• infectious: acute or chronic pyelonephritis (UTI, reflux nephropathy, etc)
• drugs induced interstitial nephritis – IgE and T-cell mediated immune reaction to drug (antibiotics, NSAIDs)
• metabolic diseases (urate, oxalate, hypercalcemia)
• multiple myeloma (light chain cast nephropathy)
• in general, tubules and interstitium are frequently involved together
• in metabolic diseases – initially mainly tubules are affected (acute uric acid nephropathy, light chain cast nephropathy) but with progression there is also involvement of interstitium
Acute tubular injury (ATI) (see also separate lecture)

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 ATN)
2. Epidemiology: most common cause of acute renal failure
3. Etiology/pathogenesis: tubular injury + disturbances in blood flow (intrarenal vasoconstriction), reduced GFR, diminished delivery of oxygen/nutrients to tubular epithelial cells; toxic injury
4. Pathology: FOCAL necrosis of segments of tubules (typically proximal tubules) with casts in distal tubules, interstitial edema
5. Laboratory: renal failure; diagnosis 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 and sustained 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 with interstitial component - discussed later)

Toxic ATI due to antifreeze poisoning: calcium oxalate can be seen in tubules (under polarized light)
In toxic ATI due to mercury poisoning granular acidophilic inclusions can be seen.
Chronic mercury nephropathy may be nonspecific and associated with dystrophic calcifications seen on H&E stained sections.
ATI – toxic and ischemic – typical presentation:

A college student was involved in a motorcycle accident in which he sustained severe blunt trauma to the abdomen and extremities. Over the next 3 days, he developed oliguria and dark brown urine. The urine dipstick analysis was positive for blood, but microscopic urinalysis showed no RBCs. His serum BUN increased to 38 mg/dL and he underwent dialysis for the next 3 weeks.

Clinical diagnosis:
- acute tubular injury (ATI), toxic and ischemic

His condition improved, but his urinary output was >3 L/24 hrs for 1 week before his BUN became normal.

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.

**Urinary tract obstruction** – please see lectures by Urology faculty
- Infection, tumors…
- Stones – chemical analysis! Dietary changes…
- Hydronephrosis