Lecture Two + Three

Pathology of upper and lower

Urinary Tract Infections

*432 **Pathology** Team*

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Renal Block

NOTE: female-side notes are written in purple. **Red is important.** Orange is explanation.

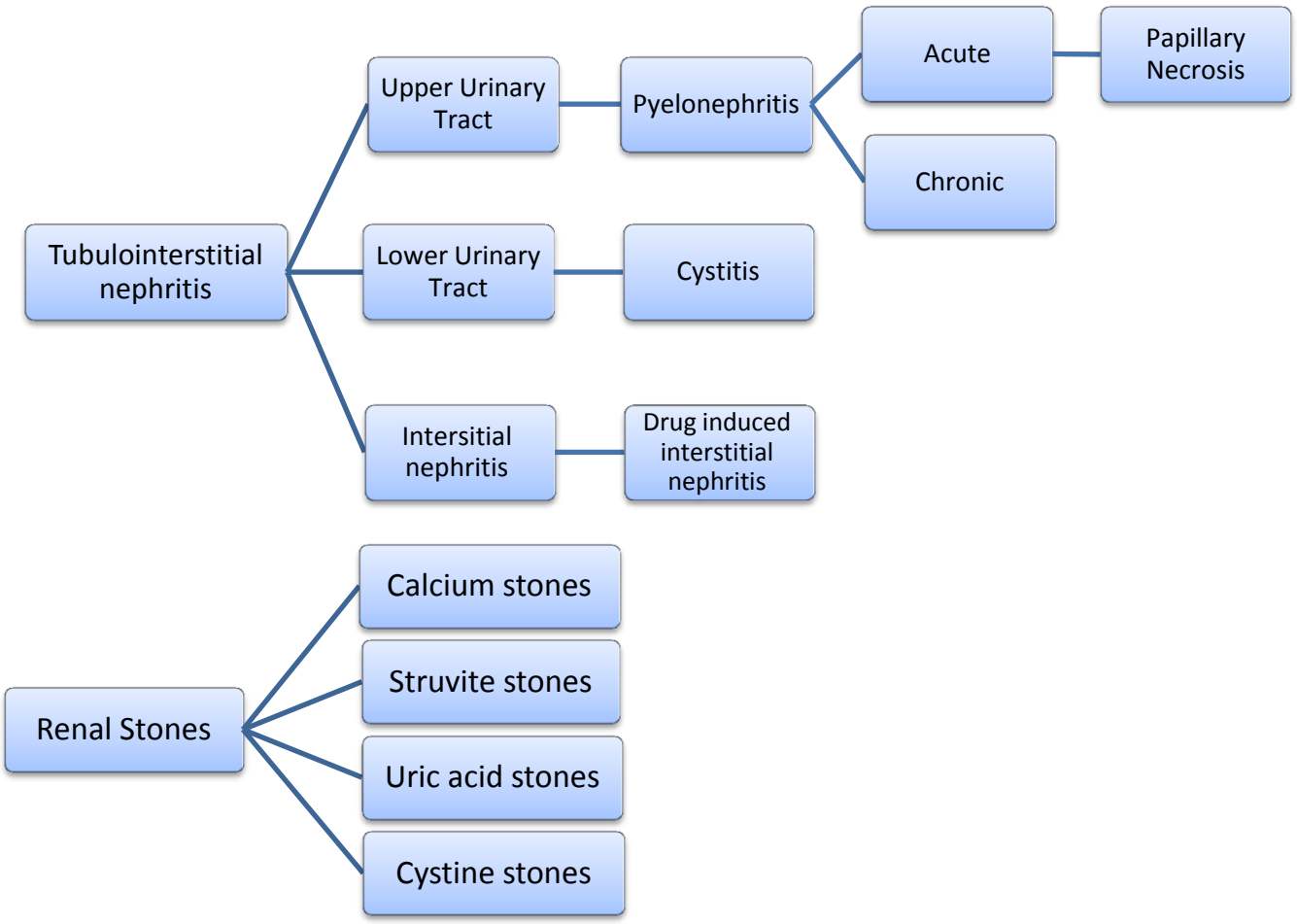
Pathology of upper and lower Urinary Tract Infections

Lecture Objectives:

At the end of this lecture the student should be capable of:

- *Definition*
- *Distinguish types of infections of urinary tract- pyelonephritis urethritis, cystitis, and ureteritis.*
- *Recognize the pathophysiology of the most common infections of the kidney and urinary tract*
- *Complications of infections of the urinary tract*

Mind Map:



General Considerations in Urinary Tract Infections

Infections of the Kidney and Urinary Tract

Routes of Infections:

1- ***Ascending:*** by external entry of organisms through the urethra into the bladder then ureters (vesicoureteral reflux) then kidney. **(Depending on the case)**

REMEMBER: ***Bacteria that can cause ascending urinary tract infections: KEEPS***

***K*lebsiella**

E*scherichia Coli (E.Coli)** ***(It is the normal flora of the colon)

***E*nterobacter**

***P*roteus Vulgaris**

***S*erratia**

2- ***Hematogenous:*** **(very dangerous)** from another focus of infection (endocarditis, septic emboli.) through the blood the bacteria will reach the kidney. **Usually by Staphylococcus Aureus**

Predisposing Factors:

1. ***Female Gender*** because of:
   a. Short urethra.
   b. Urethra is close to the anus **(source of gram negative bacilli like E.Coli)** as well as vagina.
   c. Female hormones **(like estrogen and progesterone)** relax the smooth muscles in the urethra causing stasis which allows bacterial overgrowth.
   d. In pregnancy the uterus compresses the bladder.

For all these reasons when a female presents with a UTI* for the first time we just treat it without looking for an underlying condition that predisposed her to it whereas when a male presents with a UTI we have to do investigation because it is a sign that something might be wrong with his renal system even if it's the first time.

2. ***Obstruction of urinary flow*** such as:

(Obstruction ➔ Stasis ➔ bacterial growth)

   a. Urethral obstruction in benign prostatic hyperplasia **(most common cause in men especially those >50 years)**
   b. Stones
   c. Tumors
   d. Vesicoureteral reflux

* Urinary Tract Infection

3. ***Instrumentalization (Iatrogenic *):*** Mainly catheters inserted into the bladder which introduce infection
4. ***Gynecological abnormalities***
5. ***Surgery in the kidney or urinary tract***
6. ***Diabetes mellitus***
7. ***Immunosuppression and Immunodeficiency***
8. ***Preexisting renal lesions, causing intrarenal scarring see the figure(1)*** (scars are more prone to infections)

Figure (1)

Clinical Manifestations :

1- **Urinary frequency:** a compelling necessity void small amounts of urine at frequent intervals.
2- **Dysuria**: Painful, burning sensation on urination
3- **Pyuria:** large numbers of neutrophils in the urine
4- **Haematuria:** blood in the urine; urinary red cells are a nonspecific finding in urinary tract infection
5- **Bacteriuria:** usually defined as more than 10^5 organisms per milliliter of urine. *It must be distinguished from contamination of urine precimen by external flora.*

Important Note After the first year of life (when congenital anomalies in males commonly become evident) and up to around age 40 years, infections are much more frequent in females. With increasing age the incidence in males rises as a result of prostatic hypertrophy and instrumentation

Tubulointerstitial Nephritis

Refers to a group of inflammatory diseases of the kidneys that primarily involve the interstitium and tubules. The glomeruli may be spread altogether or affected only late in the course. Tubulointerstitial nephritis regardless of the etiologic agent, can be divided into acute and chronic categories. Discussed next is acute pyelonephritis, which is always of bacterial origin, followed by consideration of other (papillary necrosis, cystitis and chronic pyelonephritis), nonbacterial forms of interstitial nephritis (drug induce interstitial nephritis and others).

Note: we organized the titles depend on the book which is more organized than Prof. Al-Rikabi. But the contents here are from the doctor.

* Illness caused by medical examination or treatment

A- Acute Pyelonephritis

Acute Pyelonephritis is an acute infection and inflammation of the renal parenchyma (tubules and interstitium)

***NOTE:* all that we mentioned above applies to pyelonephritis**

Additional Diagnostically Significant Finding:

1- **Fever**
2- **Pyuria:** Urinary white cells (mostly Polymorph neutrophils PMN because it's *acute*)
3- **Dysuria**
4- **Polyuria**
5- **Flank tenderness**
6- **Leukocytosis**
7- **White cells casts** This feature is pathognomonic* of Acute Pyelonephritis
8- **Micro-abscesses in the kidney cortex** (The kidney is of normal size)
9- **Greatly increased frequency in women, especially during pregnancy**

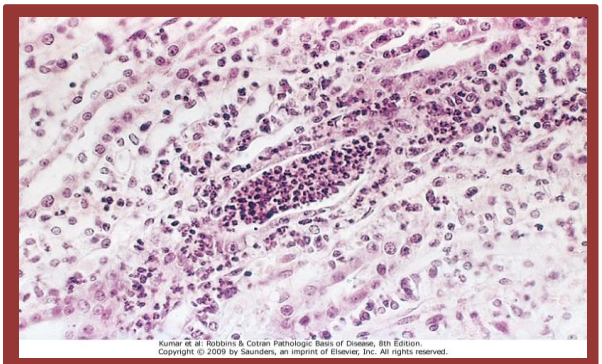
Important note: What is the difference between POLYUREA and URINARY FREQUENCY?

Polyuria: Production of abnormally large volumes of dilute urine

Urinary Frequency: Urination at short intervals without increase in daily volume or urinary output, due to reduced bladder capacity

Microscopical Findings:

Neutrophil infiltration in interstitium and around the tubules and sometimes tubular necrosis (not as much tubular necrosis as acute renal failure)



Acute pyelonephritis marked by an acute neutrophilic exudate within tubules and interstitial inflammation

Complications :

1- **Renal abcess (perinephric abscess)**
2- **Chronic pyelonephritis** If acute pyelonephritis is not treated properly
3- **Necrotizing papillitis**
4- **Pyonephrosis:** Collection of puss in the kidney

Both the pyonephrosis and the abscess need to be drained before commencing treatment because they are compartmentalised without vascularization so the drugs won't reach them.

* specifically characteristic or indicative of a certain disease

Cystitis:

Characteristics:

1- **Pyuria**
2- **Hematuria**
3- **NO urinary white cell casts**

Hemorrhagic cystitis (the patient comes with hematuria and inflammation, the bladder mucosa is very congested)

Etiology:

- ***Candida albicans*** → **catheterization, sexually transmitted**
- **Schistosomiasis**
- ***Chlamydia*, and *Mycoplasma***
- **Bladder calculi, urinary obstruction.**
- **Diabetes mellitus, instrumentation, and immune deficiency.**
- **Irradiation of the bladder region gives rise to *radiation cystitis.***
- **TB → cystitis TB always follows renal TB**

  ** Women are more likely to develop cystitis*

B- Renal Papillary Necrosis (Necrotizing Papillitis)

Necrotizing Papillitis is an ischemic necrosis of the tips of the renal papillae

It is a second form of pyelonephritis

Characterized by:

- Obstruction
- Hematuria
- Sudden renal failure

It will cause infarction and necrosis of the papillae→ they will be excreted in urine→ may cause obstruction or if it's severe enough it can cause renal failure

Conditions:

1- Most often associated with **diabetes mellitus** (because they are prone to infection with coexisting vascular disease)
2- As a catastrophic consequence of **fulminant acute pyelonephritis**
3- **Sickle cell anemia** (because they are prone to emboli and infection which can both cause Necrotizing Papillitis)
4- Associated with **long-term persistent abuse of phenacetin (acetaminophen)**;
   a. Most often when phenacetin is used in association with aspirin and other analgesics. This can lead to chronic analgesic nephritis, a chronic inflammatory change characterized by loss and atrophy of tubules and interstitial fibrosis and inflammation.
   b. Phenacetin is no longer approved for over-the-counter analgesia preparations (not allowed to be sold by pharmacies without prescriptions).

C- Chronic Pyelonephritis

Chronic Pyelonephritis a Chronic tubulo-interstitial inflammation (tubules and interstitium) and renal scarring (fibrosis) associated with pathologic involvement of the calyces and pelvis.

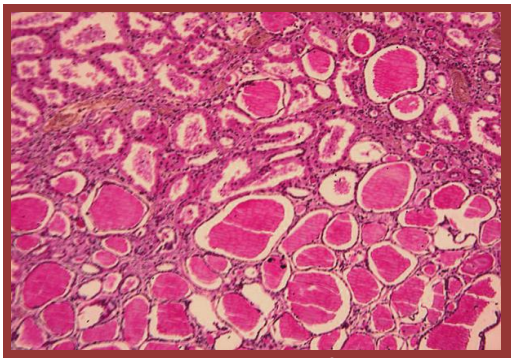
Destruction almost all the kidney. Numerous dilated calyces with yellow-brown calculi. The central necrotic areas are surrounded by dense fibrosis.

Gross appearance:

Coarse, asymmetric cortico-medullary scarring and deformity of the renal pelvis and calyces; these findings are essential for the diagnosis.

Microscopical Findings:

Include interstitial inflammatory infiltrate in the early stages (of chronic inflammatory cells like Lymphocytes, plasma cells and Macrophages sometimes) and later by interstitial fibrosis (scarring eventually) and tubular atrophy; atrophic tubules often contain eosinophilic proteinaceous casts or hyaline cast or WBC cast, resulting in an appearance reminiscent of thyroid follicles (thyroidization of the kidney).



Lymphocytes, plasma cells infiltration and atrophic tubules contain hyaline casts. (Thyroidization of kidney)

Predisposing Factors: Almost always include:

1- **Chronic urinary tract obstruction**
2- **Repeated (attacks) of acute inflammation.**
3- **Tuberculosis of the kidney** (The TB bacilli transfer through blood from the TB infected organ (Lungs \ Lymph) and affect the kidney).
   We should consider this when tests shows negative urine culture and no WBC but yet the patients present with infection symptoms (fever, pain, etc.) and Pyuria (Pus cells present in urine)
   In Microscopy we find large caseous necrotic area filled with TB bacilli.

Complications:

1- **Renal hypertension**
2- **End-stage renal disease (chronic renal failure)**

Important note what is Malakoplakia?

It's a form of infection which can affect the upper urinary tract and the lower (kidneys and bladder) and lead to chronic pyelonephritis and cystitis.

Microscopically, malakoplakia is characterized by the presence of foamy histiocytes (macrophages) with dark central area in cytoplasm and light area in the periphery, which are known as Michaelis-Gutmann bodies.

REMEMBER:

- When there's a **hyaline** or **WBC** or **cellular *casts*** (in urine or tissue) this means the infection in the ***kidney*** not in the bladder (upper urinary tract infection not lower) in bladder the WBC will show not in cast form
- **Chronic pyelonephritis** can affect the glomeruli because of the fibrosis in advanced stages will obstruct the afferent and efferent arterioles and lead to ischemia.
- **Chronic pyelonephritis** ultimately will lead to the end-stage kidney disease **(renal failure).**
- When **renal failure** occurs all other body systems get affected not only the renal system: ***HTN***, ***pericarditis***, ***pleural effusion***, ***edema***, ***pigmentation***, ***urea frosting*** *or* ***skin frosting*** *subcutaneously,* ***bone pain*** *due to hypocalcaemia (hypocalcemia),* ***anemia*** *(due to reduced erythropoietin production),* ***heart failure***, ***dyspnea***, *and* ***myopathies***.
- In **chronic pyelonephritis** the gross appearance is: Both kidneys are **shrunken** and **small in size** with scars on cortex due to fibrosis *(unlike in acute pyelonephritis, kidneys size are almost normal not atrophic but with scattered yellowish abscesses in the cortex).*

Nonbacterial forms of Interstitial Nephritis

Acute Drug-Induced Interstitial Nephritis

Clinical Manifestation:

1. **Fever**
2. **Skin rash**
3. **Disturbed renal function** (↑Urea, creatinine)

Causes:

1- **Penicillin derivatives:** Like methicillin, amoxicillin, and ampicillin
2- **Synthetic antibiotics:** rifampicin
3- **Aminoglycosides:** Like gentamicin
4- **Non-steroidal anti-inflammatory drugs (NSAIDs):** Panadol, Paracetamol
5- **Diuretics:** Thiazides

Other Information:

- The disease is most likely of immune etiology.
- Acute interstitial renal inflammation including many eosinophils is characteristics.
- The nephritis resolves on cessation of exposure to the inciting drug.

Urinary Tract Obstruction

General information:

1- **This obstruction may occur anywhere in the urinary system**

2- **In children, the condition is most often due to congenital malformations** (associated with **vesicoureteral reflux (VUR)** which is the most common cause of urinary tract infections in children or other causes)

Important note: What is Vesicoureteral Reflux? Usually when the bladder contracts it occludes the ureter passing obliquely inside its wall and thus prevents the urine from flowing back up the ureter because of the increased pressure inside the bladder. In Vesicoureteral reflux the muscle of the bladder is weak around the ureters and so when the bladder contracts the pressure of the urine inside it is enough to push the urine back up the ureters causing the reflux. (i.e. instead of going down, the urine will go up)

3- **In adults, the condition is most often acquired and usually occurring as a consequence of:**

   a. **Renal stones**
   b. **Benign prostatic hyperplasia**

Clinical Manifestation:

1. **Renal colic**: which is an excruciating pain caused by acute distention of the ureter, usually due to the transit (movement) of a stone.
2. **Hydronephrosis:** which is progressive dilation of the renal pelvis and calyces causing thinning of the cortex
3. **Infection:** which is localized proximal to the site of obstruction and may lead to infection of the renal parenchyma.

Urolithiasis (Urinary Tract Stones)

This condition is characterized by the formation of calculi (stones) in the urinary tract. The incidence is increased in men (it loves men just like how UTI loves women)

It can be symptomatic or asymptomatic:

❖ **With Symptoms**

1- Pain in the lower back part (Flank pain) or in the lower abdomen, which might move to the groin. Pain may last from hours to minutes (Renal colic).
2- Nausea, vomiting.
3- Blood in urine (hematuria).
4- Burning pain during urination, foul smell in urine, chills, weakness and fevers for urinary tract infection.

❖ **Without symptoms:** they goes silent until we discover them by their complications: obstruction, acute renal failure, recurrent UTI, hydronephrosis (advanced stage)

Renal colic is a very severe pain due to the movement of the small stones which irritates the nerves and cause the pain.

Types of Kidney stones:

A- Calcium stones account for 80% -85% of urinary stones (most common)

1. The stones consist of calcium oxalate or calcium phosphate, or both.
2. They are radiopaque (can be seen by using x-rays).
3. They are associated with hypercalciuria (elevated calcium in urine) , which is caused by:
   a. Increased intestinal absorption of calcium.
   b. Increased primary renal excretion of calcium
   c. Hypercalcemia, which may be caused by:
      - **Hyperparathyroidism** leads to nephrocalcinosis (calcification of the kidney), as well as urolithiasis.
      - **Malignancy** leads to hypercalcemia because of osteolytic metastases or ectopic production of parathyroid hormone (often by a squamous cell carcinoma of the lung).
      - Other causes include sarcoidosis, vitamin D intoxication, and the milk-alkali syndrome.

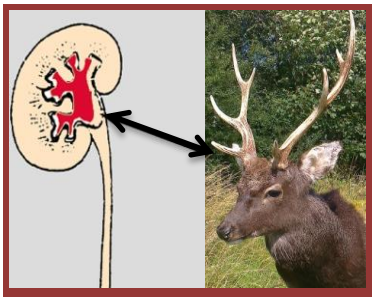
B- Ammonium Magnesium phosphate (Struvite) stones also called staghorn calculi (stones) (they resemble the antlers of a male deer) or ammonia magnesium phosphate stones are the **second most common** form of urinary stones.


Staghorn kidney stone

1- These stones are formed in alkaline urine (in order to be formed), which is caused most often by ammonia producing or "splitting" (urease-positive) organisms, such as Proteus Vulgaris or Staphylococcus Aureus (urea splitting organs) stones formed in the presence of these bacteria and cause UTI.

2- They are **radiolucent** (no calcium).

3- They can form large Staghorn (struvite) calculi (casts of renal pelvis and calyces). (They're very big stones always sit in renal pelvis, and they increase in size with the accumulation of bacteria, debris, Mg .. and eventually cover the renal pelvis and calyces مثل الصبة)


On the left you can see a staghorn stone and on the right is a stag and you can see how the stone looks like its horn which is why they called it STAGHORN!

NOTE: If the urine was in acidic medium then it will never develop staghorn stones, hence the cause of the UTI isn't Proteus Vulgaris nor Staphylococcus Aureus

C- Uric acid stones are associated with hyperuricemia (elevated uric acid in blood) in approximately half of the patients; hyperuricemia can be secondary to **gout** or to increased cellular turnover, as in the leukaemias (cancer of the blood or bone marrow) or Myeloproliferative syndromes (Also because of the cytotoxic drugs in tumors, they kill the tumor cells and damage the DNA which contain purines which break down into uric acids)

D- Cystine stones are almost always associated with **Cystinuria** (an inherited autosomal recessive disease that is characterized by the formation of cystine stones) or **genetically determined aminoaciduria** (may result from an inherited metabolic abnormality)

Complications of Renal stones:

1. **Hydronephrosis** (distension and dilation of the renal pelvis and calyces)
2. **Renal failure**
3. **Recurrent UTI**
4. **Development of Renal colic (very severe pain) (2nd after delivery pain)**

Remember: kidney with obstructed stones get VUR **(In this category the valvular mechanism is intact and healthy to start with but becomes overwhelmed by raised vesicular pressures associated with obstruction, which distorts the ureterovesical junction)** results in, (hydronephrosis) dilated renal pelvis and calyces, atrophy of cortex and mega ureters

Important note: What is Xanthogranulomatous pyelonephritis

A rare form of chronic pyelonephritis and represents a chronic granulomatous disease resulting in a non-functioning kidney. It's associated with staghorn calculus and foamy macrophages in the infiltrate.

Multiple acquired diverticula → a feature seen in chronic cystitis, associated with obstruction mostly by prostatic hyperplasia, affect the mucosa.

Summary: "from robbin's"

- **TIN consists of inflammatory disease primarily involving the renal tubules and interstitium.**
- **Acute pyelonephritis is a bacterial infection caused either by ascending infection as a result of reflux, obstruction, or other abnormality of the urinary tract, or by hematogenous spread of bacteria; characterized by abscess formation in the kidneys, sometimes with papillary necrosis.**
- **Chronic pyelonephritis usually is associated with urinary obstruction or reflex; results in scarring of the involved kidney, and gradual renal insufficiency.**
- **Drug-induced interstitial nephritis is an IgE and T cell mediated immune reaction to a drug; characterized by interstitial inflammation, often with abundant eosinophils, and edema.**

Questions from Pathology Recall book

1- What is urolithiasis?
Stones in the urinary tract.

2- Which sex is more often affected?
Males.

3- What is the most common type of stone?
Calcium oxalate.

4- Name 3 causes of hypercalciuria?
1/ Increased absorption of Ca from GIT
2/ Increased renal excretion of calcium
3/ Hypercalemia

5- What type of the stones cause staghorn calculi?
Struvite stones

6- List 3 significant findings of acute pyelonephritis?
1/ Fever
2/ Flank tenderness
3/ White cell casts in urine

7- What is thyroidization?
Atrophic tubules filled with eosinophilic proteinaceous casts causing an appearance similar to thyroid follicles.

8- What is the probable cause of acute interstitial nephritis?
Immune etiology

9- What is the characteristic finding in the urine in acute interstitial nephritis?
Eosinophils

10- Name 3 common causes of obstruction?
1/ prostatic enlargement
2/ calculi
3/ tumors

11- Proteus infection is most likely to lead to what type of stone formation?
Struvite stones

اللهم إني استودعتك ما قرأت و ما حفظت و ما تعلمت فرده عليّ عند حاجتي اليه انك على كل شيء قدير

432 Pathology Team

*Good Luck ^_^*