

PATHOLOGY TEAM 431

(renal block)

PATHOLOGY OF THE INFECTIONS OF THE UPPER AND

LOWER URINARY TRACT (2nd & 3rd lectures)

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Pathology of pyelonephritis, Nephrolithiasis and Cystitis

URINARY TRACT OBSTRUCTION

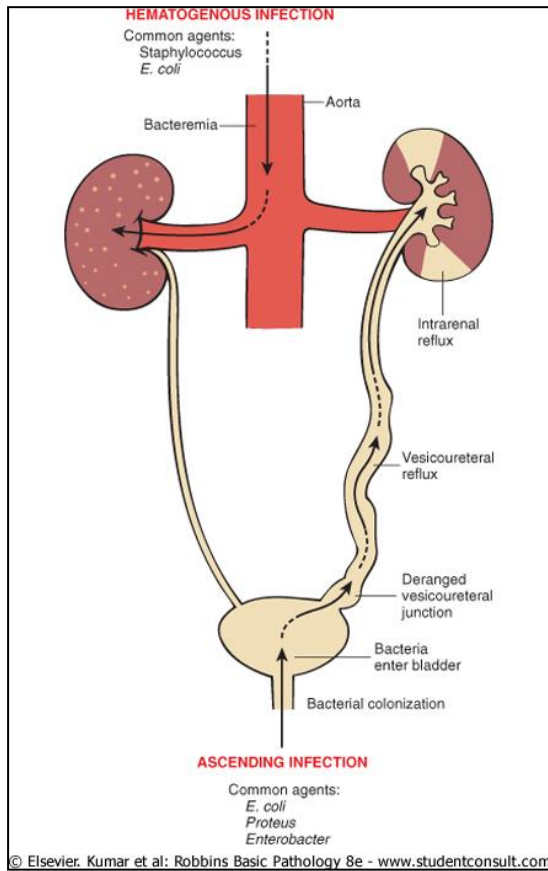
- A. This obstruction may occur anywhere in the urinary system.
- B. In children, the condition is most often due to congenital malformations (associated with reflux or other causes).
- C. In adults, the condition is most often acquired and usually occurring as a consequence of renal stones or benign prostatic hyperplasia.
- D. Clinical manifestations include:
 - 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.
 - 3. Infection, which is localized proximal to the site of obstruction and may lead to infection of the renal parenchyma.

INFECTIONS OF THE URINARY TRACT AND KIDNEY (PYELONEPHRITIS AND CYSTITIS)

A. General considerations

- 1. The incidence of infection of the urinary tract and kidney is greatly increased in women, presumably because of the **shorter length of the female urethra** and the incidence is increased during pregnancy (because of pressure by the uterus).
- 2. This condition can be caused by two routes of infection :
 - A. **hematogenous bacterial dissemination (Rare)** to the kidney e.g.
(tuberculosis , infective endocarditis) or by
 - B. **external entry of organisms through the urethra** into the bladder and in this case infection can spread upward from the bladder into the ureters (vesicoureteral reflux) and through the ureters to the kidney (ascending infection) ,**This is the most common route of infection.**
 - C. **lymphatic but it's very rare.**

3. Most frequently, the infection involves or is caused by the normal flora of the colon, most often *Escherichia coli*.



B. Predisposing factors

1. Obstruction & stagnation of urinary flow, such as that occurring with
 - A. benign prostatic hyperplasia.
 - B. Renal stones
 - C. Congenital Malformation of the ureter
 - D. Tumors in urinary system
 - G. Pregnancy (big uterus compresses the bladder → to stagnation of urine , hormones cause relaxation of smooth muscle fibers of bladder)
2. Surgery on the kidney or urinary tract.
3. Instrumentation (Catheters inserted into the bladder).
4. Gynecologic abnormalities.
5. neurogenic bladder (bladder lost its innervation)
6. vesicoureteric reflux (most common cause for recurrent UTI in children)

C. Clinical manifestations

1. Urinary frequency: a compelling necessity to 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 specimen by external flora.

7. malaise

8. Bed wetting in children with the above symptoms may indicate a UTI .

D. **Additional diagnostically significant findings in acute pyelonephritis (acute infection of the renal parenchyma).**

1. Fever, leukocytosis, flank tenderness, urinary white cells, and **white cells casts in the urine (this latter finding is pathognomonic of acute pyelonephritis).**
2. Greatly increased frequency in women, especially during pregnancy.

E. **Cystitis: Characteristics include pyuria and often hematuria, but urinary white cell casts are not found.**

TUBULAR AND INTERSTITIAL DISORDERS OF THE KIDNEY

Diseases characterized by inflammatory involvement of the tubules and interstitium , caused usually by bacterial infection , diagnosed by signs & symptoms , and confirmed by urine analysis & culture. We will discuss the following disorders :

1-Acute & chronic pyelonephritis

2- Renal papillary necrosis (as a complication of Acute pyelonephritis)

Acute pyelonephritis

A. Definition

A common suppurative inflammation of the kidney and the renal pelvis, is caused by bacterial infection

B. Causative agents

The principal causative organisms are the enteric gram-negative rods.

Klebsiella

Escherichia coli

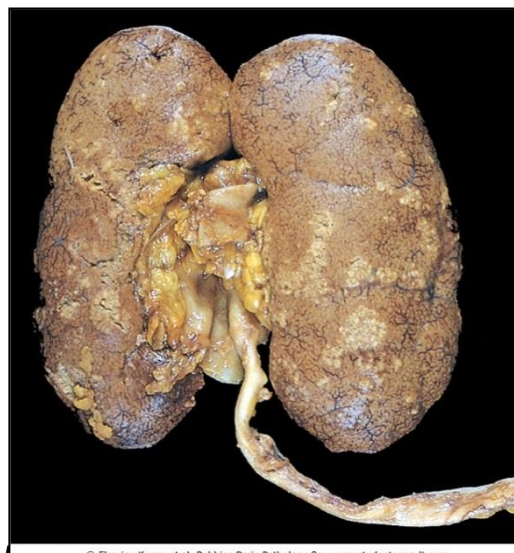
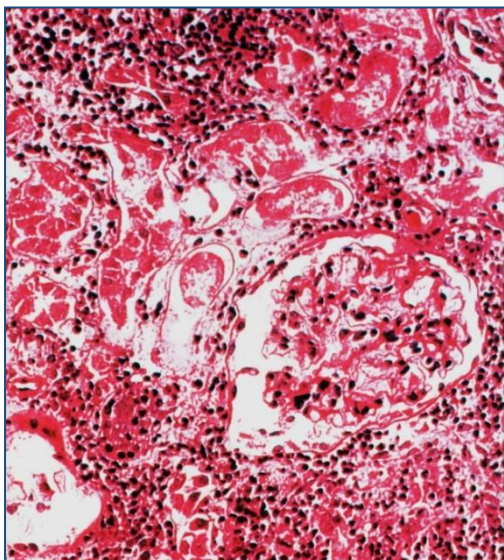
Enterobacter

Proteus mirabilis

Serratia marcescens

C. Morphology

- edematous kidneys
- Characteristically, discrete, yellowish, raised abscesses are grossly apparent on the renal surface
- Does not affect the glomeruli
- Neutrophil infiltrate in interstitium (edematous)
- Tubulitis (neutrophils are attacking the wall of tubules)
- **The hallmarks of acute pyelonephritis are:**
 - Patchy interstitial suppurative(pus) inflammation → Intratubular aggregates of neutrophils
 - → Tubular necrosis.



Complications of acute pyelonephritis

1-Renal papillary necrosis (necrotizing papillitis) is ischemic necrosis of the tips of the renal papillae.

A) This form of necrosis is most often associated with **diabetes mellitus**, in which it is related to renal infection and coexisting vascular disease. It is occasionally a catastrophic consequence of **acute pyelonephritis**.

B) Renal papillary necrosis is also associated with long-term persistent abuse of **phenacetin**; 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. Phenacetin is no longer approved for over-the-counter analgesia preparations (not allowed to be sold by pharmacies without prescriptions).

2-**Pyonephrosis** seen when there is total or almost complete obstruction

Pyonephrosis is Pus collects in the **renal pelvis** and causes distension of the **kidney**.

3-**Perinephric abscess** extension of suppurative inflammation through the renal capsule into the perinephric tissue.

microscopic

characterized microscopically by tubular atrophy, interstitial fibrosis, and a lymphocytic infiltrate in a characteristic **patchy, jigsaw pattern** with intervening preserved parenchyma.

Chronic pyelonephritis

1. **Coarse, discrete, and flattening of the papillae** asymmetric corticomedullary **scarring** and deformity of the **renal pelvis and calyces** occurs; these findings are essential for the diagnosis.

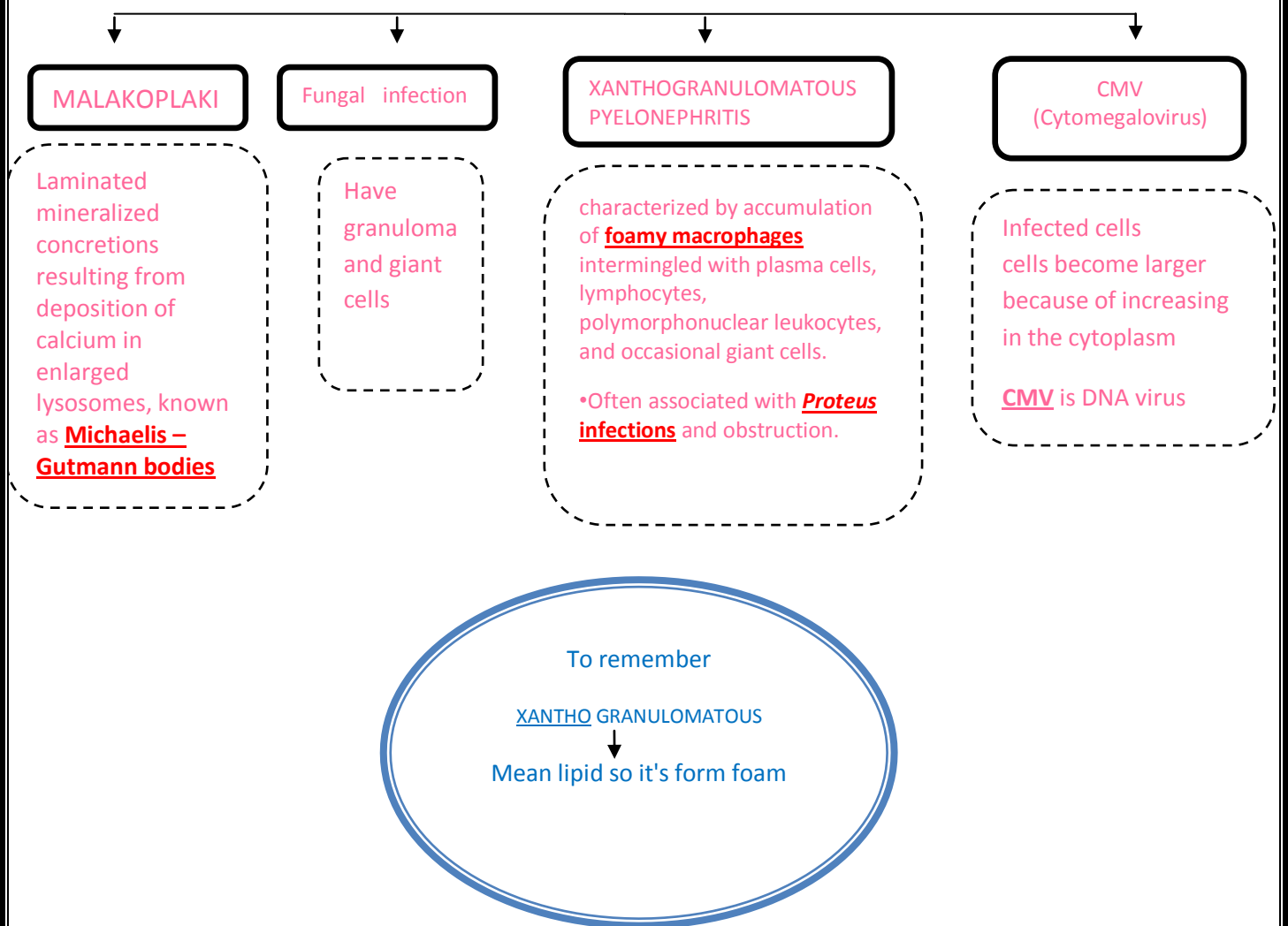
2. Characteristics include interstitial inflammatory infiltrate in the early stages and later by interstitial fibrosis and tubular atrophy; atrophic tubules often contain **eosinophilic** proteinaceous casts, resulting in an appearance reminiscent of thyroid follicles (**thyroidization** of the kidney).

Thyroidization When the tubules are dilated, filled with a hyaline casts giving the kidney a thyroid like appearance

3. Causes almost always include chronic urinary tract obstruction and repeated bouts (attacks) of acute inflammation.

4. Consequences include renal hypertension and **end-stage renal disease**.

other Infections of the Kidney



UROLITHIASIS

This condition is characterized by the formation of **calculi (stones)** in the urinary tract. The incidence **is increased in men**.

- A. **Calcium stones** account for 80% - 85% of urinary stones.
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, which is caused by:
 - a. Increased intestinal absorption of calcium.
 - b. Increased primary renal excretion of calcium.

c. Hypercalcemia, which may be caused by:

(1) Hyperparathyroidism leads to nephrocalcinosis (calcification of the kidney), as well as urolithiasis.

(2) Malignancy leads to hypercalcemia because of osteolytic metastases or ectopic production of parathyroid hormone (often by a squamous cell carcinoma of the lung).

(3) Other causes include sarcoidosis, vitamin D intoxication, and the milk-alkali syndrome.

B. Struvite (Ammonium magnesium phosphate stones) are the second most common form of urinary stones , account for 10% urinary stones.

1. These stones are formed in alkaline urine, which is caused most often by ammonia producing or "splitting" (urease-positive) organisms, such as **proteus vulgaris or staphylococcus**, Moreover, bacteria may serve as particulate **nidi** for the formation of any kind of stone.

2. They are radiolucent.

3. They can form large staghorn (struvite) calculi (casts of renal pelvis and calyces).

C. Uric acid stones , account for 6-7% urinary stones.

are associated with hyperuricemia in approximately half of the patients; hyperuricemia can be secondary to gout or to increased cellular turnover, as in the leukaemias or myeloproliferative syndromes, they **are radiolucent**.

D. Cystine stones , account for 1-2% urinary stones.

are almost always associated with cystinuria or genetically determined aminoaciduria, they **are radiolucent**.

Clinical Course

Stones may be present without producing either symptoms or significant renal damage. This is particularly true with large stones lodged in the renal pelvis.

Smaller stones may pass into the ureter, producing a typical intense pain known as **renal or ureteral colic**, characterized by **paroxysms of flank pain radiating toward the groin**. Often at this time there is gross hematuria. The clinical significance of stones lies in their capacity to obstruct urine flow or to produce sufficient trauma to cause ulceration and **bleeding**. In either case, they *predispose the sufferer to bacterial infection*. Fortunately, in most cases the diagnosis is readily made radiologically.

Summary:

Inflammatory disease primarily involving the renal tubules interstitium.

- Acute pyelonephritis is a bacterial infection caused either by ascending infection as a result of reflux, obstruction, or by hematogenous spread of bacteria: characterized by abscess formation in the kidneys, sometimes with papillary necrosis.
- Chronic pyelonephritis is usually associated with urinary obstruction or reflux: 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

Case :

A 53-year-old white woman presents to her physician complaining of **flank pain and fever**. She has noted **burning on urination** for the last week without discoloration of the urine. Her past history is significant for **diabetes mellitus** for the last 13 years, She has been treated before for bladder infections, Upon physical exam, she is a moderately obese woman with a **temperature of 41° C**, x-ray of the kidneys is ordered and reveals a **small radioopaque stone** in the left renal pelvis.

Urinalysis: protein 1+ , **glucose 3+** , **blood 1+**, **nitrite 4+** , **leukocyte esterase 3+**

Micro: 5-10 RBCs/HPF, **>41 WBCs/HPF**, **few WBC casts**, **many bacteria**

1. What is the most likely diagnosis ?
2. what can be found in urinalysis that is pathognomonic of acute pyelonephritis ?
3. What risk factors did this patient have for urinary tract infection?
4. What are the predisposing factors for necrotizing papillitis in this patient?
5. What are the four main types of renal stones?
6. What are the complications of stones?

Answers

1- Acute pyelonephritis

2- white cell casts

3- female sex, diabetes mellitus, history of bladder infections , and renal stone

4- Diabetes, urinary tract infection, and obstruction by a stone

5- Calcium stones (80% - 85%) , Triple stones: Mg⁺⁺, NH₃, PO₄ (10%) ,Uric acid stones (6-7%) , Cystine stones (rare)

6. Stones in the ureter may cause intense pain (renal colic); they may cause hematuria, and, most importantly, they predispose to urinary tract infection.

E. Cystitis: Characteristics include pyuria and often hematuria (but urinary white cell casts are not found.)

dysuria (pain while urination), and often hematuria

The mucosa is very hemorrhagic and very congested because of the exudates and vascular dilatation that happens because of inflammation

Often associated with obstruction (large prostate, stone, women that is frequently get pregnant) which causes pressure in the bladder wall

The gross appearance of the bladder of a person who has large prostate we call it trabeculation of the bladder wall with hypertrophy and hyperplasia of the smooth muscles because of the pressure.

The patient will have on top of that stagnation in the urine , proliferation of the bacteria and recurrent cystitis

Sometimes patient develop diverticulum (a herniation of parts of the mucosal wall through the muscular wall of the bladder)

If you want to treat it the cause (the obstruction that make the person press himself to urinate which leads to herniation) then treat the herniation

Female can get UTI because of:-

The urethra is short and wide, when she enters the toilet she doesn't clean herself very well (the infection here is called retrograde infection that is caused by reflux of bacteria) and often get pregnant

Women are more likely to develop cystitis

- Tuberculous cystitis always a sequel to renal TB
- Candida albicans
- Schistosomiasis (Schistosoma haematobium)),
- Chlamydia, and Mycoplasma may also cause cystitis.
- Predisposing factors include bladder calculi, urinary obstruction, diabetes mellitus, instrumentation, and immune deficiency.

- Finally, irradiation of the bladder region gives rise to radiation cystitis.

Hyperemia of the mucosa seen in acute cystitis .

Clinical features of UTI

- Frequency
- Urgency
- Dysuria–painful voiding
- suprapubicPain
- Cloudy or foul–smellingurine

Ureteritis:

Though associated with inflammation, is typically not associated with infection and is of little clinical consequence.

Morphology

The accumulation or aggregation of lymphocytes forming germinal centers in the subepithelial region may cause slight elevations of the mucosa and produce a fine granular mucosal surface (ureteritis follicularis). It is the urethral inflammation

- Classically divided into gonococcaland nongonococcal. Gonococcal urethritis is one of the earliest manifestations of this venereal infection.
- Nongonococcal urethritis is common and can be caused by a variety of bacteria, among which E. coli and other enteric organisms predominate.
- Mycoplasma (Ureaplasma urealyticum) also accounts for the symptoms of urethritis in many cases.
- Urethritis is also one component of Reiter syndrome, which comprises the clinical triad of arthritis, conjunctivitis, and urethritis

Interstitial Cystitis (Chronic Pelvic Pain Syndrome)

- This is a persistent, painful form of chronic cystitis occurring most frequently in women.
- It is characterized clinically by intermittent, often severe supra-pubic pain, urinary frequency, urgency, hematuria and dysuria without evidence of bacterial infection.
- Although mast cells are characteristic of this disease, there is no uniformity in the literature about their specificity and diagnostic utility.
- Late in the disease, transmural fibrosis may ensue, leading to a contracted bladder.

Polypoid cystitis

- It is an inflammatory condition resulting from irritation to the bladder mucosa.
- Although indwelling catheters are the most commonly cited culprits, any injurious agent may give rise to this lesion.
- The urothelium is thrown into broad bulbous polypoid projections as a result of marked submucosal edema.
- Polypoid cystitis may be confused with papillary urothelial carcinoma both clinically and histologically.

TUBULAR AND INTERSTITIAL DISORDERS OF THE KIDNEY

A. Acute drug-included interstitial nephritis

Most often the trigger is penicillin derivatives, such as methicillin, and other drugs, such as nonsteroidal anti-inflammatory drugs and diuretics.

a. antibiotics (methicillin, ampicillin (both for ordinary bacterial infection) and rifampin (for T.B.))

b. NSAID (phenylbutazone and acetaminophen)

c. cimetidine (used for peptic ulcer)

d. some antihypertensive drugs

3. Acute interstitial renal inflammation including **many eosinophils is characteristic.**
4. The nephritis resolves on cessation of exposure to the inciting drug

pathogenesis: -

some patients have increase in serum IgE suggesting type I hypersensitivity reaction.

Some patients have small granuloma without caseation which indicates type IV hypersensitivity

These drugs may act as haptens (a substance on its own is non antigenic but when it combine with protein or other substance it become antigen and create antigen-antibody reaction) and combine with cytoplasm of the cells or the proteinaceous material of the tubules to become antigenic which do antigen-antibody reaction which do inflammation

Many eosinophils presented in some patients means that it is an allergic reaction

When you do biopsy you will see inflamed interstitium, fibrosed and eosinophils. you will see some time small granuloma

N.B. you can differentiate diabetic nephropathy and drug induced interstitial nephritis by the area of infection (in diabetic nephropathy it effects the glomeruli but in drug induced interstitial nephritis it effect the interstitium)

Those patients may present with acute renal failure (one of acute renal causes is toxic causes which may be drugs or heavy metals)

B. Renal papillary necrosis (necrotizing papillitis) is ischemic necrosis of the tips of the renal papillae.

Causes:-

1. This form of necrosis is most often associated with **diabetes mellitus**, in which it is related to renal infection and coexisting vascular disease. It is occasionally a catastrophic consequence of **acute pyelonephritis**.

2. Renal papillary necrosis is also associated with long-term persistent abuse of **phenacetin or acetaminophen**; most often when phenacetin is used **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. Phenacetin is no longer approved for over-the-counter analgesia preparations (not allowed to be sold by pharmacies without prescriptions).

Q why people that use aspirin with acetaminophen can have renal papillary necrosis?

Because aspirin is antiprostaglandin which do vasoconstriction which can lead to local ischemia in the papillary. Diabetes can do many disease like:- acute pyelonephritis, acute cystitis and necrotizing papillary

Summary:-

Cystitis: Characteristics include pyuria (but urinary white cell casts are not found.), dysuria (pain while urination), and often hematuria

Acute drug-induced interstitial nephritis:- is characterized by many eosinophils

Renal papillary necrosis (necrotizing papillitis):- can be a complication of acute pyelonephritis in persons with **diabetes mellitus** or it can be caused by drugs.

Questions:-

1-choose from the following a characteristic that it is in pyelonephritis and it isn't in Cystitis

a-pyuria

c-dysuria

b- urinary white cell casts are found

d- hematuria

2-what is hepaten

a-a drug

b-protainatase material

c- a substance on its own is non antigenic but when it combine with protein or other substance it become antigen and create antigen-antibody reaction

d-a disease

3-which one of the following represent the pathogeneses of Acute drug-included interstitial nephritis

a-some patiens have increase in levels of IgA

b- Some patient have small granuloma with caseation

c- drugs may act as hepaten and combine with cytoplasm of the cells or the proteinases material of the tubules to become antigenic which do antigen-antibody reaction which do inflammation

d-all of the above

answers:-

1-b

2-c

3-c