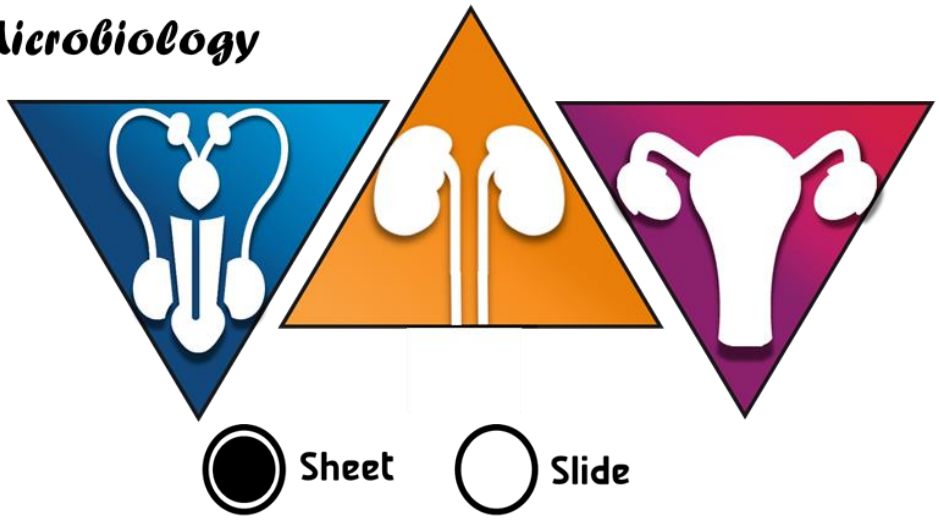
Urogenital system

Microbiology



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In the previous lecture we started talking about the epidemiology of UTIs, we said that it is much more common in females and how the prevalence is different between ages, then we talked about the etiological agents and we said that uropathogenic E.coli cases the majority of UTIs, then we talked about the virulence mechanisms that uropathogenic E.coli has in order to establish infections in the urinary tract.

Also, we talked about the pathophysiology of UTIs, we said that the urethra is contaminated first, then the pathogen makes its way up from the urethra into the bladder, it needs to have some fimbria to attach and adhere to the epithelium and start the infection process causing cystitis in the bladder, if the infection ascends into the kidneys it becomes pyelonephritis which is a more serious condition than cystitis, also the infection can spread to the blood and causes sepsis.

1-Bladder—cystitis

2-Kidneys—pyelonephritis

3-Blood--sepsis

How do UTI patients present?

The term urinary tract infection (UTI) encompasses a variety of clinical entities, including:

- **Asymptomatic bacteriuria (ASB):** there is no symptoms but still we can find bacteria in the urine.
- **Cystitis**: inflammation of the bladder
- **Pyelonephritis**: inflammation of the kidneys
- **Prostatitis**: inflammation of the prostate.

Now we'll talk about cystitis and pyelonephritis and how the patients of these two diseases present to the clinic.

The typical symptoms of cystitis are:

1. **Dysuria**: pain on urination.
2. Urinary **frequency**: the patient has to go to the bathroom more often.
3. **Urgency**: the patient has to go to the bathroom immediately.

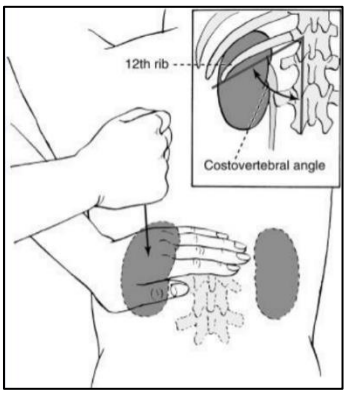
Less common symptoms:

1. **Nocturia**: having to wake up at night to go to the bathroom.
2. **Hesitancy**: going to the bathroom but there is no need to void.
3. **suprapubic discomfort** and sometimes pain.
4. **gross hematuria** (blood in the urine). If you remember from the pathophysiology the epithelium of the bladder epithelium starts to exfoliate so we will have epithelial cells, white blood cells and red blood cells (if a vessel was injured) going out with the urine. Gross hematuria means that you can see it with your eyes because the color of the urine changes a little bit, in contrast, **pyuria** which is having pus or WBCs in the urine can't be seen or detected by looking at the urine so you have to use the microscope.

Symptoms of pyelonephritis

the infection ascends to the kidneys from the most common route which is what we call **the ascending route**, which is basically from the bladder up through the ureters to the kidneys, more than 90% of pyelonephritis cases come from the ascending route and very few cases come from the hematogenous route, so before pyelonephritis usually you expect some cystitis symptoms but there are symptoms that are associated with pyelonephritis that aren't seen in cystitis which are:

1. **fever**:if you see fever you suspect that the infection ascended to the kidneys.
2. **flank and /or loin pain**
3. **costovertebral-angle pain or tenderness**: this symptom can be tested by **murphy's percussion test (murphy's punch)**, in this test basically you percuss or hit the costovertebral-angle which is almost the anatomical place of the kidney, if the kidneys are involved in the infection the patient will feel pain and you know that this is pyelonephritis.



4. **Severe constitutional symptom** like rigors, nausea and vomiting in severe pyelonephritis.

Now we will compare cystitis and pyelonephritis in regard to risk factors, clinical symptoms and causative organisms:

Risk factors of cystitis

1. **Female sex**
2. **History** of UTI predisposes to recurrences, 20-30% of patients with previous UTI will have another UTI again.
3. **Sexual activity**: for example, some bacteria is introduced to the vagina during sexual activity which is near the urethra which will be easier to establish infection
4. **Vaginal ecology** (normal flora) work in inhibiting the establishment of an infection, but with an abnormal ecology or vaginal infection we have a higher risk of having infection in the urethra.
5. **Genetic susceptibility**: for example, sometimes if a mother has recurrent episodes of UTI you expect the daughter also to have the same episodes.

Risk factors of pyelonephritis

In pyelonephritis the risk factors are related to **immunosuppression**, so the patient must have some element of immunosuppression, in other words something has to be abnormal in order for the infection to be established in the bladder and to ascend upwards to cause an infection in the kidneys, these risk factors are:

1. **HIV/AIDS**
2. Taking medications (**iatrogenic immunosuppression**) like steroids
3. **Diabetes**
4. **Congenital or acquired urodynamic abnormalities**: the urine flows normally from the kidneys through the ureters to the bladder, but in some patients when the bladder contracts during urination some urine flows back to the ureters because there is a problem in the junction between the ureters and the bladder, this is what we call **vesicoureteral reflux**, this reflux increases the chance of having pyelonephritis.

Clinicalsymptoms and causative organisms of cystitis and pyelonephritis

	Cystitis	Pyelonephritis
Clinical symptoms	Dysuria, frequency, urgency and suprapubic pain…	In addition to the symptoms of cystitis we have fever, chills, back or flank pain and constitutional symptom (nausea, vomiting…)
Causative organisms	Uropathogenic E.coli (UPEC)	• Uropathogenic E.coli (UPEC) • Staphylococcus aureus (because of the hematogenous spread)

*the most common causative organism in cystitis and pyelonephritis is UPEC.

**virulence factors in cystitis and pyelonephritis are quite similar.

How to diagnose cystitis or pyelonephritis patients?

- In a study that was conducted on a large number of women coming to the clinic with symptoms of UTI, it was found that women **presenting with at least one symptom of UTI** (dysuria, frequency, hematuria, or back pain) and without complicating factors, the probability of acute cystitis or pyelonephritis is 50%.

- If we rule out STDs so there is no vaginal discharge and there is history of previous UTIs or any other of the risk factors that we talked about, then the probability of UTI is close to 90%. So, **history is quite important** and informative in diagnosing UTIs. And even some women self-diagnose UTIs because they get UTIs all the time so they know the symptoms.

- Some people say that if the probability of UTI is close to 90% so there are history and predisposing factors of UTIs, then there is **no need for laboratory tests** before initiating therapy, but we should take urine sample so that we culture it to know the pathogen that is causing the infection.

- One significant concern is that sexually transmitted disease (STD) may be inappropriately treated as UTI –like if we give the wrong antibiotics- because of the overlapping in the symptoms. So, to assure that the patient has UTI we have more laboratory tests that we can use, one of them is dipstick and urinalysis test.

Dipstick and Urinalysis

- Dipstick along with urinalysis are simple tests which also called **point-of-care tests**, which means we use them directly at the clinic so there is no need to send the urine sample to a microbiology laboratory in order to investigate and detect UTIs.

- in this test you have a dipstick that you dip it in urine, the dipstick has several panels on it and each panel contains a certain reagent which identifies a certain material, for example, in the picture you will see a dipstick that reacts with **nitrite** so the panels will change color when the urine has nitrite in it, after you dip it and the panels change their colors you compare the dipstick with the guide which is the sticker on the container in the picture and by that you can know how much nitrite is in the sample, for example in the test that is shown in the picture we have around 1 microgram of nitrite .

- **Nitrite** comes from the conversion of nitrate through the action of any of the Enterobacteriaceae family (E. coli, klebsiella and proteus) so if we detect nitrite by the dipstick method, we can assure that there is UTI.

- In addition to nitrite, when we use dipstick tests, we look for **leukocyte esterase** which is an enzyme found within WBCs which they secret it, so when you find it in urine this means that there is WBCs which probably means there is an infection.

- **The downside** to these test is that for example the dipstick can ONLY detect nitrite when it's under a certain level, in patients with UTI one of the symptoms as we mentioned before is frequency, so the patient keeps drinking water and going to the bathroom so nitrite will be diluted to the extent that it might not be detectable by the dipstick test which shows as negative although the patient has a UTI and its just diluted in the urine plus not all E.coli produce nitrite.

- So, if the dipstick test was negative for nitrite or leukocyte esterase and the patient shows symptoms of UTI then you should consider other tests to confirm the diagnosis.

- In pregnant women **bacteriuria** can be quite harmful to the pregnancy so we need more tests assure the presence of bacteria in urine, dipstick tests alone are not enough and **the gold standard for the diagnosis is culturing**.

Urine culture

- In urine culture method, you ask the patient to pee in a cup, you take the urine sample and dip an inoculation loop in it then you draw a vertical line on the agar plat then you streak around and the you put the plate in the incubator, after 24 hours you go back and take the agar plate from the incubator, if you find something like what you see in the picture, which there are streaks of colonies and you see that all the colonies are of the same type then you suspect that this is UTI.

- If there are a lot of different colonies then you suspect contamination because there are a lot flora on distal urethra, vagina or skin for example, so when the patient urinates some of these bacteria may get in the urine which goes in the urine sample and contaminate it especially if we let the sample set for some time at room temperature these bacteria will keep replicating and the contamination will be stronger.

- To avoid contamination we use what we call **midstream clean catch specimen**, simply you give the patient a towel or a tissue so that before they start peeing they wipe the penis or the vagina and they start peeing in

the toilet and midstream they put the cup to collect the urine, because the first stream contains the flora found on the skin which will be flushed out so when the patient collects from midstream there will be less chance for contamination.

- If the patient couldn't pass urine or you keep getting contamination in your sample you can do something called **suprapubic aspiration**, where you aspirate urine directly from the bladder.

- After taking out the agar plate from the incubator the microbiologist counts the colonies, this is done by **estimation**, he doesn't go around counting every colony, he just looks at the plate and estimates the number of colonies and sends the result.
- After counting the colonies on the agar plate the microbiology lab should decide whether this is a UTI or not based on a certain cutoff, so if the number of colonies counted on the agar plat is less than the cutoff then this is not a UTI and if it is above then it is a UTI, recently the **colony count threshold or cutoff** for UTIs was changed from 10^5 to **10^2** bacteria/ml, they say that 10^2 bacteria/ml is more sensitive and specific.

- Culture results do not become available until 24 hours after the patient's presentation (until you see the colonies on the agar plate), but to identify what those colonies are we have to do more biochemical tests which will take an additional 24 hours.

- So, we have a period of 48 hours that we don't know the pathogen, but in the mean while the patient has symptoms of UTI and should be treated.

- If you want to prove that certain pathogen is the causative agent for UTI, you retrieve the pathogen from the infection site and inoculate it into an animal to replicate the symptoms of the infection, this is what we call **Koch's postulate**.

UTI treatment

- We have certain antibiotics that are known to be effective in UTI treatment like **Nitrofurantoin, Trimethoprim-sulfamethoxazole combination (TMP-SMX) and Fluroquinolones**, these drugs can be used **empirically** so after the patient gives you the sample you can start the empiric treatment immediately.

- Trimethoprim-sulfamethoxazole combination (TMP-SMX) work on **folate synthesis**, Nitrofurantoin and Fluroquinolones cause **bacterial DNA damage**.

- Nitrofurantoin has **good accumulation in the urine** that's why its one of the better antibiotics to use in UTI
- **The empiric treatment of UTI depends on the sensitivity of the bacteria in your region, because Antimicrobial resistance among uropathogens varies from region to region** for example Dr. Azmi is a microbiologist that has an experience of 20 years in this field, when he reads a sample and recognizes that this is a UTI, depending on his knowledge of the sensitivity of the microbes that he commonly encounters he suggests a certain antibiotic even before getting the actual sensitivity test results because it might take 48, so he suggests an antibiotic that is effective for UTIs in his region.

UTIs in Jordan

- The doctor looked up the data for UTIs in Jordan and he found a paper that talks about a study that was conducted in Jordan, in this study they took 100 patients with UTIs and they looked at the most common causative agents between them, they found that **the most common is E.coli** like everywhere else, but in a much less proportion (53.24%) than what we see in the text books and in other regions (75%-90%). There is also **enterococcus fecalis** and there's even **20% staph. Aureus** which we didn't

mention it as a common causative agent but in Jordan it is common for some reason.

- For the treatment they found that **ciprofloxacin** (fluroquinolone) was the most effective antimicrobial agent for treatment of UTIs in Jordan, while they found that **beta lactams** were the least effective because enterobacteriaceae and gram negatives are usually resistant to those antibiotics.

Complication of UTIs

If we want talk about the complications of UTIs in general, we can say that cystitis is a simple infection so there aren't many complications with it, we said that the majority of women will have one form of UTIs in their life and mostly it's in the form of **uncomplicated cystitis**. The difference between uncomplicated and complicated UTI is the presence of predisposing factors (immunosuppression for example) in the complicated ones. But cystitis can cause pyelonephritis which has a lot of complication.

Complications of pyelonephritis

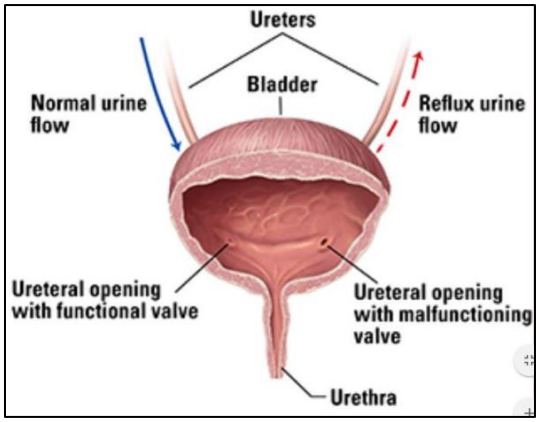
- A single episode of acute pyelonephritis in an adult woman can lead to **renal scarring**.

- Pyelonephritis becomes potentially fatal when secondary conditions develop such as **emphysematous pyelonephritis** (gas build up), **abscess formation or sepsis**, these conditions have high mortality rates.

- In a patient with UTI symptoms and not responding to antibiotics then you should suspect the presence of an **abscess** because antibiotics do not penetrate well into abscesses, so even when you're giving antibiotics the symptoms will still be there.

- Also, as we said before, if the infection reaches the kidneys it can also spread to the blood vessels causing **sepsis**, so sepsis can also be considered as one of the serious complications to pyelonephritis.

- Another complication is what we call **chronic pyelonephritis**, this happens when a patient has a congenital abnormality that affects the urodynamics, we mentioned this case earlier which is when the urine stars to flow backwards, so instead of the normal urine flow through the ureters to the bladder and then to the urethra, when the bladder contracts the urine flows back into the ureters this is what we call vesico-ureteric reflux (VUR), this reflux causes chronic pyelonephritis.

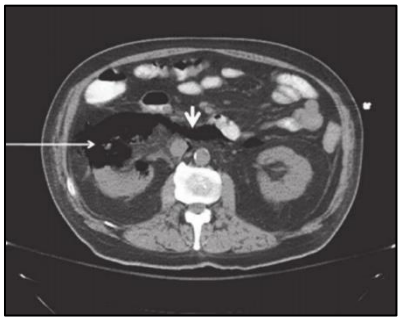


Emphysematous pyelonephritis

- A severe, necrotizing, acute, **multifocal** bacterial nephritis with the extension of the infection through the renal capsule. Part of the tissue and the parenchyma of the kidney is being destroyed by the infection **leaving spaces**, these spaces get **filled up with gas**.

- The patient will reach this complication of pyelonephritis after prolonged symptoms of UTI, if the patient is diabetic or immunosuppressed and if the patient isn't responding to antibiotics. So, we need further investigation to know what the problem that is causing emphysematous pyelonephritis is.

- Diagnosis is confirmed by **CT scan**, you can see in the picture below that there is a collection of gas in the area where the color is darker which reflects the presence of gas.



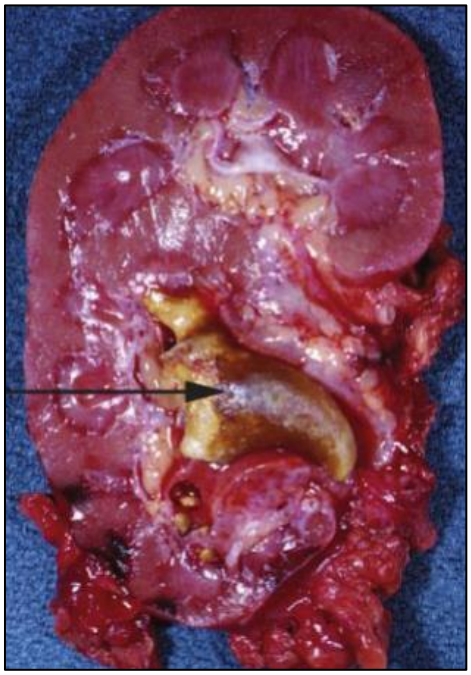
- Treatment involves **antibiotics** and **drainage** because there will be a space in the kidney that is going to be filled up with bacteria. If the patient is not doing well even with antibiotics and the constitutional symptoms are severe then **nephrectomy** is the solution, the patient can survive because he has two kidneys so taking one kidney out is not fatal.

- Mortality is high (around 60%)

Xanthogranulomatous pyelonephritis

- A rare, serious, debilitating illness characterized by a **chronic inflammatory mass** originating in the renal parenchyma.

- The chronic inflammation is caused by a **staghorn calculus** which is a stone shaped like the horn of a stag that fills up the calyces of the kidney and obstructs urine, the infection becomes severe within the kidney parenchyma leading to areas of **hemorrhage and necrosis**, some areas become yellowish because of **lipid filled macrophages**. So, the whole anatomy and gross structure of the kidney is missed up.



- How does an infection lead to stone formation?

  If you remember from the previous lecture that the bacteria **alter the PH** of the urine, this alteration will lead to precipitation of certain magnesium and calcium ions which causes the formation of stones like staghorn calculus. This is commonly associated with **proteus** and its **urease enzymes**, but also other Enterobacteriaceae can form urease like **E. coli and pseudomonas**.

Prostatitis

- Up to 50% of men will experience symptoms of prostatitis at some time in their lives probably in the older age.

- Prostatitis includes both infectious and non-infectious abnormalities of the prostate gland.

- Gives symptoms similar to cystitis like **dysuria and frequency**, in addition we can have **fever and chills** which are similar to the symptoms of pyelonephritis **but there is no flank pain or costovertebral tenderness**.

- **Pain in the perineal area** is a special symptom of prostatitis, this happens when comprising on the inflamed prostate like **pain when defecating**.

- Also, you will expect **obstructive symptoms** because the prostate will be inflamed and the inflammation will cause it to be edematous, the edema will block the urethra which will lead to these obstructive symptoms.

- **Chronic/ recurrent bacterial prostatitis** occurs in young and middle- aged men. Risk factors include **previous acute prostatitis and history of prior manipulation** of the urinary tract for example if the patient has been catheterized before and the catheter has injured the prostate, the patient becomes more susceptible to having chronic/recurrent prostatitis

Is urine sterile or not?

If you remember, in the previous lecture we said that urine is sterile, but some people doubted that and said that urine is not sterile, so they conducted a study "The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms Journal of clinical microbiology 2016" to prove their theory.

In this study, they show that in a negative urine sample if you changed the media a little bit and changed the condition for example let it sit in the incubator for 48 hours instead of 24 hours or increase the CO2 concentration,you will start seeing colonies. So, the idea here isn't that we don't have bacteria in the urine or the bladder, maybe we don't have the techniques to retrieve it. So maybe there is microbiota in urine.

BEST OF LUCK ☺