Urogenital System

Sheet 1

Subject | microbiology

Done by | Doctor2016

Correction | ...

Doctor | Anas

In this lecture we will talk about epidemiology, pathophysiology and etiology (pathogenesis) of the urinary tract infections.

There is no need to go back to slides since **everything** is included here.

- Similar to the CNS the urinary tract (UT) is a sterile environment; there shouldn't be any microbiota in the urinary bladder, ureters, urethra and kidneys. But the epithelial surface of the UT is with direct contact with the external environment (**through urethra**) which makes it in **direct contact** with the bacteria all the time.

- As you remember, the CNS mounts an exaggerated immune response if bacteria get an access to it which is the cause behind the damage that occurs in CNS infections. Fortunately this is not the case in the UT, the UT is able to maintain **a balance between sterilization** (prevention of colonization) and **unexaggerated immune response** (to lessen the damage caused by the immune system as this tract is in direct contact with bacteria so it will be harmful to mount an exaggerated immune response each time of encountering these pathogens).

* The urinary tract is typically a sterile environment, and bacterial colonization of the bladder epithelium does not go unchallenged. This happens in several ways: [mechanical, chemical, proteins and factors mediated]

1- The bulk flow of urine through the bladder and micturition can work to rinse away nonattached or weakly adherent microbes from the bladder surface.

-This **mechanical** form of defense is mediated by the continuous flow of urine from kidneys then through the ureters to reach the bladder and finally exits from the urethra by contraction of bladder.

2- The low pH and osmolarity of urine can be inhibitory to bacterial growth, and the salts, urea, and organic acids present in urine can reduce bacterial survival.

-This chemical form of defense is achieved because the low ph and osmolarity of urine are not suitable for the growth of bacteria.

3- Lactoferrin within urine can scavenge essential iron away from incoming microbes.

-This **protein** binds the ferrous and sequesters it which deprives the bacteria from the iron needed for their growth and survival.

-Transferrin can also play a same role by sequestering iron.

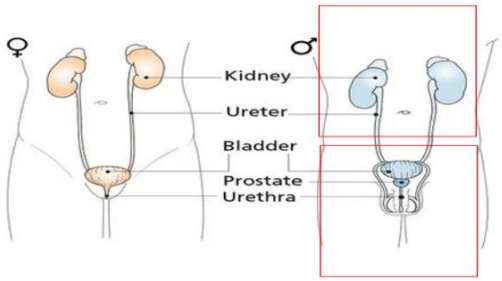
4- A number of soluble and cell associated factors within the bladder, including TammHorsfall protein, low molecular weight sugars, secretory IgA, and uromucoid, can act as anti-adherence factors, competitively inhibiting bacterial attachment to the bladder surface.

- Secretory IgA are found at mucosal surfaces so they prevent the attachment of bacteria to the surface (by blockading epithelial receptors) because once the bacteria can attach they start colonizing then the can form an infection

*Both mechanical defences & soluble and cell associated factors inhibit the first step of infection which is the attachment.

Here you can see the gross anatomy of the male and female urinary system which consist of:

Two kidneys, two ureters, a urinary bladder, a urethra, and a prostate gland only in males.



*Notice the differences between male and female:

- males have prostate while the female don't.
- the urethra of the male is quite longer than that it in female, that is why females get UTI's more than males.

The classifications of UTIs

1. upper and lower UTIs .

The disease	pyelonephritis	cystitis	prostitis	urethritis
The Location	kidney	bladder	prostate	urethra
The classification	Upper UTI	Lower UTI		

- You have to be familiar with this classification as it affects the diagnosis and treatment.

2. symptomatic and asymptomatic infection

- There is another entity called **asymptomatic bacteriurea** that is when we can find bacteria in the urine but without any symptoms of infection which is opposite to the aforementioned infections.

*Some symptoms of UTI are: dysuria (painful urination) , urinary frequency and urgency.

EPIDEMIOLOGY

• As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases.

- As we said that the anatomical differences between males and females affect the epidemiology of UTIs and make females more prone to develop UTIs.

-This is a high percentage which indicates that the majority of females will suffer from UTI at least once in their lives.

• About 20–30% of women who have had one episode of UTI will have recurrent episodes.

-Recurrence is an extra problem.

• Early recurrence (within 2 weeks) is usually regarded as **relapse** rather than **reinfection** and may indicate the need to evaluate the patient or a sequestered focus.

-**RELAPSE (recurrence):** indicates that the first bacteria hasn't been cleared from the UT and it causes the infection again, while if it happens after two weeks it's probably a **REINFECTION** an infection with new bacteria.

• Asymptomatic bacteriuria occurs in all age groups and does not necessarily result in clinical infection.

• Asymptomatic bacteriuria occurs in 1– 3% of non- pregnant women and 2– 9.5% of pregnant women.

Epidemiology of UTIs in the hospital : UTIs can be classified into community-acquired or hospital-acquired.

• Urinary tract infections are the most common type **of healthcare-associated infection**, accounting for more than 30% of infections reported by acute care hospitals.

• Virtually all healthcare-associated UTIs are caused by instrumentation. (Catheter-associated urinary tract infection (CAUTI)) - The urinary catheter: a tube that is inserted into the urethra to drain the urine from the urinary bladder.

• The source of microorganisms causing CAUTI can be endogenous, typically via meatal, rectal, or vaginal colonization, or exogenous, such as via contaminated hands of healthcare personnel or equipment (non-sterile tool).

-Endogenous: the source of bacteria is the patient's own bacteria (microbiota) as it goes with the catheter during the catheterization and causes infection (a complicated type of infection)

* To know the meaning of complicated type read the third point of classification of UTI in the next page.

As you notice from the table:

1- In the preschool, school and reproductive age groups there is a huge difference in female to male ratio in relation with the UTI

Table 1 Incidence of Urinary Tract Infection According to Age and Sex

Age Group	Incidence (%)	Approximate Sex Ratio (Male:Female)
Neonatal	1.0	1.5:1.0
Preschool age	1.5-3.0	1:10
School age	1.2	1:30
Reproductive age	3-5	1:50
Geriatric	10-30	1:1.5

Explanation:

-The anatomical differences between male and female (the shorter urthera in females) make the UT of females more accessible by pathoges.

2- In the two extreme groups of ages; the neonates and geriatric (above the age of 60) the ratio is almost equivalent

Explanation:

-The occurrence of UTI in male neonates is equivalent or even more than females because males have more chances to have congenital abnormalities in the urinary tracts which increase the chance of UTI (certain abnormalities prevent the normal flow of urine and causes stasis, in turn, increases the probabilities of bacterial attachment and infection by impairing the normal mechanical defenses).

- Males of old age most often develop benign prostatic hyperplasia (BPH) or hypertrophy so the prostate get enlarged and blocks the flow of urine to the urethra and causes UTI (a complicated infection) so stasis of urine disrupts the normal mechanical defense against infections.

3.complicated and uncomplicated UTI's (the third classification of UTI's)

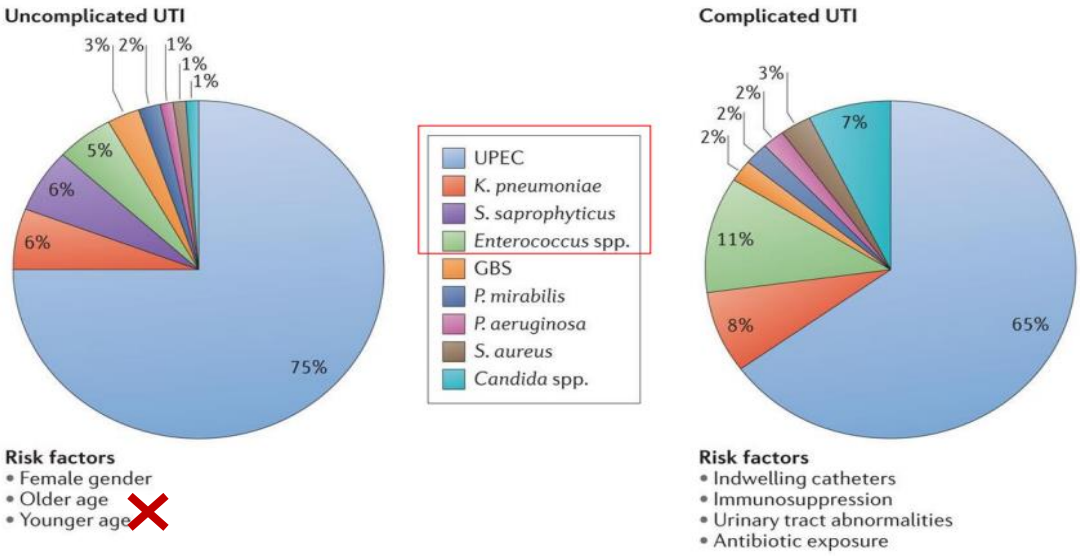
*this is a clinical classification. It is important to know this classification because there are different pathogens(etiological factors) that cause each type of UTI .

Clinically, UTIs are categorized as uncomplicated or complicated:

• Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities [no predisposing factor].

• Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defence, including urinary obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi or indwelling catheters.

Etiological factors:



1- In both cases the most common causative pathogen is uropathogenic E.coli (UPEC).

-Some strains of E.coli are part of the normal flora of GIT

- UPEC is a strain of E.coli that has some virulence factors that enable it to cause UTI.

2- Klebsiella pneumoniae another bacteria of the **Enterobacteriaceae family**

3- Staphylococcus saprophyticus (it is a Gram-positive coccus belonging to the coagulase-negative genus) which is part of the microbiota of the skin along with staphylococcus epidermedis and others.

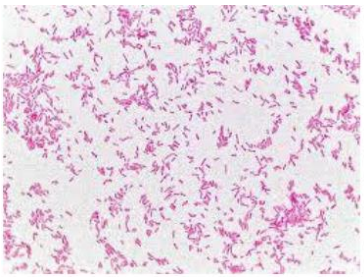
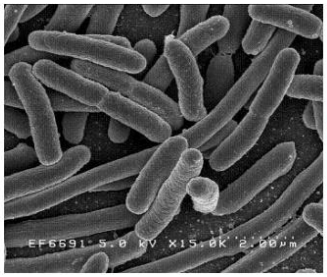
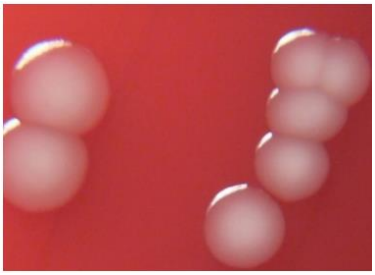
4- Enterococcus species (this type of bacteria is more common in complicated infection, so suspect this type of bacteria in catheterized patients who have UTI)

- Here are some risk factors to UTI:

*Complicated type: Immunosuppression, catheterization, congenital abnormalities in UT, antibiotic exposure.

*Uncomplicated type: female gender as healthy females have a 50% chance to have uncomplicated UTI at certain age (other risk factors are mentioned in the figure above like older age and younger age; the doctor said that they're not sensible)

Let us talk more about the etiological agents:

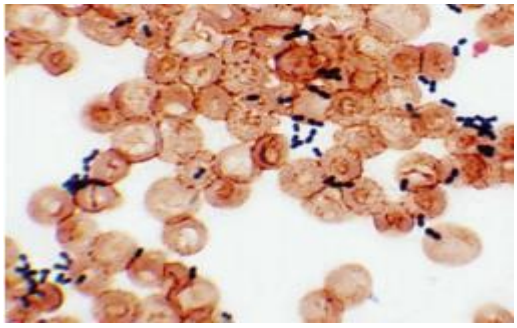
1-**UPEC**

• A gram negative rod, facultative anaerobe. The optimum growth temperature is 37°C. On Nutrient agar, colonies are large, thick, greyish white, moist, smooth.

• E. coli and other facultative anaerobes constitute about 0.1% of gut microbiota

-some strains of e.coli gain certain virulence factors and cause UTI (UPEC) while other strains are non- pathogenic and harmless and stay in the intestine.

-A subtype can cause epidemic diarrheal diseases.



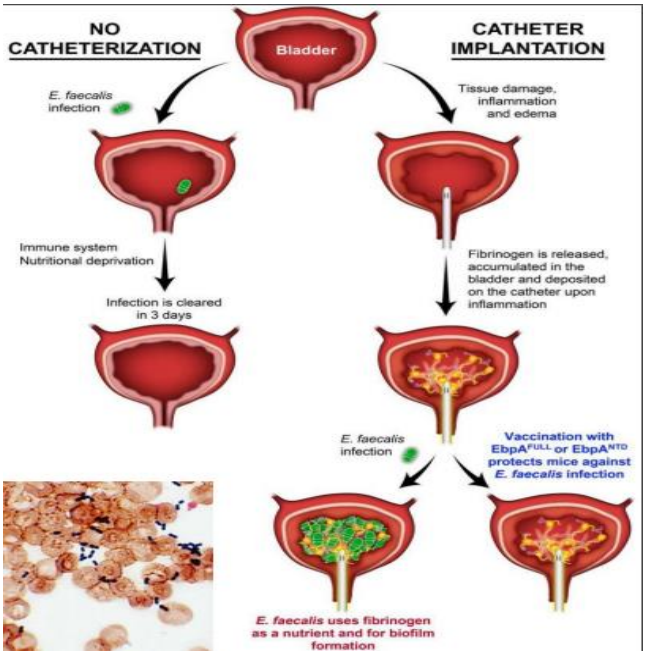
2- Enterococcus faecalis

• The enterococci are gram-positive cocci, typically arranged in pairs and short chains.

• E. faecalis is found in the large intestine in high concentrations (e.g., 105 to 107 organisms per gram of feces) and in the genitourinary tract.

• Enterococci are one of the most common causes of infections acquired in the hospital (nosocomial infection). The urinary tract is the most common site of enterococcal infections, and infections are frequently associated with urinary catheterization or instrumentation (**complicated UTI**).

- Resistant to many antibiotics



-If this bacteria manages to get into the bladder the urinary flushing and normal immune system will help its clearance, while if there is a catheter inserted to the urethra this will offer a surface for the bacteria to adhere to, and also the insertion of a catheter damages the tissue releasing fibrinogen which is a good factor for the bacteria to attach and adhere, then the bacterial growth begins causing UTI.

-pass antibiotic-resistance genes to other bacteria by horizontal gene transfer either by conjugation of plasmid or transformation with naked DNA, S.aureus specifically MRSA gets its resistant to vancomycin from Enterococcus fecalis in certain settings both bacteria are found at the same place and s.aureus will acquire genes of resistance from Enterococci.

3- Klebsiella pneumonia

- Enterobacteria

• Klebsiella species are routinely found in the human nose, mouth, and gastrointestinal tract as normal flora.

• The ability of K. pneumoniae to colonize the hospital environment, including carpeting, sinks, flowers, and various surfaces, as well as the skin of patients and hospital staff, has been identified as a major factor in the spread of hospital-acquired infections

- It becomes problematic now because it is found in hospitals more often and causes hospital-acquired infections.

- Antibiotic resistant which is another problem.

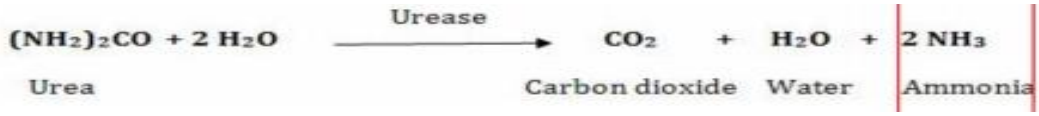
- Pass antibiotic-resistance genes to other bacteria by horizontal gene transfer either by conjugation or transformation with naked DNA.

4- Proteus mirabilis

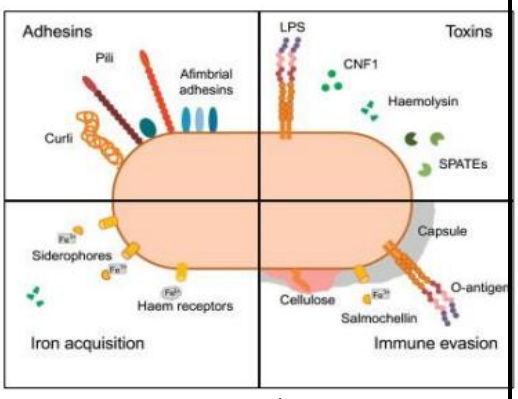
Proteus mirabilis is a Gram negative, facultatively anaerobic, rod-shaped bacterium. It shows swarming motility and urease activity.

*swarming pattern: the unique pattern of movement of the bacteria on agar (it is very important to identify this type of bacteria as the doctor said)

*urease enzyme breaks down urea in the urine to ammonia and other constituents. The urine is supposed to have a low pH so the increase in the level of ammonia in the urine raises the local pH of it.



A direct result of urease activity and ammonia generation is an increase in local pH. In the urinary tract alkaline pH leads to precipitation of calcium and magnesium ions and the formation of urinary stones composed of magnesium ammonium phosphate (struvite) and calcium phosphate (apatite).(notice that the normal pH of urine prevents the formation of such stones, so when you see urinary stones in a patient you should suspect an infection with p.mirabilis).



<u>Virulence factors</u>

in order to these pathogenic bacteria to cause an infection they should have certain virulence factors that enable them to

overcome the defense mechanisms we talked about in the bladder and the most important is the adhesion.

virulence factors in UPEC (many factors are shared with other bacteria causing UTI):

1-Adhesive fimbriae, which enable bacteria to adhere avidly to specific receptors on the urothelium. Almost every successful UT pathogen should be able to adhere strongly to the epithelium of the UT ,otherwise it will be removed with the urine and it will not be able to colonize and causes UTI.

2- Flagella that enable bacteria to swim along the urinary tract including 'upstream' from the urethra to bladder to the kidneys.

3- Toxins, such as haemolysin and cytotoxic necrotizing factor, which disrupt the epithelial barrier and enable access to the underling tissue and even sometimes kill white blood cells that start to attack the bacteria.

4- siderophores, which enable bacteria to chelate iron that is important for growth proteins secreted by the bacteria, this protein chelate iron which is important for the bacterial growth, remember that we said there is some proteins in our body like lactoferrin and transferrin that bind iron so what the bacteria does is that it secretes this protein and try to take the unbound iron and aquire it

5- expression of cell surface capsules, which enable them to resist the bactericidal actions of complement and phagocytic cells

6- Certain surface antigens that help in immune evasion, and antigen switching mechanism in some G-ve enterobacteriacae which makes it unrecognizable by immune system.

-If E.coli acquires these virulence factors by a mutation or through horizontal gene transfer then it will become uropathogeinc (UPEC) and it will be able to cause a UTI.

<u>The triad of pathogenesis of UTI</u> this triad is applied to any sort of infection. We have 3 things that act together in order to generate the final result of infection, colonization or elimination of the bacteria.

Elements/factors of this triad are:
(study the figure)

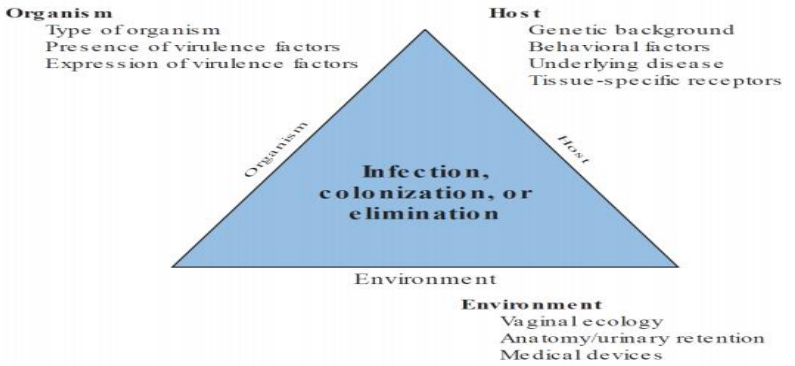


FIGURE 33-1
Pathogenesis of urinary tract infection. The relationship among specific host, pathogen, and environmental factors determines the clinical outcome.

1. Factors in the **organism,** most importantly the existence and the expression of virulence factors.

2. Host factors, which include:

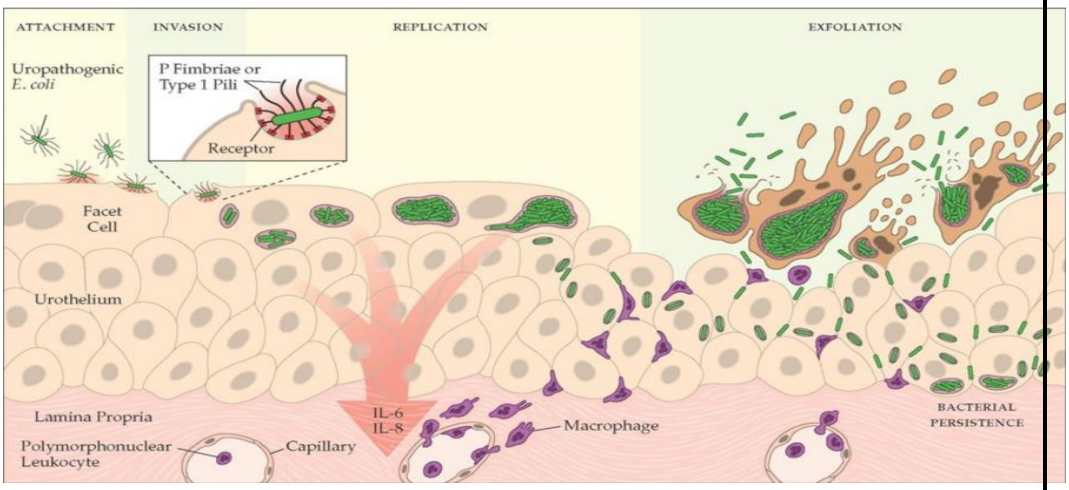
a) **The immune response.** for example : immunocompromised patients are more likely to get UTI.
b) **Behavioral factors related to the host;** sexual intercourse is an independent factor that increases the risk of UTI. Also multiple sexual partners increase the risk of UTI.
c) **Genetic background ;** certain people have a higher risk of having UTI

-It's found that females who have UTIs their daughters or mothers also have a higher chance of getting a UTI

- There are certain proteins that the bacteria can adhere to and hence adhere to the epithelium **or** the absence of certain protein leads to decrease clearance of the Bacteria which will affect the final outcome mentioned before (the presence or absence of these proteins is genetically-determined)

3. The environment in which this interaction takes place, in the environment we have foreign object like catheter which predisposes to having UTI. Also in females vaginal ecology plays a role.

-now let us dig deeper to see how the infection takes place:



1. We have the bacteria with the most important virulence factor; the fimbria attaching to the epithelial cells

2. Then the bacteria go inside the cell where they start the replication (within the uroepithelium). This will lead to 2 outcomes:

a. if the bacteria gets to the inside of the cell → the cell will recognize the bacteria by pattern recognition molecules and starts secreting cytokines like IL-6 and IL-8 .

b. another outcome is that the cell will die either because of necrosis ; (there is too many bacteria inside it which will blow it up) or the cell commits itself to die by apoptosis (programmed cell death). They are mechanisms by which the uroepithelium tries to eliminate the bacteria.

3. Infiltration of immune cells which will also try to clear the infection but the bacterium in certain cases can persist in pockets hidden away which will then cause a **relapse of the infection. (Symptoms will disappear & the infection recurs within two weeks)**

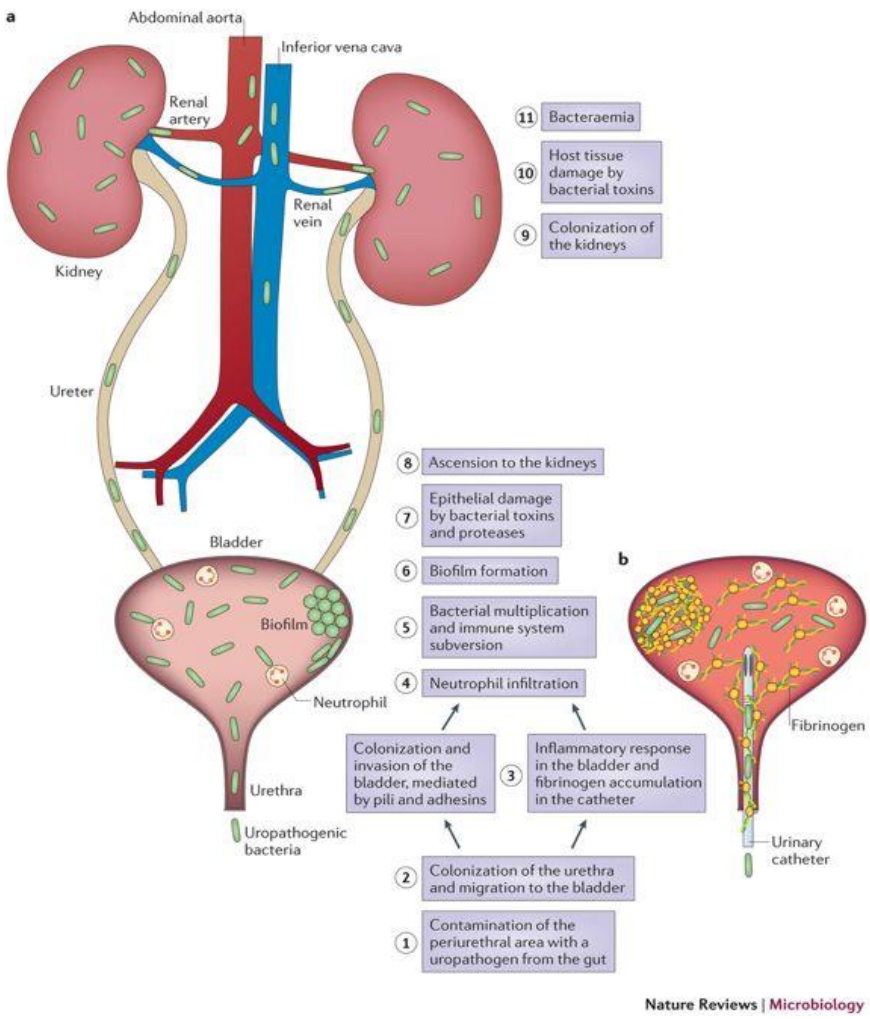
*remember that the main source of uropathogenic E .coli is the gut, it reaches the urethra through the anus & perineum (it is difficult for the bacterium to reach the male urethra than that in female due to the anatomical differences).

The doctor read this diagram as it shows the pathophysiology of UTI in steps: (these steps are required, study them from the figure in the next page)

Notes regarding the figure:

- biofilm is composed of proteins, macromolecules, DNA and sugars that the bacteria secretes in order to make this thin layer (film) which helps the bacterium to keep in protection from defense mechanisms of host and also from antibiotic.

-in the case of complicated UTI where we have a catheter for example it is easier for the bacteria to get attached to fibrinogen and the surface of catheter and form an infection and later on the bacteria can even ascend up through ureters to the kidney and causes upper urinary tract infection or it can reaches the blood causing bacteremia.



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