Infectious Diseases

Lesson 8

GENITOURINARY TRACT INFECTIONS AND SEXUALLY TRANSMITTED DISEASES

Part A – Genitourinary Tract Infections

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Objective and learning goal

Objective

- To review all relevant information on urinary tract infection in the different clinical contexts

Learning goal

To understand the different types of urinary tract infections and know how to diagnose and treat them

Contents

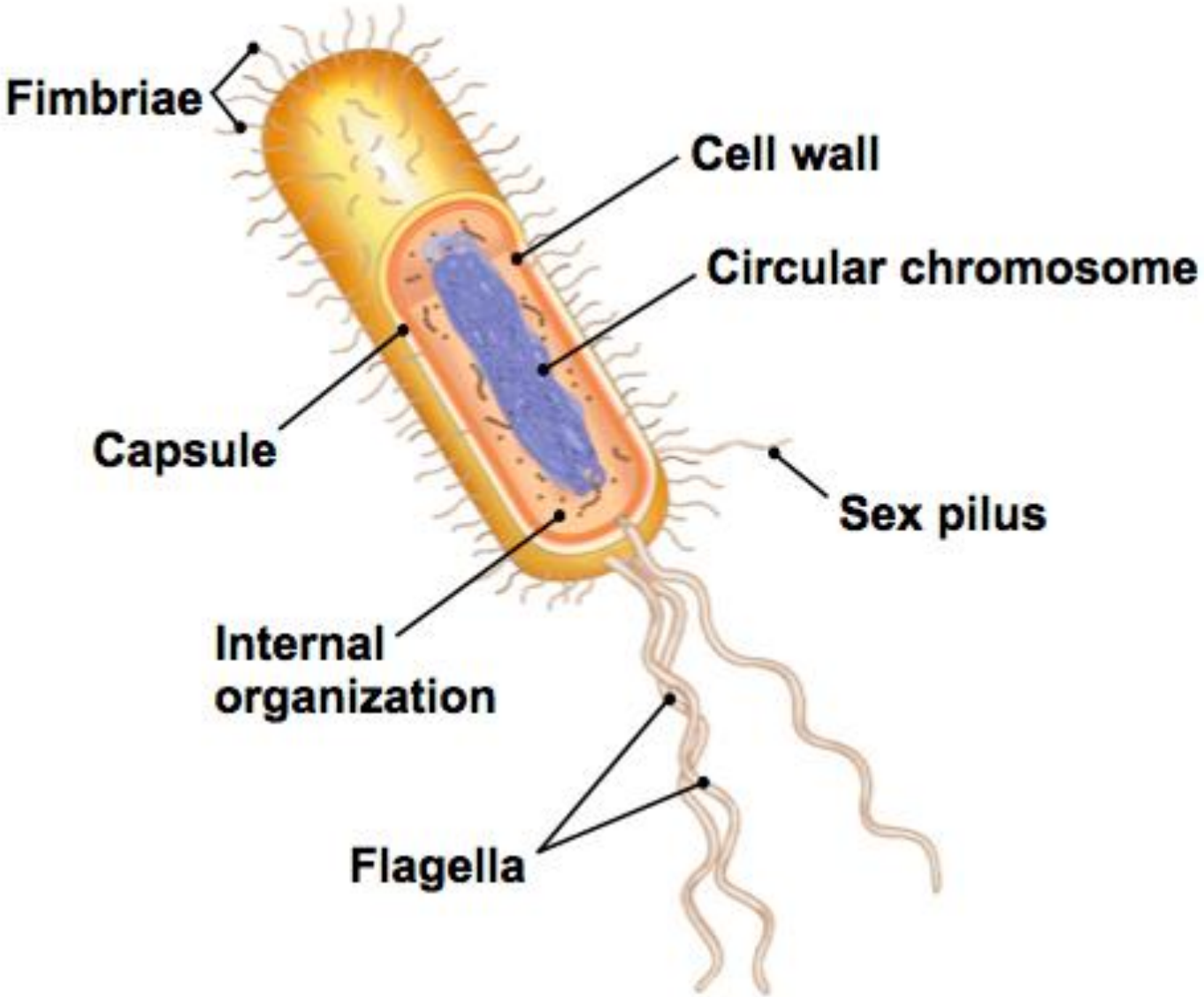
UTI: pathogenesis

Introduction

- One of most common infections
- Key determinants of pathogenesis:
  - **Bacterial** virulence factors
  - **Host** factors

Bacterial virulence factors

- Bacteria enter the **urethra** → **bladder** → ureters → kidneys
- The most common: *Escherichia coli*, strains with:
  - Increased **resistance** to serum bactericidal activity and **hemolysin** production
  - Increased ability to **adhere** to the epithelial cells of the urethra; *E. coli* adhere by their **fimbria** or **pili**, distinct protein hairlike structures on the bacterial surface:
    - Pyelonephritis strains are the most adherent
    - Cystitis strains tend to be intermediately adherent


Fimbriae
Cell wall
Circular chromosome
Capsule
Sex pilus
Internal organization
Flagella

Pathogenic properties of bacteria I

- Two types of *E. coli* fimbriae:
  - **Type I**, adhere to mannosylated proteins on the surface of bladder epithelial cells ("mannose-sensitive", detached on mannose exposure) → cystitis
  - **P**, adhere to glycophospholipids in surface of the plasma membrane of uroepithelial cells ("mannose-resistant") → upper tract infection
- Trimethoprim-sulfamethoxazole reduces the synthesis and expression of the fimbria adhesion molecules

Pathogenic properties of bacteria II

- Bacteria must be capable of synthesizing essential nutritional factors before they can grow in urine: guanine, arginine, and glutamine are required for optimal growth
- *Proteus mirabilis* →
  - → ureases → ammonium → ↑ urine pH > 7 → renal stones → bacterial growth → pyelonephritis
  - → immunoglobulin A (IgA) protease
  - → hemolysin

Pathogenic properties of bacteria III

- Motile bacteria can ascend the ureter against the flow of urine
- **Endotoxins** can decrease ureteral peristalsis, slowing the downward flow of urine and enhancing the ability of gram-negative bacteria to ascend into the kidneys and grow there

Host factors I

- Urine contains:
  - High concentrations of urea
  - Generally has a low pH

  } Inhibit bacterial growth

- Conditions that increase risk of infection:
  - Diabetes, glucose in urine makes it a better culture medium
  - Pregnancy, urine tends to be more suitable for bacterial growth
- Mechanical factors probably are the most important determinants for the development of UTI

Host factors II

- Flushing of the bladder clears bacteria when present → protection against infection
- Urinary flow disturbance, an important factors for UTI:
  - Prostatic hypertrophy and urethral strictures
  - Defective bladder contraction in spinal cord injury → poor bladder emptying → "increased post-void residual"
  - Intrarenal obstruction caused by renal calculi, polycystic kidney disease, and sickle cell disease
  - Vesico-ureteral reflux (defective bladder-ureteral valves)

Host factors III

- Incidence of UTI in women 1-3 % per year; by age 32, half of women have had at least one UTI; risk factors:
  - Women's **short urethra** → ↑ risk of bacteria entering the bladder
  - Colonization of the vaginal area near the urethra
  - Trauma to the urethra by sexual intercourse
  - Spermicide use
  - History of past UTI
- Men have a much lower incidence of UTI (< 0.1% per year)
- Within 3-4 days of **bladder catheterization**, cystitis generally develops; sterile closed drainage only delays the onset of infection

Pathogenesis of upper UTI

- Growth of bacteria in the bladder → chemoattractants released by epithelial cells → acute inflammatory response
- Bacteria may migrate up the ureters and reach the kidney; renal medulla is particularly susceptible to invasion by bacteria
- High concentrations of **ammonia** in the medulla inactivate complement, and the high **osmolality** in this region inhibits migration of polymorphonuclears
- Once bacteria enter the renal parenchyma, they are able to enter the bloodstream and cause septic shock

UTI: microbiology

Etiologic agents

- Most organisms causing UTIs come from fecal and vaginal flora
- *E. coli* is by far the most common cause in uncomplicated cases
- *Klebsiella* spp. and *Proteus* spp. are less common
- In young, sexually active women, *Staphylococcus saprophyticus* accounts for 5–15% of cases of cystitis
- In recurrent infections, after instrumentation, in patients with anatomic defects or renal stones:
  - *Enterobacter* spp.
  - *Pseudomonas* spp.
  - Enterococci

Etiologic agents

- In hospitalized patients receiving broad-spectrum antibiotics and have a bladder catheter: *Candida* spp.
- Other nosocomial pathogens: *S. epidermidis* and *Corynebacterium* group D2
- Group B streptococci
- In 95% of cases, UTIs are caused by a single organism; patients with structural abnormalities are more likely to have polymicrobial infections

UTI: clinical manifestations

Cystitis

- Acute-onset **dysuria** (pain, tingling, or burning in the perineal area during or just after urination), from inflammation of the urethra
- Need to **urinate frequently**, from inflammation of the bladder → suprapubic discomfort when the bladder is distended, bladder spasms may occur
- Urgency, and tenesmus
- May appear blood in the urine, generally caused by inflammatory damage to the bladder wall

Upper-tract infection: pyelonephritis

- Symptoms of cystitis
- In addition:
  - Fever and chills
  - Costovertebral angle pain
  - Nausea and vomiting
  - Hypotension
- Risk factors:
  - Diabetes mellitus, often subacute pyelonephritis with mild symptoms
  - Advanced age
  - Untreated symptoms of cystitis present for more than 7 days

Asymptomatic bacteriuria

- Defined as a positive urine culture without symptoms
- Urinalysis usually shows no white blood cells or an insignificant number
- Most commonly encountered in elderly women
- Treatment unnecessary unless the patient is a:
  - Pregnant woman, because of increased risk of pyelonephritis
  - Child of preschool age, because of risk of renal scarring → interference with normal growth of the kidneys

Urethritis and vaginitis

- Urethritis
  - Inflammation of urethra
  - Can be confused with cystitis
  - Primary symptom is burning on urination
  - Colony counts from urine culture < 10^5 organisms per milliliter
  - Suprapubic pain or urinary frequency absent
- Vaginitis
  - Can also experience burning on urination
  - Vaginal discharge: pelvic examination needed

Physical findings in UTI

- Usually minimal
- Cystitis: suprapubic tenderness
- Pyelonephritis:
  - Often acutely ill and appearing toxic, febrile, hypotensive, with elevated heart rate
  - Costovertebral angle or flank tenderness resulting from inflammation and swelling of the infected kidney
- In elderly patients, confusion and somnolence

UTI: diagnosis

Urinalyses

- **Unspun** midstream **urine**, after cleaning of perineal area: **> 10 leukocytes** per mm^3 = **pyuria**, 96% specificity for cystitis, pyelonephritis, or urethritis
- Dipstick leukocyte esterase test is rapid, sensitive, and specific for detecting pyuria, but false-negatives occur
- Microscopic examination of urinary sediment: leukocyte casts are strong evidence for pyelonephritis
- Increased protein common in UTI

Microbiology tests I

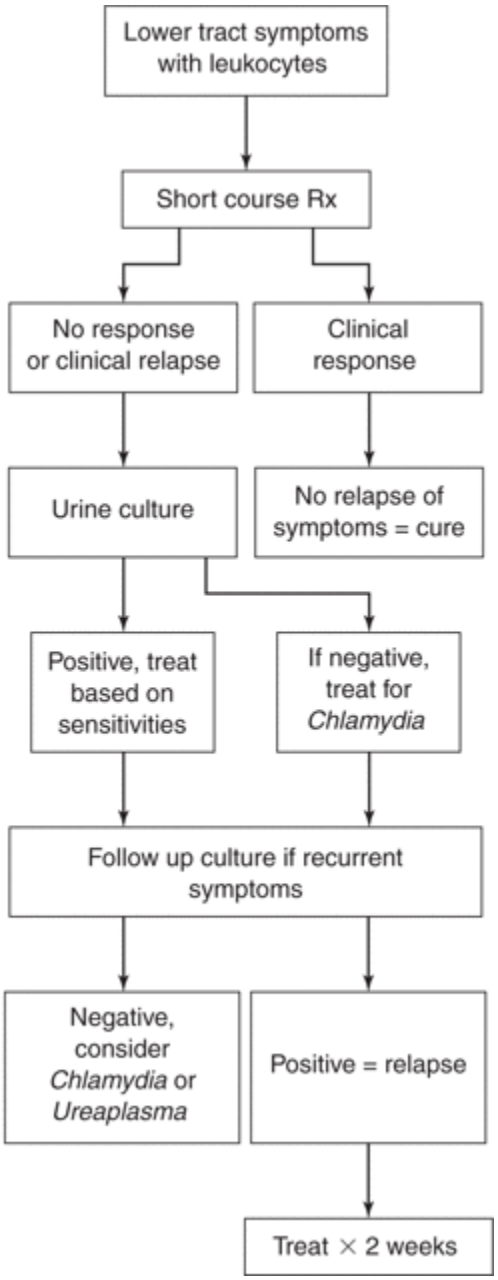
- Unspun urinary **gram** stain should be performed if pyelonephritis suspected, etc.; presence of **one or more bacteria per oil immersion field** = > 10^5 organisms per milliliter, in combination with pyuria and symptoms, indicates active infection
- Urine **culture** is not required initially in young sexually active women with suspected cystitis, and required in all other patients

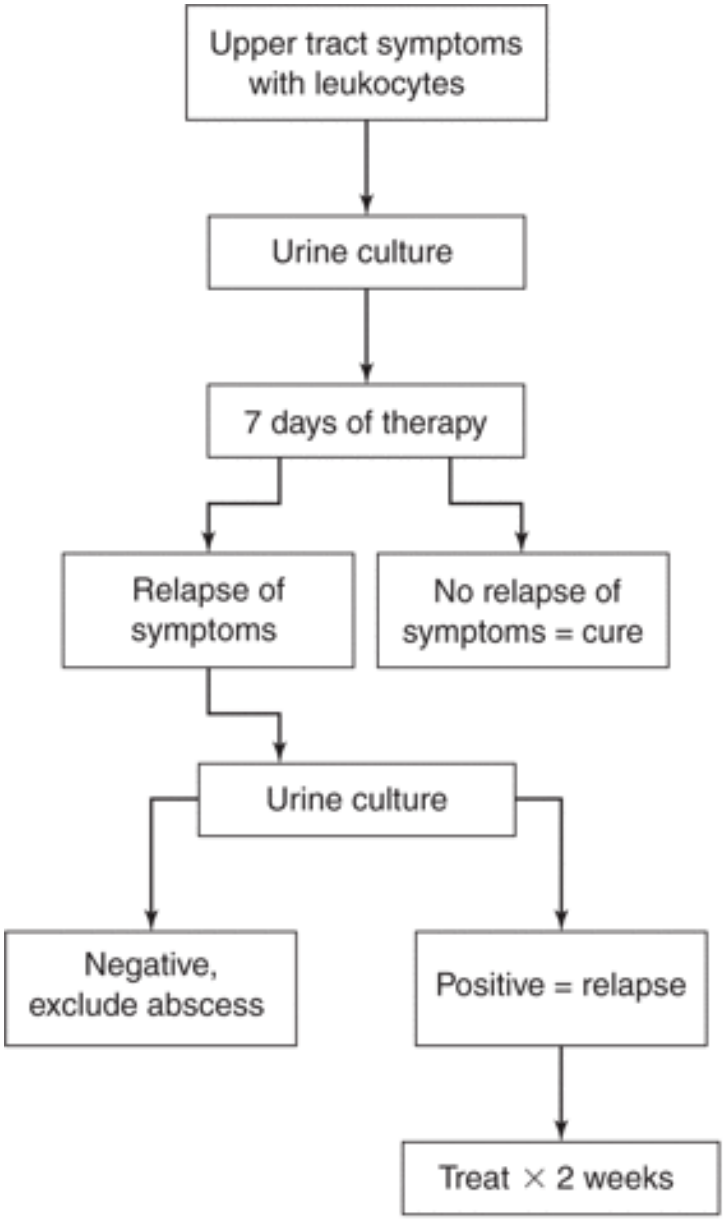
Microbiology tests II

- Urine in the bladder is normally sterile
- Because the urethra and periurethral areas are very **difficult** to sterilize, even carefully collected specimens are contaminated
- By quantitating bacteria in midstream, clean-voided urine **culture**, it is possible to differentiate contamination from infection:
  - Women, in infection generally > 10^5 organisms per ml; with symptoms 10^3 organisms per ml suggestive of infection
  - Men, in infections generally > 10^3 per ml

Microbiology tests III

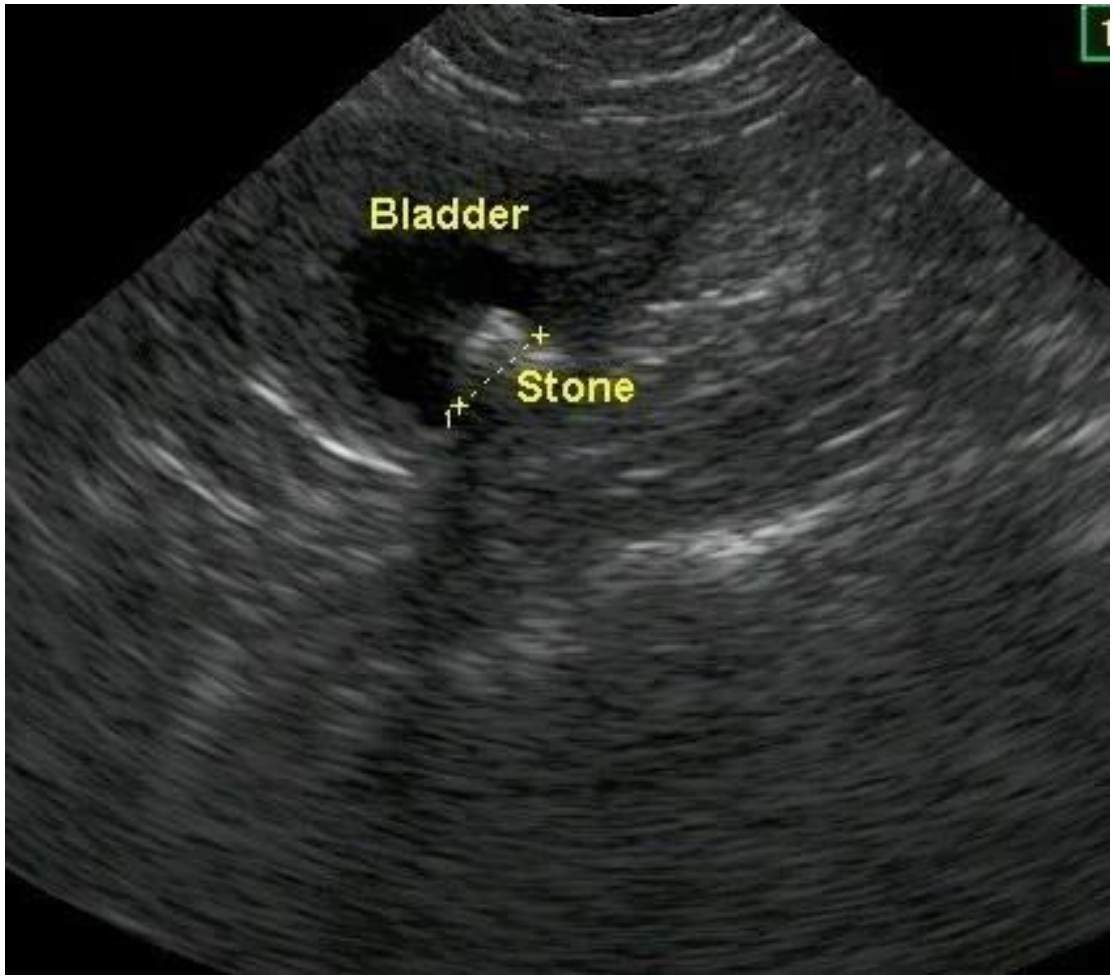
- Cultures should be processed **immediately** or **stored** at 4 °C for **< 24 hours** before the sample is plated on growth media
- Improper handling of urine renders colony counts unreliable
- Routine follow-up urine cultures after completion of therapy is not cost-effective, but is indicated in recurrent symptoms
- Patients with presumed cystitis who experience **recurrent** symptoms and have a positive urine culture following short-course therapy may:
  - Be infected with an antibiotic-resistant organism
  - Have upper-tract disease


Lower tract symptoms with leukocytes
Short course Rx
No response or clinical relapse
Clinical response
Urine culture
No relapse of symptoms = cure
Positive, treat based on sensitivities
If negative, treat for *Chlamydia*
Follow up culture if recurrent symptoms
Negative, consider *Chlamydia* or *Ureaplasma*
Positive = relapse
Treat × 2 weeks

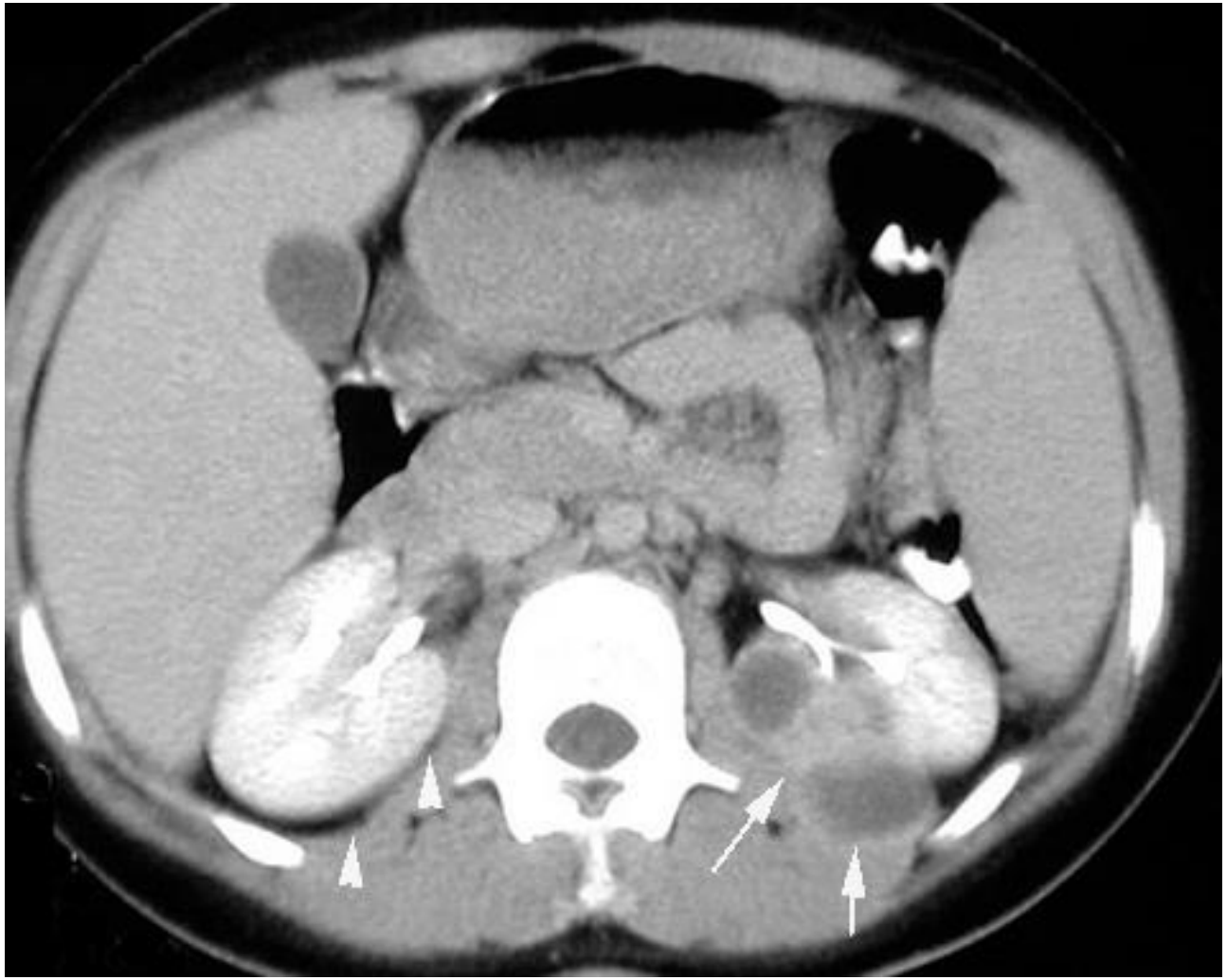

Upper tract symptoms with leukocytes
Urine culture
7 days of therapy
Relapse of symptoms
No relapse of symptoms = cure
Urine culture
Negative, exclude abscess
Positive = relapse
Treat × 2 weeks

Imaging studies

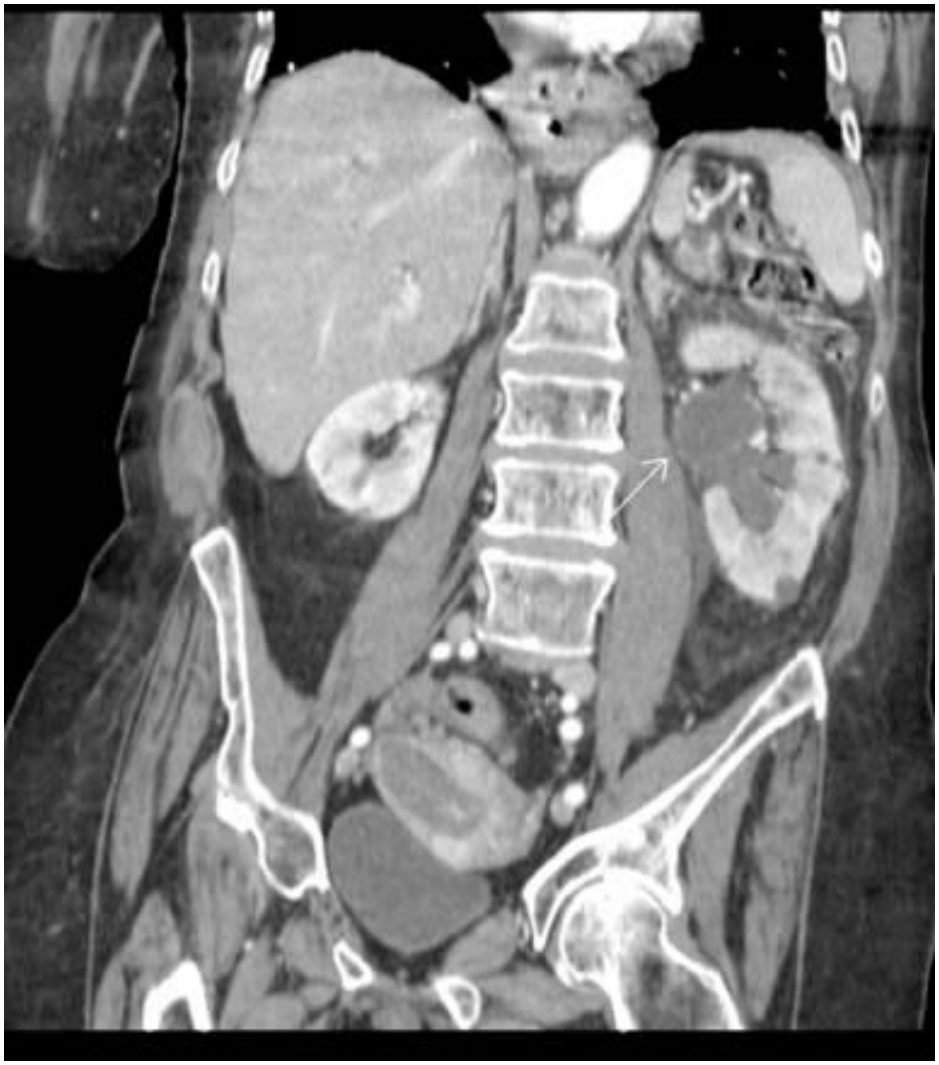
- In sexually active women indicated after:
  - Two recurrences of pyelonephritis
  - Pyelonephritis that fails to defervesce within 48–72 hours of treatment
  - Second UTI in a preschool girl
  - UTI in a boy or a man at any age
- **Ultrasonography**, imaging study of choice, can detect: congenital anatomic abnormalities, renal stones, hydronephrosis, kidney swelling, bladder distension, etc.
- Intravenous pyelogram and CT scan required in some cases
- In renal failure or multiple myeloma, intravenous contrast often exacerbates renal dysfunction and should best be avoided



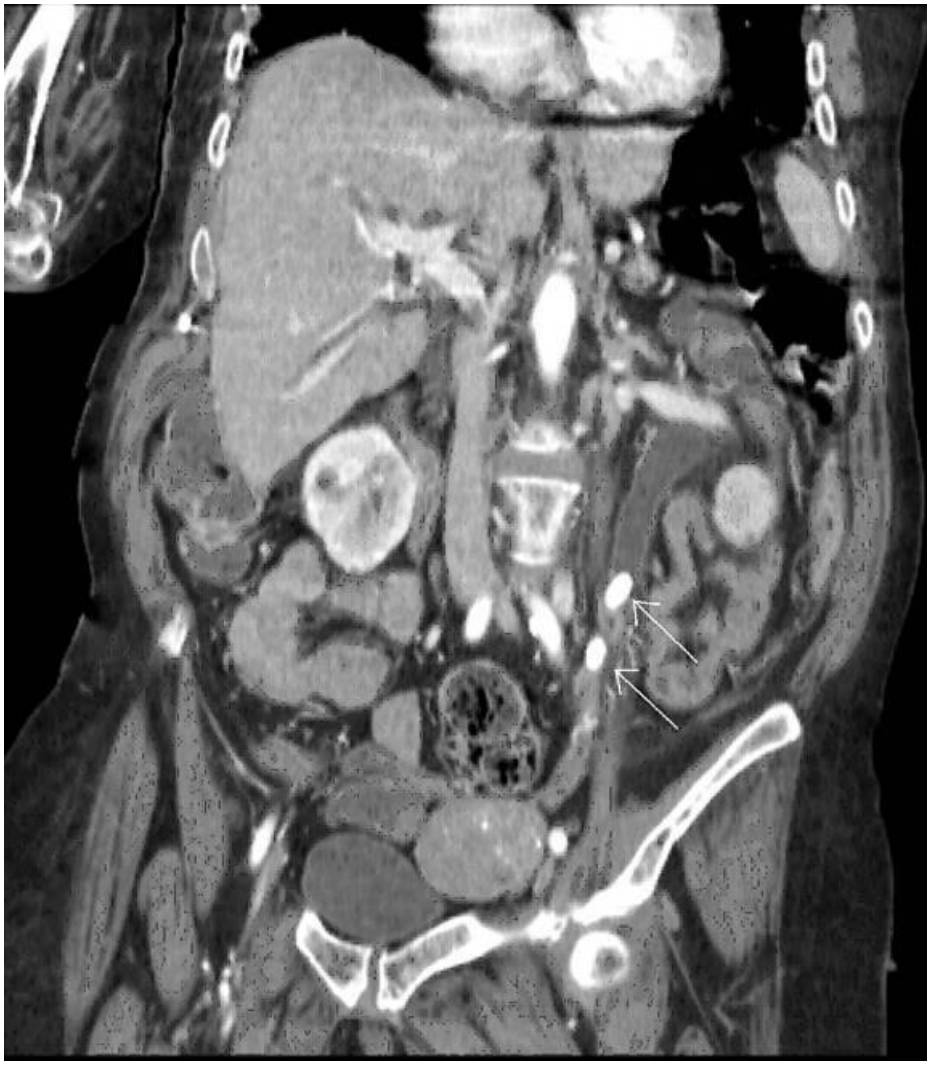
A stone in the bladder



Perinephric abscess



Coronal image, hydronephrosis and dilation of left renal pelvis (arrow).



Coronal image, 2 stones in the dilated left ureter (arrow).

Non contrast CT scan

UTI: treatment

Lower tract infection

- Single-dose therapy effective, but preferred regimen is 3-7 days
- Trimethoprim-sulfamethoxazole, nitrofurantoin, or fosfomycin are the preferred agents
- Longer course therapy should be used in
  - Men
  - Women whose symptoms span more than 7 days
  - Patients with upper-tract symptoms
  - Diabetic patients
- Fluoroquinolones and β-lactams effective but avoided if possible, because their broad spectrum markedly alters the normal mouth and bowel flora and may select for resistant pathogens

Upper tract infection

- Uncomplicated disease: 7 days of oral fluoroquinolone
- Trimethoprim-sulfamethoxazole, beta-lactams, etc. also adequate
- Culture and sensitivities useful in many cases
- Severe sepsis or vomiting: hospitalization for intravenous antibiotic therapy: imipenem, aminoglycoside + cephalosporin, etc. usually, 10-14 days
- All patients with relapse should be studied for anatomic defects or stones

UTI: prevention

Preventive therapy

- Patients with frequent symptomatic recurrences should receive preventive therapy
- Sexually active women
  - Voiding immediately after intercourse
  - **Trimethoprim-sulfamethoxazole single dose immediately after intercourse**
- Children and other patients with anatomic defects:
  - Low dose (½ tablet) trimethoprim-sulfamethoxazole daily
  - Nitrofurantoin daily
- Patients with indwelling bladder catheters: **antibiotic** prophylaxis is **not effective**, and selects **resistant** pathogens

Prostatitis

Etiology

- ***E. coli*** the most frequent cause, followed by ***Klebsiella* spp.**, ***Proteus* spp.**, *Pseudomonas* spp., *Enterobacter* spp., and *Serratia marcescens*
- With the exception of enterococci, gram-positive pathogens are uncommon
- Cause of culture-negative prostatitis may be *Chlamydia* spp.
- Prostate infection is commonly associated with a UTI and may serve as a **reservoir** for recurrent UTI

Pathogenesis

- The mechanism by which bacteria usually reach the prostate is **reflux** of infected urine
- The prostate contains a potent antibacterial zinc-containing compound called **prostatic antibacterial factor**; production ↓ in prostatitis
- Pathologic findings: leukocyte infiltrate, edema, **intraductal desquamation**, and cell necrosis

Clinical findings

- Fever, chills, dysuria, and urinary frequency
- If the prostate becomes extremely swollen, bladder outlet **obstruction** may develop
- The patient often appears septic
- Moderate tenderness of the suprapubic region
- Rectal examination: prostate is **exquisitely tender** and enlarged; vigorous palpation may precipitate bacteremia

- **Chronic prostatitis**: back pain, low-grade fever, myalgias, and arthralgias; recurrent dysuria, and urinary frequency

Diagnosis

- **Acute prostatitis**: massage of the prostate contraindicated
- The causative agent can usually be identified by urine culture
- Blood cultures may also be positive

- **Chronic prostatitis**: difficult diagnosis:
  - Quantitative culturing of the first void urine
  - Midstream urine analysis
  - Prostatic massage sample or post-prostatic massage urine sample are used to differentiate cystitis and urethritis from chronic prostatitis

Treatment

- Acute prostatitis:
  - Ciprofloxacin or trimethoprim-sulfamethoxazole, or based on culture, for 4-6 weeks
  - Most antibiotics do not penetrate the lipophilic, acidic environment of the prostate; however marked inflammation permits antibiotic penetration
- Chronic prostatitis:
  - Antibiotic penetration is critical for effective treatment
  - Trimethoprim-sulfamethoxazole and quinolones are effective
  - For 6–12 weeks
  - Relapses frequent, and prostatectomy may be required

Key messages

To remember…

- Urinary tract infection is a common disease
- In young sexually active women prognosis is generally good with antibiotic treatment
- However in debilitated patients sepsis and related conditions are common and prompt treatment is key to minimize complications and mortality

Further reading

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- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapter 288.
- Singh KP, Li G, Mitrani-Gold FS, Kurtinecz M et al. Systematic review and meta-analysis of antimicrobial treatment effect estimation in complicated urinary tract infection. Antimicrob Agents Chemother 2013; 57: 5284-90.

Preparing the exam

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 9.
- These slides.