Speaker: Barbara Trautner, MD



Infections of Upper and Lower Urinary Tract Infections

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- · Disclosures of Financial Relationships with Relevant **Commercial Interests**
 - · Advisor for Phiogen (past)
 - · Stockholder in Abbott Laboratories, Bristol Myers Squibb, AbbVie, and Pfizer (past)
 - · Research funding from Genentech and Peptilogics
 - Research funding from STRIVE (Shionogi arm)

Topics to cover

- Acute cystitis in women
- Recurrent cystitis in women
- Asymptomatic bacteriuria
- Catheter-associated UTI
- Pyelonephritis
- · Urosepsis and worse





The Great Divide

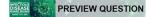
My patient populations

- Older adults in long-term care
- Persons who require urinary catheters for bladder drainage
- Persons with neurogenic bladders

UTI treatment evidence base

- Pre-menopausal women
- Female college students and university staff

Question #1



A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms three months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

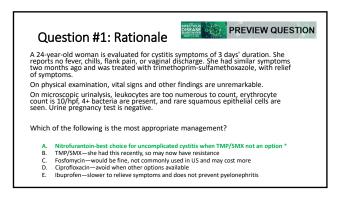
On physical examination, vital signs and other findings are unremarkable. On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

- A. Nitrofurantoin
 B. TMP/SMX
 C. Fosfomycin
 D. Ciprofloxacin
 E. Ibuprofen

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

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IDSA Cystitis Guidelines (2010)

First-line agents

- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin

Alternative choices

- Fluoroquinolones
- Beta-lactams

bid, twice daily; DS, double strength



How long do you treat acute cystitis?

First line choices (5, 3, 1)
Nitrofurantoin X 5
Trimethoprim/sulfamethoxazole X 3
Fosfomycin X1

IDSA Guidelines on Uncomplicated Cystitis, 2010

Nitrofurantoin: Clinical Use

- Interferes with several aspects of bacterial metabolism
- E. coli resistance uncommon
- Great for *E. coli* cystitis and prophylaxis
- Inadequate levels in tissue and blood
- Dyes urine yellow
- Intrinsic resistance in *Pseudomonas, Proteus, Serratia*
- Resistance frequent in Klebsiella and Enterobacter
- Renal excretion but OK to use if GFR >30 mL/min

GFR, glomerular filtration rate

Cunha et al, Eur J Clin Microbiol Infect Dis 2017; 36(7) Singh, CMAJ 2015; 187(9) AGS Beers Criteria 2019

Nitrofurantoin Adverse Events

- Pulmonary toxicity--RARE
 - Acute: reversible hypersensitivity reaction
 - Subacute or chronic: diffuse pneumonitis
 - Dose dependent?
 - Favors use of lowest possible dose/less frequent dosing for chronic prophylaxis
- Hepatitis—RARE
- Nausea—common
 - Worse with micro- (QID) than macro-crystalline (BID) formulation

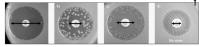
QID, four times daily

Santos, JAGS 2016, PMID: 27100576

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Fosfomycin: Clinical use for UTI

- High levels in urine for over 24 hours
- Single 3 gm dose for cystitis
- Developing niche for ESBL- and KPC- Enterobacterales
 - 3gm every 48-72 hours
- IV fosfomycin associated with hypokalemia and elevated LFTs (not approved in United States)



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

Potential Harms of Quinolones: FDA warnings

- · Dysglycemia
- Tendon rupture/damage
- Interstitial nephritis
- Neuropathy
- Diarrhea-with or without C. diff
- Aortic aneurysms?
- Arrhythmias

C. diff. Clostridioides difficile



New Oral Drugs in the Pipeline for Cystitis

FDA approved for uUTI

- Pivmecillinam
 - April 24 2024
 - In use in Europe and Canada
 - Endorsed in 2010 IDSA guidelines
 - . Pro-drug of mecillinam
 - Binds to PBP-2 in Gram-negative cell wall
 - 185 mg tid for 3-7 days
 - Use for
 - Enterobacterales, including ESBL+
 Staph saprophyticus

Not FDA approved

- Gepotidacin
- Sulopenem
- Tebipenem



Question #2



A 38-year-old woman comes in for recurrent UTI. This is her 3rd episode of symptomatic, culture-proven cystitis in the past 12 months. The recurrent UTIs are very inconvenient to her. She notes that her UTI symptoms usually begin within 2 days of sexual intercourse.

You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

- Nitrofurantoin daily for 24 months
- Nitrofurantoin one dose after intercourse for 6 months Ciprofloxacin daily for 6 months Trimethoprim-sulfamethoxazole twice daily for 6 months
- Cranberry tablets

Question #2: Rationale

PREVIEW QUESTION

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Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

- Nitrofurantoin daily for 24 months –duration usually 3-6 months Nitrofurantoin one dose after intercourse for 6 months—use an trigger situations *
- trigger stuations "
 Ciprofloxacin daily for 6 months—not a good drug for prophylaxis
 Trimethoprim-sulfamethoxazole twice daily for 6 months—dose is too high
 Cranberry tablets—minimal data to support

Prevention and Management of Recurrent UTI

- Self-treatment coupled with urine collection for culture is an appropriate strategy
- Use the most focused antibiotic and as sparingly as possible
- If the woman's episodes are related to sexual intercourse, one dose of antibiotics after intercourse is an effective strategy
- Guidelines suggest treating daily for 3-12 months
- · No clarity on which antibiotic to use, other than to avoid fluoroquinolones given side effects and resistance

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022) https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti

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Non-antibiotic Strategies to Prevent Recurrent UTI

Likely helpful (FDA approved)

- Increasing fluid intake
- Vaginal estrogen in postmenopausal women
- Methenamine (?)

Uncertain benefit (not FDA approved)

- · Other behavioral changes
- Cranberry products (?)
- D-mannose
- Probiotics
- · Other supplement (liquid or

Fluid intake: Hooton TM, et al. JAMA Intern Med. 2018
Methenamine trials: Harding C, et al. Health Technol Assess. 2022
Botros, C, et al. Int Utagynecol. J. 2022
Systematic review of cranberry products: Williams G, et al. Cochrane Database Syst Rev. 2023

Audience Response Question #3

A 69-year-old woman comes in for an annual checkup. No change in her baseline health status. When she coughs or sneezes, she notes slight leakage of urine. Her medical history is significant for three vaginal births, and she has hypertension and type 2 diabetes mellitus.

Her BMI is 30. Her vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

Which of the following is the most appropriate management?

A. Nitrofurantoin

B. Ciprofloxacin

- Cystoscopy Urine culture and sensitivities No further infectious workup

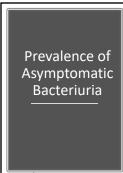
Audience Response Question #3: Rationale

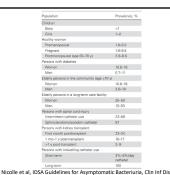
A 69-year-old woman comes in for an annual checkup. No change in her baseline health status. When she coughs or sneezes, she notes slight leakage of urine. Her medical history is significant for three vaginal births, and she has well-controlled hypertension. Her BMI is 30. Her vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 24 for bacteria.

Which of the following is the most appropriate management?

- A. Nitrofurantoin
 B. Ciprofloxacin
 C. Cystoscopy
- Urine culture and sensitivities
- —this is a case of asymptomatic bacteriuria *









Five Things Physicians and Patients Should Question

Don't treat asymptomatic bacteruria with antibiotics.

Indepropriate use of antibiotics to test asymptomatic bacterium (ASV) or a significant number of bacteria in the urine that occurs without symptoms such as burning of frequent unration, is a major combinator to antibiotic oversice in patients. With the exception of preparat patients, patients used provided to the patients of the pat

IDSA Guidelines on ASB 2019

Screening and Treatment Indicated

- ✓ Pregnant women
- ✓ Prior to urologic surgery with mucosal trauma
 Pre-operative urine culture recommended

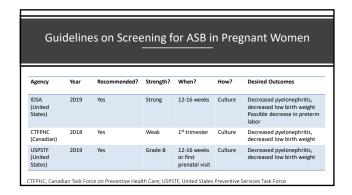
 - Treat with 1-2 doses of antibiotics shortly prior to surgery

- X Infants and children
- X Non-pregnant womer X Functionally-impaired older adults
- X Diabetic adults
- X Patients >1 month from kidney transplant

Screening and Treatment Discouraged

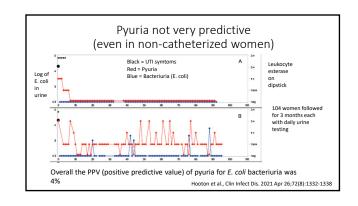
- X Neutropenic patients X Patients with solid organ transplant
- X Persons with spinal cord injury X Patients with indwelling catheters
- X Prior to non-urologic surgery

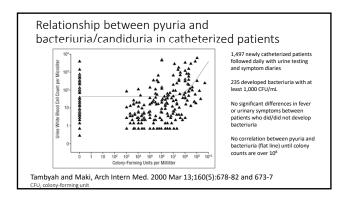
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Myth-Busting (True Facts!) Bacteriuria ≠ UTI Bacteriuria in the urine can be bladder colonization or symptomatic urinary tract infection Pyuria ≠ UTI The presence of WBC in the urine doesn't help much with diagnosis of UTI Absence of pyuria suggests to look for a non-UTI diagnosis Foul smelling urine ≠ UTI Sediment or cloudy urine in catheter tubing ≠ UTI All catheterized bladders develop high level bacteriuria Flushing the catheter to make sure it is patent is a good idea Healthy bladders are not sterile in many people Take home points: Order urine tests only in patients with urinary symptoms The best thing you can do with asymptomatic bacteriuria is leave it alone Pyuria is not a reliable marker for UTI Changes in the urine are not reliable markers for UTI





Audience Response Question #4 A 75-year-old man is seen in the pre-operative clinic. He is scheduled to undergo cystoscopy and possible biopsy for persistent hematuria. He is also scheduled for elective left total knee replacement, shortly after the urinary procedure. Other than the hematuria, he denies urinary-specific symptoms. He underwent kidney transplantation 3 years earlier, related to complications of diabetes. On physical examination, vital signs are normal. His left knee has an effusion but is not red or excessively painful. No change in his baseline creatinine clearance. On urinalysis, leukcyte count is 10/hpf, erythrocyte count is 100/hpf, 4+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew >10,000-<100,000 colony-forming units of Klebsiella pneumoniae. Kidney ultrasonography is unremarkable. Which of the following is the primary indication for antimicrobial therapy in this patient? A. Cystoscopy and biopsy B. Diabetes mellitus C. Kidney transplant D. Knee prosthesis placement

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Audience Response Question #4: Rationale

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On urinalysis, leukocyte count is 10/hpf, erythrocyte count is 100/hpf, 4+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew >10,000-<100,000 colony-forming units of *Klebsiella pneumoniae*.

Kidney ultrasonography is unremarkable.

- Which of the following is the primary indication for antimicrobial therapy in this patient?

 - Diabetes mellitus-no, see ASB guidelines
 - C. Kidney transplant—not necessary to treat ASB after >1 month post transplant
 D. Knee prosthesis placement—not fully addressed in the 2019 ASB guidelines

Audience Response Question #5

A 46-year-old man is admitted to the hospital for urgent repair of aortic dissection. An indwelling urinary catheter is inserted prior to surgery. Endovascular aortic aneurysm repair is successful, and he is transferred to the surgical intensive care unit. He has underlying diabetes and systolic heart

In addition to removing the urinary catheter as soon as possible, which of the following will decrease this patient's risk of catheter-associated urinary tract infection?

- Daily cleansing of the meatal area of the catheter with antiseptics
- Routine catheter change every 3 days Screening for and treatment of bacteriuria
- D. Keeping the collecting bag below the level of the bladder
- Use of antiseptic- or antibiotic-coated urinary catheters

Audience Response Question #5: Rationale

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In addition to removing the urinary catheter as soon as possible, which of the following will decrease this patient's risk of catheter-associated urinary tract infection?

- A. Daily cleansing of the meatal area of the catheter with antiseptics
- B. Routine catheter change every 3 days
- C. Screening for and treatment of bacteriuria
- · Ineffective AND confers excess antibiotic use D. Keeping the collecting bag below the level of the bladder
- rity helps prevent reflux to kid E. Use of antiseptic-coated urinary catheters
 - Minimal impact and approved only for short-term use



Audience Response Question #6

A 37-year-old woman with a history of recurrent UTIs developed typical symptoms of urgency, frequency, and dysuria five days ago. On the advice of her close friend, she decided to treat this UTI with a nutritional supplement instead of antibiotics. Symptoms did not resolve, and she developed worsening low back pain. This morning she vomited once. In the office, her temperature is 100.5F, BP 135/70, HR 110, RR 16. She is not currently vomiting and can sip water.

You do not have any prior urine cultures to guide your therapy. Assuming you can manage her as an outpatient, what treatment would you offer?

- Oral trimethoprim-sulfamethoxazole for 5 days
- Oral ciprofloxacin for 14 days
 One dose of ceftriaxone IM plus oral ciprofloxacin for 7 days
- Cephalexin for 7 days
- Nitrofurantoin for 10-14 days

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

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You do not have any prior urine cultures to guide your therapy. Assuming you can manage her as an outpatient, what treatment would you offer?

- Oral trimethoprim-sulfamethoxazole for 5 days—duration for TMP/SMX is 7-14 days
- Oral ciprofloxacin for 14 days—duration for fluroquinolones to treat pyelo is 5-7 days
- One dose of ceftriaxone IM plus oral ciprofloxacin for 7 days—this is your safest option, as you do not know if she has an organism that is susceptible to fluoroquinolones (or any other oral agents) *
- Cephalexin for 7 days—oral beta lactams are not as effective for UTIs and need a longer course
- Nitrofurantoin for 10-14 days—NTF does not achieve adequate levels in tissue or blood

Management of Pyelonephritis

- Many clinical trials included pyelonephritis with complicated UTI
- Complicated UTI increasingly means urinary tract infection that has spread beyond the bladder (to kidneys, bloodstream)
- Empiric oral therapy
 - Trimethoprim-sulfamethoxazole 7-14 days
 - Fluroquinolones 5-7 days
 - Consider a one-time dose of IM ceftriaxone or gentamicin while awaiting
 - · Oral beta-lactams (cephalosporins, amoxicillin-clavulanate) 10-14 days
- Empiric intravenous therapy
 - · IV cephalosporins, piperacillin-tazobactam, carbapenems, fluoroquinolones
- To avoid: nitrofurantoin and fosfomycin

Johnson and Russo, NEJM 2018. 378;1



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Audience Response Question #7

68-year-old diabetic man with CHF, vascular disease, BPH presented with 2 days of vomiting, abdominal pain, and confusion.

Vital signs: T 99.9 BP 47/39, HR 110, RR 22

Physical exam: patient was obtunded but appeared to have tenderness in the epigastric area Labs: WBC 23.7 (94% segs), platelets 96K; Creatinine 3.1 (from 1.7 baseline)

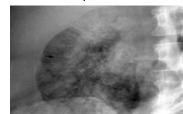
UA: WBC 250, RBC too numerous to count, no bacteria

Troponin 7.2, EKG with ST elevations; HgB A1c 10.5

He was admitted to the CCU and initiated on therapy for an ST elevation myocardial infarction. His blood pressure was labile, and he required pressor support. He required intubation. On hospital day 2, his blood cultures grew 4/4 bottles of *Klebsiella pneumoniae*.

The next slide shows an abdominal radiography (KUB) that had been performed at admission.

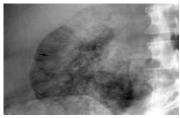
Audience Response Question #7: X-Ray of Abdomen



What would you order next?

- A. Abdominal ultrasound
- B. Abdominal CT
- C. Nasogastric tube
- D. Stool for *C. diff* testing

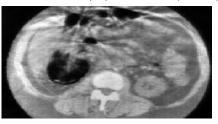
Audience Response Question #7: Rationale



What would you order next?

- A. Abdominal ultrasound
- B. Abdominal CT: you are looking at gas in the kidney *
- C. Nasogastric tube
- D. Stool for *C. diff* testing

Abdominal CT with Emphysematous Pyelonephritis



CT showing gas within the renal parenchyma

Clinical course of case #7

- Percutaneous drainage of the right kidney
- Renal drainage grew Klebsiella
- After weeks in the ICU was stable enough for nephrectomy
- 9 months later had then coronary artery bypass surgery

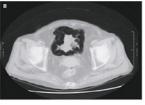
Diagnosis and management of emphysematous pyelonephritis

- 95% of cases in patients with diabetes (poorly controlled)
- Negative prognostic factors: shock, impaired consciousness, thrombocytopenia, renal failure
- Organisms: E. coli, Klebsiella, Proteus
- Diagnosis often delayed
- Differential: renal abscess, papillary necrosis
- Radiological diagnosis
- Managed initially by drainage—percutaneous nephrostomy or ureteral stent
- Nephrectomy for non-responders, severe cases

Kamei, J Infection and Chemotherapy 2021

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Emphysematous cystitis

Asada, NEJM 2003;349: 258



Tzou. NEJM 2016: 375: 18

Diagnosis and Management of Emphysematous Cystitis

- Female predilection
- Most cases in diabetics
- Commonly caused by E. coli, Klebsiella (Candida reported)
- Organisms produce gas in the bladder wall and lumen
- Can present with lower abdominal pain
- Diagnosed radiologically
- Relieve bladder obstruction if present
- Typically responds well to medical management

Audience Response Question #8

57-year-old man with spinal cord injury (T12) and a chronic indwelling urinary catheter. Two years prior he had a fever, and his blood grew *S. aureus* and *Pseudomonas*. Urine grew lactose negative GNR and gram-positive organisms.

One year prior, he again had a fever, and his blood grew Serratia, E. coli, and Pseudomonas. Urine grew Serratia and Pseudomonas.

Both times he was treated with appropriate antibiotics, with resolution of fever and stabilization. He has had many urine cultures, all of which grew multiple urinary pathogens.

Prior to entry in a research protocol, he had a screening abdominal ultrasound, which showed a hypoechoic mass in right kidney. In addition to CT scan, what will be the definitive therapy:

- A. Renal biopsy
- B. 3-6 months of antibiotics based on current urine culture
- C. Percutaneous drainage
- D. Nephrectomy

Audience Response Question #8: Rationale

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- A. Renal biopsy
- B. 3-6 months of antibiotics based on current urine culture
- C. Percutaneous drainage
- D. Nephrectomy—can you name the diagnosis? *

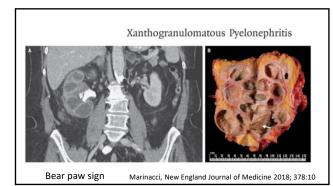




Xanthogranulomatous pyelonephritis

https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-forurologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

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Xanthogranulomatous Pyelonephritis

- Chronic polymicrobial infection of renal parenchyma
- Often starts with stone/obstruction
- Frequently insidious and mistaken for tumor
- Renal tissue is destroyed and replaced by granulomatous tissue
- Yellow from the foam cells (macrophages) full of lipids
- Requires nephrectomy plus antibiotics
- Our patient underwent right nephrectomy, with finding of a variegated tan-white mass, large amount of inflammatory reaction, purulence in right renal fossa



To Re-Cap

- Acute and recurrent cystitis in womennitrofurantoin
- Asymptomatic bacteriuria
 - Pregnant women-screen and treat
 - Urologic surgery—screen and treat
 - Everyone else—don't test the urine
- Catheter-associated UTI—ensure drainage
- Pyelonephritis—treat with tissue-active
- Urosepsis and worse
 - Emphysematous pyelonephritis-drainage
 Emphysematous cystitis-medical management

 - Xanthogranulomatous pyelonephritis-removal

Is everything clear now?

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