Urinary Tract Infections: Core Curriculum 2024

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Urinary tract infections (UTIs) are some of the most commonly encountered infections in clinical practice. Accurate diagnosis and evidence-based treatment of UTIs will lead to better clinical care for many patients and limit unnecessary antibiotic use. Urinalysis and urine cultures are helpful tools in the diagnosis of UTIs; however, it is important to recognize their limitations. Differentiating between asymptomatic bacteriuria (ASB) and true UTI is important because antibiotics are unnecessary in most nonpregnant patients with ASB and can even potentially cause harm if prescribed. Choice and duration of antibiotics varies across the spectrum of UTI syndromes such as acute uncomplicated cystitis, pyelonephritis, prostatitis, and catheter-associated UTIs. The treatment approach also depends on patients' degree of immunosuppression and their genitourinary anatomy. Therefore, patients with urological obstruction or kidney transplants may require a specialized and multidisciplinary management approach. For individuals prone to frequent UTIs, some preventative measures can be utilized, yet there is often not a "one size fits all" approach.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Urinary tract infection (UTI) is a broad term that encompasses a spectrum of infectious syndromes that affect the urinary tract anywhere from the urethra to the kidneys. UTIs are some of the most common infections, and it is reported that 50%-60% of women have at least 1 UTI in their lifetime. The usual mechanism of infection is bacteria colonizing the urethra or periurethral space migrating into the bladder and causing an inflammatory response. The bacteria that typically cause this are from the gastrointestinal (GI) tract and are collectively called Enterobacterales; examples include *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Another possible way of developing UTIs is bacteria in the bloodstream migrating to the kidneys or bladder, but this is very rare. The risk factors for UTIs include female sex, recent sexual intercourse, diabetes mellitus, and structural or functional urological abnormalities. Diagnosis and management depend on patient factors and the extent of disease. In this installment of *AJKD*'s Core Curriculum in Nephrology, we provide a review of the clinical presentation, diagnosis, and evidence-based management of common and important UTI syndromes such as cystitis, pyelonephritis, asymptomatic bacteriuria, prostatitis, catheter associated UTIs, and recurrent UTIs.

Acute Uncomplicated Cystitis

Case 1: *A 27-year-old woman calls her physician's office reporting 3 days of a burning sensation during urination with urinary frequency and discomfort in her lower abdomen. She recalls having the same symptoms a year ago, which was the only other time she was treated for a UTI. She is otherwise healthy and takes no medications. Her last menstrual period was 2 weeks ago.*

Question 1: What is the best next step in the management of this patient?

(a) Ask her to submit a urine sample for urinalysis and urine culture and recommend antibiotics pending culture results.
(b) Prescribe ciprofloxacin 500 mg twice daily for 7 days.
(c) Prescribe nitrofurantoin 100 mg twice daily for 5 days.
(d) Prescribe amoxicillin 875 mg twice daily for 5 days.
(e) Prescribe cefpodoxime 100 mg twice daily for 5 days.

For the answer to this question, see the following text.

Diagnosis and Testing

Acute uncomplicated cystitis (also known as "simple cystitis") is a type of UTI, specifically an infection of the bladder in an otherwise immunocompetent host with normal urinary tract anatomy. The classic symptoms are dysuria, urinary frequency, urinary urgency, or suprapubic pain in the absence of systemic illness (eg, fever, rigors, or vomiting) or upper urinary tract involvement (eg, flank pain or costovertebral angle tenderness). "Complicated UTI" is a broad

term that has been traditionally used to lump the UTI syndromes that do not meet the aforementioned description of simple cystitis as well as UTIs that occur in patients with severe immunosuppression or with significant anatomical abnormalities. Because complicated UTIs encompass a wide spectrum of syndromes, there is no singular approach to managing them. Therefore, rather than using the binary of uncomplicated versus complicated UTIs, this text discusses an approach to the individual syndromes that fall under the umbrella of "complicated" UTI such as pyelonephritis, prostatitis, or catheter-associated UTIs.

Diagnosis of UTIs is primarily made by the presence of typical symptoms and can be confirmed by 2 main laboratory tests: urinalysis and urine cultures. Urinalysis can help with diagnosis of UTIs. There are 2 main urinalysis tests: urine microscopy and urine dipstick. Urine microscopy can identify the presence of white blood cells (WBCs) in urine, which is termed pyuria. Having ≥10 WBCs/μL in urine is suggestive but not diagnostic of a UTI. The greatest value of checking for pyuria lies in its negative predictive value, which is reported to be more than 85%. Therefore, without pyuria it is unlikely that a patient has a UTI.

The advantage of a urine dipstick is that it is usually more readily available than microscopy or culture. The 2 main tests in a urine dipstick that can aid with UTI diagnosis are leukocyte esterase and nitrite. Leukocyte esterase, an enzyme released by lysed WBCs, acts as a surrogate marker for pyuria. Nitrites in the urine are attributed to the ability of some Gram-negative bacteria like *E coli* (the most common cause of UTIs) to convert urine nitrate to nitrite. Positive nitrite on a urine dipstick can therefore be an indicator for the presence of bacteria in the urine (bacteriuria) and specifically Gram-negative bacteria. One of the limitations of this test is that it would not detect bacteriuria with organisms that do not have the biochemical ability to create nitrite such as *Enterococci* and *Pseudomonas* species. Additionally, a false-positive nitrite can be seen in patients who use phenazopyridine, which is a common over-the-counter urinary analgesic in the United States. The reported sensitivity of both leukocyte esterase and nitrite for detecting bacteriuria was variable, but the specificity was found to be more than 90%.

Midstream voided urine cultures are a more direct way to assess the presence of pathogenic bacteria in the urine. Bacteriuria in some cases represent contamination; however, in symptomatic patients this could help confirm the diagnosis of a UTI. The classic cutoff for a positive urine culture to reflect the presence of bladder bacteriuria has been $>10^5$ colony-forming units (CFU)/mL.

Testing with urinalysis or urine culture up front is not indicated in most cases of *uncomplicated* cystitis. Having classic symptoms of acute uncomplicated cystitis, as in case 1, can be sufficient to make a clinical diagnosis (Box 1) and recommend empiric treatment. An example would be the combination of dysuria and urinary frequency *without* vaginal discharge or irritation, which has a reported positive likelihood ratio of 24 for the diagnosis of a UTI. Patients, especially if they have had prior UTIs like this patient, often recognize the symptoms and identify when they have a UTI. One study found that self-diagnosis has a positive likelihood ratio of 4.

Box 1. Clinical Features of Acute Uncomplicated Cystitis

History

Key method of diagnosis

Possible symptoms

- Dysuria
- Urinary frequency
- Urinary urgency
- Suprapubic pain
- "Feels like prior treated UTI"
- Absence of vaginal symptoms
- Absence of systemic symptoms (shaking chills, rigors)
- Absence of upper tract symptoms

Other Diagnostics[a]

Not required for all patients

- Urinalysis: pyuria (approximately >10 WBC/HPF), presence of "many" bacteria
- Urine dipstick: + nitrite, + leukocyte esterase
- Urine culture with $>10^5$ CFU growth of a pathogenic organism

Abbreviations: CFU, colony-forming units; HPF, high-power field; UTI, urinary tract infection; WBC, white blood cells.
[a]These tests can increase likelihood of a cystitis diagnosis but are not diagnostic on their own. Clinical context is necessary to interpret results.

The following are examples of situations where a urinalysis and urine culture should be sent when evaluating a patient for a UTI:

- Signs or symptoms of upper tract disease or systemic illness.
- Atypical symptoms, such as a patient who has dysuria and vaginal symptoms that are also suggestive of vaginitis.
- Patients at high risk of developing complications, such as those who are immunocompromised or have urological abnormalities.
- Patients at risk of infection with multidrug-resistant organisms (MDRO), such as those with a history of infections with MDROs or who have had recent courses of antibiotics or a recent hospitalization.
- Lack of improvement or progression of symptoms after about 48-72 hours of initial empiric antibiotics.

Another important test to consider is a pregnancy test in women of childbearing age. Pregnancy can affect the threshold to treat UTIs and the type of antibiotics used; therefore, it is important to obtain a pregnancy test if it is challenging to ascertain the likelihood of pregnancy with history alone. See Table 1 for a brief

Table 1. Safety of Oral Antibiotics in Pregnancy

Antibiotic	FDA Pregnancy Risk Category[a]	Comment
Nitrofurantoin	B	Can be used during the first and second trimester. Avoid use in the last trimester due to the risk of hemolytic anemia in the newborn.
Trimethoprim-sulfamethoxazole (TMP-SMX)	D	Avoid use if there are alternatives. Use in the first trimester is associated with an increased risk of fetal neural tube defects. In the third trimester there is an increased risk of hyperbilirubinemia and kernicterus. If necessary for use, the second trimester would be the safest window.
Fosfomycin	B	Can be used.
Oral β-lactams (eg, amoxicillin-clavulanic acid or cefpodoxime)	B	Recommended for use in pregnancy.
Fluoroquinolones (eg, ciprofloxacin)	C	Avoid use if there are alternatives.

The risk–benefit balance needs to be assessed with use of any medication in individual patients. Consider involving their obstetrician if there are any concerns.
[a]FDA Pregnancy Risk Categories:

- *Category A*: No risk in human studies.
- *Category B*: No risk in animal studies.
- *Category C*: Risk cannot be ruled out. There are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks.
- *Category D*: Evidence of risk. Studies in pregnant women have demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks.
- *Category X*: Contraindicated. Studies in pregnant women have demonstrated a risk to the fetus; and/or human or animal studies have shown fetal abnormalities. Risks of the drug outweigh the potential benefits.

overview of the safety of common oral antimicrobials in pregnancy.

Empiric Treatment

One of the main first-line agents for the treatment of acute uncomplicated cystitis is oral nitrofurantoin for 5 days (Table 2). Fosfomycin is an acceptable alternative if nitrofurantoin cannot be used. It is important to note that both nitrofurantoin and fosfomycin should be avoided if early pyelonephritis is suspected because they have poor drug penetration to renal parenchyma. Trimethoprim-sulfamethoxazole can also be used empirically as a first-line agent *except* in cases where local resistance rates to Enterobacteriales (like *E coli*) *exceed* 20% or in patients who have used trimethoprim-sulfamethoxazole for an infection in the past 3 months.

Oral β-lactams such as amoxicillin-clavulanate or cefpodoxime are effective second-line agents in treating UTIs. They are considered second-line agents because there are limited data suggesting their inferior efficacy and a longer duration of administration is needed compared with other medications. They should only be used if the previously listed first-line options are not feasible due to allergy, availability, or resistance. Fluoroquinolones like ciprofloxacin are often effective in treating UTIs but are not recommended as first-line agents for uncomplicated cystitis if there are other oral alternatives. This is due to their side-effect profile and to mitigate the increasing rates of quinolone resistance. They are reserved for more serious infections such as pyelonephritis.

Review of Question 1

This patient had symptoms that would be classic for simple cystitis (burning, frequency, suprapubic pain), so she can be started on treatment without confirmatory laboratory testing. Of the treatment options listed, nitrofurantoin is the only first-line agent. Ciprofloxacin should be reserved for pyelonephritis or more complicated infections, and β-lactams such as amoxicillin are second-line agents. Thus, the answer is (c), prescribe nitrofurantoin 100 mg twice daily for 5 days.

Pyelonephritis

Case 1, continued: *The patient then developed subjective fevers and right lower back pain despite having taken the nitrofurantoin prescribed empirically by urgent care for 3 days. The diagnosis is pyelonephritis, and the urine cultures grew > 100,000 CFU/mL E coli which was resistant to nitrofurantoin and trimethoprim-sulfamethoxazole but susceptible to ciprofloxacin. She was switched to ciprofloxacin 500 mg twice a day. She showed improvement in her symptoms by day 2 of treatment and resolution of all symptoms by day 3.*

Question 2: How many total days of ciprofloxacin would be recommended for this patient?

(a) Treat for a total 3 days
(b) Treat for a total 7 days
(c) Treat for a total 14 days
(d) Treat for a total 21 days
(e) Determine treatment based on repeat urine culture results at day 7

For the answer to this question, see the following text.

Table 2. Oral Antibiotics for the Management of Cystitis and Pyelonephritis

Antibiotic	Acute Uncomplicated Cystitis	Pyelonephritis
Nitrofurantoin	• First-line agent • 100 mg twice daily for 5 days[a]	• Avoid due to suboptimal concentrations in renal parenchyma
Trimethoprim-sulfamethoxazole	• First-line agent • 1 DS tablet twice daily for 3 days[a] • Avoid if used in the past 3 months or if prevalence of local resistance is known to exceed 20%. (Rates of TMP-SMX resistance in *E coli* isolates in most of the United States exceed 20%.)	• Can be used if bacteria are identified to be susceptible. • 1 DS tablet twice daily • *Note:* The Infectious Diseases Society of America (IDSA) recommends 14 days, but more recent data indicate that 7 days would be adequate provided the patient is improving clinically.
Fosfomycin	• First-line agent. • 3 g as 1 dose	• Avoid due to suboptimal concentrations in renal parenchyma
Oral β-lactams (eg, amoxicillin-clavulanic acid or cefpodoxime)	• Use only if the above first-line agents cannot be used • *Example* (not comprehensive list): ◇ Amoxicillin, clavulanic acid 500/125 mg twice daily for 5-7 days[a] ◇ Cefpodoxime, 100 mg twice daily for 5-7 days[a]	• Not recommended as an initial agent. • Can consider using oral β-lactam agent if pathogen known to be susceptible and after the patient receives an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone.
Fluoroquinolones (eg, ciprofloxacin)	• Effective but use only if alternative oral antimicrobials for acute cystitis are not available or possible • *Example:* Ciprofloxacin 250 mg twice daily for 3 days[a]	• Ciprofloxacin 500 mg twice daily for 7 days

Doses listed in this table are for creatinine clearance > 60. Abbreviations: DS, double strength; TMP-SMX, trimethoprim-sulfamethoxazole.
[a]Duration of therapy for cystitis are based on guideline recommendations for *women*. For uncomplicated cystitis in men, consider duration of ~7 days provided there is no evidence of prostatitis.

Pyelonephritis is a UTI that extends to the kidneys. The typical symptoms include flank pain, fevers, rigors, nausea, or vomiting. In contrast to cystitis, obtaining urinalysis and urine cultures is recommended for all cases of suspected pyelonephritis.

The diagnosis of pyelonephritis should be made by clinical assessment and laboratory testing (urinalysis and urine culture). Imaging is not required for all comers and can be reserved for cases where the patient is critically ill, not improving on initial therapy, or suspected to have an obstruction or a complication. Complications of pyelonephritis include but are not limited to sepsis, acute renal failure, renal or perinephric abscess, kidney stones (eg, staghorn calculi), and emphysematous pyelonephritis (a serious necrotizing infection). Computed tomography (CT) scan of the abdomen with intravenous (IV) contrast is typically the primary mode of imaging in the majority of these cases. Renal ultrasound is less sensitive than a CT scan but is a reasonable alternative for patients where exposure to radiation or contrast is of concern. Management of these complications may require drainage of collections and a multidisciplinary approach involving specialties such as urology, interventional radiology, or infectious diseases.

In patients who are clinically stable and can tolerate oral medications, the treatment can be via a highly bioavailable drug such as oral ciprofloxacin. Note that some of the agents typically used for cystitis (nitrofurantoin and fosfomycin) are not recommended for use with pyelonephritis because of their suboptimal penetration to renal parenchyma (Table 2). With regard to the duration of treatment, there have been multiple randomized clinical trials showing that 7 days of antibiotic therapy was noninferior to longer courses for treatment of pyelonephritis in most patients.

Review of Question 2

The patient's fever and flank pain indicated that she had progressed to pyelonephritis. The recommended duration for treatment of pyelonephritis with ciprofloxacin is 7 days, provided the patient is clinically improving as in this case. Tests of the cure with repeat urine cultures is not recommended. Thus, the answer is (b), 7 days.

Case 2: *A 53-year-old man with diabetes mellitus, incomplete bladder emptying, and a deceased donor renal transplant 2 years ago who is taking mycophenolate mofetil and tacrolimus presents to the emergency department (ED) with 5 days of dysuria, urinary frequency, and fatigue. On the fifth day, he developed fever with rigors, so he presented to the ED. In the ED he is hemodynamically stable with WBC of 15,000 with urinalysis showing >182 WBC, 2 red blood cells (RBC), + leukocyte esterase, and 4+ bacteria. Within 24 hours, his urine and a single blood culture bottle grow E coli that is multidrug resistant (see the table below). His renal transplant ultrasound is normal. The patient has an estimated glomerular filtration rate (eGFR) of 48 (creatinine clearance of 50) and normal electrolytes; he clinically responds within 24 hours of appropriate antibiotic therapy.*

	E coli (Urine) > 10^5 CFU	
	MIC	Interpretation
Ampicillin-Sulbactam	≥32	Resistant
Ceftriaxone	≥4	Resistant
Meropenem	<0.25	Susceptible
Ertapenem	<1	Susceptible
Ciprofloxacin	0.5	Intermediate
Nitrofurantoin	≥128	Resistant
Trimethoprim-sulfamethoxazole	<1	Susceptible
Fosfomycin	≥256	Resistant

Abbreviations: CFU, colony-forming unit; MIC, minimum inhibitory concentration.

Question 3: With which antibiotic and for what duration would you treat this patient?

(a) 3 days of ertapenem
(b) 7 days of nitrofurantoin
(c) 9 days of trimethoprim-sulfamethoxazole after 5 days of ertapenem
(d) 21 days of trimethoprim-sulfamethoxazole
(e) 14 days of ciprofloxacin

For the answer to this question, see the following text.

Comparable to the second part of case 1, this is a case of pyelonephritis but in a renal transplant recipient and has an associated bloodstream infection. In this case, imaging of the genitourinary tract is performed to exclude an abscess or other transplant complication because these will likely impact management if found. The choice and duration of antibiotic in this case involves consideration of the host, the pathogen's susceptibility profile, and the associated bloodstream infection. The Infectious Disease (ID) Committee of Practice for the American Society of Transplantation recommends 14 days of treatment for complicated UTI/pyelonephritis. Yet in practice there is variability, as published by authors who surveyed the ID committee's providers and transplant nephrologists.

Review of Question 3

In general, 14 days of treatment is favored, but shorter durations are sometimes utilized based on newer data. Further, when acceptably bioavailable oral options exist, the total duration of treatment does not need to be parenteral. For that reason, answer (a) is incorrect; 3 days of ertapenem only is an insufficient course for pyelonephritis in general. Answer (b) is incorrect as well; nitrofurantoin should only be used for cystitis and never for upper tract disease or bacteremia. Although treatment with trimethoprim-sulfamethoxazole alone is reasonable, a 21-day course is excessive without abscess and raises the risk of complications, thus making answer (d) incorrect. Answer (e) is also incorrect, while some providers might choose to use a quinolone with an intermediate MIC for cystitis, given the pharmacokinetics of this drug class, where the concentration in the urine usually exceeds the intermediate MIC. The pharmacokinetics are not comparable for the bloodstream where the concentration is unlikely to exceed the intermediate MIC, thus, this strategy should be avoided in bacteremia. Finally, although the use of trimethoprim-sulfamethoxazole in this case is reasonable based on the favorable eGFR of 48 (creatinine clearance > 30), many transplant recipients may not fit this description. In those cases, eGFR should factor into the antimicrobial selection and dosing, which are complex and not generalizable to a case-based review. Thus, in this case with the caveats as described, the best answer listed to this question is (c).

Additional Readings

- Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? *JAMA*. 2002;287(20):2701-2710. https://doi.org/10.1001/jama.287.20.2701
- Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 days of antibiotic therapy on resolution of symptoms among afebrile men with urinary tract infection: a randomized clinical trial. *JAMA*. 2021;326(4):324-331. https://doi.org/10.1001/jama.2021.9899
- Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection—7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2013;68(10):2183-2191. https://doi.org/10.1093/jac/dkt177x
- Expert Panel on Urological Imaging; Smith AD, Nikolaidis P, Khatri G, et al. ACR appropriateness criteria acute pyelonephritis: 2022 update. *J Am Coll Radiol*. 2022;19(11S):S224-S239. https://doi.org/10.1016/j.jacr.2022.09.017
- Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269-284. https://doi.org/10.1038/nrmicro3432
- Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13507. https://doi.org/10.1111/ctr.13507
- Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-120. https://doi.org/10.1093/cid/ciq257 ★ESSENTIAL READING

- Kumar R, Pereira M, Taimur S, True K, Detwiler R, van Duin D. Duration of antibiotic treatment for acute graft pyelonephritis: what's the standard of care? *Transpl Infect Dis*. 2023;25(1):e13996. https://doi.org/10.1111/tid.13996
- McAteer J, Lee JH, Cosgrove SE, et al. Defining the optimal duration of therapy for hospitalized patients with complicated urinary tract infections and associated bacteremia. *Clin Infect Dis*. 2023;76(9):1604-1612. https://doi.org/10.1093/cid/ciad009
- Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol*. 2019;11:1756287219832172. https://doi.org/10.1177/1756287219832172
- Voora S, Adey DB. Management of kidney transplant recipients by general nephrologists: core curriculum 2019. *Am J Kidney Dis*. 2019;73(6):866-879. https://doi.org/10.1053/j.ajkd.2019.01.031
- Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. *Clin Infect Dis*. 2019;69(7):1091-1098. https://doi.org/10.1093/cid/ciy1054

Asymptomatic Bacteriuria

Case 3: *A 33-year-old woman with diabetes mellitus presents to her primary care doctor's office for a routine follow-up visit. She feels well and has no acute complaints. The urine sample she submitted for annual screening for albuminuria was also sent for urine microscopy and urine culture due to a processing error. The urine microscopy was notable for 5-10 WBC/high-power field (HPF), and the urine cultures grew more than 10^5 CFU/mL of pan-susceptible* Klebsiella oxytoca.

Question 4: In which of the following scenarios would antibiotic treatment targeted at urine culture results be indicated for this patient?

(a) Pregnancy
(b) Elective hernia repair scheduled in the next 48 hours
(c) Elective cystoscopy in the next 48 hours
(d) Placement of a Foley catheter
(e) Liver transplant in the past year

For the answer to this question, see the following text.

Asymptomatic bacteriuria (ASB) is defined as $\geq 10^5$ CFU/mL in a voided urine specimen without signs or symptoms attributable to UTI. This is regardless of whether pyuria is present. ASB is a common benign finding in many populations including healthy women, residents in long-term care facilities, and patients with urinary tract abnormalities. Studies have shown that antimicrobial treatment for the majority of patient populations with ASB does not confer significant benefit but can increase the risk of antimicrobial resistance or *Clostridioides difficile* infection. One study by Rotjanapan and colleagues showed that the 3-month risk of *C difficile* was 8.5 times higher in patients who were treated for ASB. Therefore, screening or treatment for ASB should be avoided in most patients.

The main exceptions to this are the following 2 populations (Box 2). The first is pregnant women because treatment decreases the risk of pyelonephritis and negative fetal outcomes. The second population that may benefit from a course of antibiotics are patients who will undergo urologic procedures associated with significant mucosal bleeding and trauma (eg, transurethral surgery of the prostate or the bladder, or percutaneous stone surgery). Relatedly, most of the data available do not support treatment of ASB in renal transplant patients. This, however, continues to be studied; currently, because of the lack of data on the immediate transplant period (1-2 months after transplant), many centers will treat ASB if found coincidently during this time, but they do not routinely screen for such.

Review of Question 4

Pregnancy is an indication for the treatment of ASB, so the answer is (a). Uncomplicated diagnostic cystoscopy or Foley catheter placement have a low risk of infection. Although urine culture results can help guide the standard 1-2 doses of perioperative prophylaxis for cystoscopy, a UTI treatment course with multiple days of antibiotics is considered unnecessary. Patients with solid organ transplants, other than early renal transplant, do not require treatment for ASB.

Additional Readings

- Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13507. https://doi.org/10.1111/ctr.13507
- Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):e83-e110. https://doi.org/10.1093/cid/ciy1121 ★ESSENTIAL READING
- Rotjanapan P, Dosa D, Thomas KS. Potentially inappropriate treatment of urinary tract infections in two Rhode Island nursing homes. Arch Intern Med. 2011;171(5):438-443. https://doi.org/10.1001/archinternmed.2011.13

Box 2. Main Indications to Treat Asymptomatic Bacteriuria

- Pregnancy
- Urologic procedures associated with mucosal bleeding or trauma

Catheter-associated Urinary Tract Infection

Case 4: *You are seeing a 64-year-old man with diabetes mellitus and heart failure with reduced ejection fraction who was admitted to the cardiac intensive care unit with acute decompensated heart failure. He did not have a fever or leukocytosis on presentation. An indwelling urinary catheter was placed on hospital day 1 to assist with intravenous diuresis. On hospital day 4, the patient was noted to have a fever to 38.5°C. Blood cultures were drawn and are pending. The urinalysis revealed moderate leukocyte esterase and >182 WBC/HPF. The urine culture grew >100,000 CFU/mL of Klebsiella pneumoniae.*

Question 5: Which of the following is consistent with the Centers for Disease Control and Prevention (CDC) surveillance definition of a catheter-associated urinary tract infection (CAUTI)?

(a) Indwelling catheter in place for at least 2 weeks
(b) Urine culture with 1 organism with bacterium of $>10^5$ CFU/mL
(c) Hemodynamic instability (ie, hypotension, tachycardia)
(d) Presence of *E coli* or other Gram-negative rod isolated in urine culture
(e) Admission to a hospital for less than 48 hours

For the answer to this question, see the following text.

The CDC surveillance definition of a CAUTI necessitates that patients meet the following 3 criteria:

1. Indwelling catheter in place for more than 2 consecutive days in an inpatient location.
2. Urine culture with no more than 2 organisms present and 1 organism with bacterium of $>10^5$ CFU/mL.
3. Presence of at least 1 of the following: fever (38°C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, or dysuria.

The patient in case 4 above meets each of the 3 CAUTI criteria. CAUTI is the most frequent health care–related infection worldwide, and it has been associated with the development of bacteremia and increased mortality. The diagnosis of CAUTI can be difficult because pyuria is an expected finding in patients, and the symptoms are often nonspecific if the catheter is still present.

The treatment for CAUTI includes first discontinuing the indwelling catheter or replacing the catheter (if still needed) if it has been in place for more than 2 weeks. Because urine cultures from long-term indwelling catheters may reflect the microbiology of the catheter's biofilm instead of the infection in the bladder, obtaining a urine culture from a newly placed catheter is recommended to guide antimicrobial therapy.

Antimicrobial therapy should be initiated in patients with suspected CAUTI and tailored to the urine culture results. Common bacterial causes of CAUTI include *E coli*, *Klebsiella* spp, *Pseudomonas aeruginosa*, and *Enterococcus* spp. A duration of 7 days of antimicrobial therapy is likely sufficient, provided that the patient improves clinically after starting antimicrobials.

Review of Question 5

The CDC surveillance definition of CAUTI includes the 3 criteria detailed previously. Of the answer choices, only (b) is consistent with 1 of the criteria: urine culture with 1 organism with a bacterium of $>10^5$ CFU/mL. Note that indwelling catheters only need to be in place for 2 consecutive days in an inpatient location to meet the surveillance definition. Also, although CAUTI often are caused by Gram-negative organisms, *Enterococcus* spp, *Staphylococcus* spp, and *Candida* spp are also possible causative pathogens.

Additional Readings

- Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(5):625-663. https://doi.org/10.1086/650482 ★ESSENTIAL READING
- Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. *J Urol*. 2000;164(4):1254-1258. https://doi.org/10.1016/S0022-5347(0567150-9)
- National Healthcare Safety Network. Urinary tract infections (catheter-associated urinary tract infection [CAUTI] and non-catheter-associated urinary tract infection [UTI]) events. US Centers for Disease Control and Prevention, updated January 2023. https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccautiicurrent.pdf
- Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37(11):1288-1301. https://doi.org/10.1017/ice.2016.174

Acute Bacterial Prostatitis

Case 4, continued: *After CAUTI was diagnosed in the previous patient, he was started on intravenous ceftriaxone. However, he continued to have temperatures above 38.0°C over the next 2 hospital days. A digital rectal examination revealed that the patient's prostate was tender and swollen. A CT scan of his abdomen and pelvis showed a heterogeneous-appearing prostate without abscesses or other intra-abdominal pathology. The patient slowly begins to show clinical improvement, and you plan a treatment course for acute bacterial prostatitis (ABP).*

Question 6: If ABP is diagnosed, as with the patient in case 4, how long should the patient receive antibiotics, assuming continued clinical improvement?

(a) 3-5 days
(b) 7 days

(c) 7-14 days
(d) 14-28 days
(e) 42 days or longer

For the answer to this question, see the following text.

ABP is typically characterized by the abrupt onset of voiding symptoms and is also often accompanied by systemic symptoms, though it can be difficult to diagnose because helpful diagnostics are limited. As in this case, an indwelling urinary catheter or urinary manipulation is a risk factor for development of ABP in men. On digital prostate palpation (which should be done gently to avoid risk of bacteremia), the prostate is often tender, swollen, and warm. In one retrospective, multicenter study of patients with an acute prostatitis diagnosis, 63% had pain with palpation of the prostate, and 83% had an "abnormal digital rectal examination." Prostatic abscess is a rare complication of ABP in general, but it may be more common in patients with ABP in the setting of recent urinary tract manipulation. Imaging to assess for prostatic abscess should be pursued if clinical improvement is not seen with antimicrobial therapy. Imaging modalities to diagnose prostatic abscess include prostate ultrasonography, CT, and magnetic resonance imaging.

The management of ABP typically requires 2-4 weeks of antimicrobial therapy, ideally tailored to the results of the urine culture if available. ABP is most commonly caused by *E coli*, *P aeruginosa*, *Klebsiella* spp, and *Enterococcus* spp; in sexually active men, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should also be evaluated with urine nucleic acid amplification testing. Though most antibiotics will penetrate acutely inflamed prostate tissue as these patients improve clinically, care should be taken to ensure antimicrobial agents are chosen that achieve adequate concentration in prostate tissue such as fluoroquinolones or trimethoprim-sulfamethoxazole.

Review of Question 6

Though there is a relative paucity of data regarding optimal treatment duration of ABP, most guidance recommends 2-4 weeks of therapy. Therefore, the correct answer is (c), 14-28 days.

Additional Readings

- Brehm TJ, Trautner BW, Kulkarni PA. Acute and chronic infectious prostatitis in older adults. *Infect Dis Clin North Am*. 2023;37(1):175-194. https://doi.org/10.1016/j.idc.2022.09.004
- Coker TJ, Dierfeldt DM. Acute bacterial prostatitis: diagnosis and management. *Am Fam Physician*. 2016;93(2):114-120. ★ESSENTIAL READING
- Etienne M, Chavanet P, Sibert L, et al. Acute bacterial prostatitis: heterogeneity in diagnostic criteria and management. Retrospective multicentric analysis of 371 patients diagnosed with acute prostatitis. *BMC Infect Dis*. 2008;8:12. https://doi.org/10.1186/1471-2334-8-12
- Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis*. 2010;50(12):1641-1652. https://doi.org/10.1086/652861 ★ESSENTIAL READING
- Millán-Rodríguez F, Palou J, Bujons-Tur A, et al. Acute bacterial prostatitis: two different sub-categories according to a previous manipulation of the lower urinary tract. *World J Urol*. 2006;24(1):45-50. https://doi.org/10.1007/s00345-005-0040-4

Case 4, continued: *The patient clinically improves while on parenteral ceftriaxone, and his discharge to home is planned. He is transitioned to oral levofloxacin to complete a 21-day antimicrobial course. On review of his discharge medications, you notice that the patient is currently taking the sodium/glucose cotransporter 2 (SGLT2) inhibitor empagliflozin for his heart failure.*

Question 7: The above patient asks whether he should continue the empagliflozin because as he has read it they can predispose individuals to infection. You recommend:

(a) Continue the empagliflozin at same dose
(b) Continue the empagliflozin but decrease the dose
(c) Stop empagliflozin
(d) Stop empagliflozin and start an alternative medication for the patient's diabetes
(e) Switch to a different SGLT2 inhibitor

For the answer to this question, see the following text.

Though SGLT2 inhibitors (eg, empagliflozin, dapagliflozin, canagliflozin) have been associated with genital infections, the literature regarding their association with UTI is conflicting. In a large, recent population-based cohort study, SGLT2 inhibitor use was not associated with serious and nonserious UTI. If SGLT2 inhibitors are otherwise indicated for management of diabetes or heart failure, providers should generally not discontinue the medications in the setting of UTI.

Review of Question 7

Because SGLT2 inhibitors are not clearly associated with UTI, they can generally be continued if patients have UTI, especially if there are other clear risk factors for the development of UTI as was the case with this patient (the presence of indwelling urinary catheter). The correct answer is (a) because no change is necessary.

Additional Reading

- Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: a population-based cohort study. *Ann Intern Med*. 2019;171(4):248-256. https://doi.org/10.7326/M18-3136

Nephrostomy Tube

Case 5: *A 43-year-old woman with metastatic ovarian cancer is admitted to the hospital for fever, nausea, vomiting, and*

back and abdominal pain. She has bilateral nephrostomies placed 3 months ago for tumor-related ureteral obstruction. They were last exchanged 3 weeks ago. Fresh urine collected from the tube (not the urine collecting in the bag) grew a pan-susceptible E coli. Her blood cultures are without growth, and the CT scan shows that the left tube is malpositioned and the left kidney had perinephric stranding with no abscess. She was started on IV ceftriaxone. After 72 hours she had resolution of her fever and tolerated a full diet. Her nephrostomy tube was exchanged, and the next one is scheduled in 4 weeks.

Question 8: What is the most appropriate next step in management?

(a) Continue IV ceftriaxone for a total of 4 weeks (until next exchange)
(b) Continue IV ceftriaxone for 10 days followed by oral ciprofloxacin until next exchange
(c) Switch to oral ciprofloxacin for a total of 4 weeks (until next exchange)
(d) Switch to oral ciprofloxacin for a total of 7-10 days of antibiotics
(e) Switch to oral nitrofurantoin for a total of 7-10 days of antibiotics

For the answer to this question, see the following text.

Obstruction is a common indication for placement of percutaneous nephrostomy tubes. It is important to note that the urine in a nephrostomy bag is not sterile and therefore not appropriate for conducting microbiological testing. If there is a clinical suspicion for UTI, testing should only be performed on fresh urine draining directly from the tube. If the patient is undergoing an invasive procedure, urine can also be sampled directly from the renal pelvis. However, even when sampling directly from the tube it is important to only test the urine if there are clinical signs or symptoms of an infection because patients with nephrostomy tubes can have ASB. This does not require treatment and was reported at a rate of ~7.5% in a study involving patients with cancer.

Review of Question 8

There are limited data and no guideline recommendations on duration of therapy for pyelonephritis in patients with percutaneous nephrostomies. However, extrapolating from the pyelonephritis and CAUTI approaches, 7-10 days of treatment would likely be adequate provided there is clinical improvement and no abscess or other foreign body. Treating patients routinely for a longer period of time can lead to these patients being colonized with resistant organisms and can expose them to preventable drug toxicities. If a case is more complicated and does not meet the conditions described, then we would recommend a multidisciplinary approach including involvement of an infectious diseases team to decide on an appropriate duration of therapy.

Ciprofloxacin is highly bioavailable, and the patient can be switched to this to complete her course because she can tolerate an oral medication. As a reminder, nitrofurantoin does not achieve adequate concentrations in the upper urinary tract. Therefore, the correct answer is (d), switch to oral ciprofloxacin for a total of 7-10 days of antibiotics.

Additional Readings

- Bahu R, Chaftari AM, Hachem RY, Ahrar K, Shomali W, El Zakhem A, et al. Nephrostomy tube related pyelonephritis in patients with cancer: epidemiology, infection rate and risk factors. *J Urol*. 2013;189(1):130-135. https://doi.org/10.1016/j.juro.2012.08.094
- Kar M, Dubey A, Patel SS, Siddiqui T, Ghoshal U, Sahu C. Characteristics of bacterial colonization and urinary tract infection after indwelling of Double-J ureteral stent and percutaneous nephrostomy tube. *J Glob Infect Dis*. 2022;14(2):75-80. https://doi.org/10.4103/jgid.jgid_276_21

Approaching Candiduria

Case 6: *A 64-year-old man is admitted to the intensive care unit after a coronary artery bypass graft procedure. A Foley catheter was placed during the procedure. On postoperative day 3, the patient has a fever of 38.3°C. Blood cultures are obtained and are pending. His urinalysis is notable for the presence of leukocyte esterase and >50 WBC/HPF. The urine culture ultimately grows >100,000 CFU/mL Candida albicans.*

Question 9: What is the most appropriate next step in management?

(a) Initiate antifungal treatment with fluconazole.
(b) Replace the indwelling urinary catheter and repeat the urine culture.
(c) Obtain a renal ultrasound.
(d) Replace the indwelling urinary catheter and start treatment with fluconazole.
(e) Initiate antifungal treatment with micafungin.

For the answer to this question, see the following text.

The task of clinicians when approaching patients with candiduria is to determine whether the isolated *Candida* indicates contamination, colonization, or infection. For patients with indwelling catheters and *Candida* isolated from urine culture, the catheter should be discontinued (if possible) and a repeat urine culture obtained to investigate whether *Candida* is still present. If an indwelling catheter is still required, the catheter should be exchanged and a new culture obtained to again assess for persistence of candiduria.

If *Candida* is again isolated, the clinician must then determine whether the patient has continued colonization versus cystitis or upper tract infection. Note that pyuria is an expected finding in patients who have indwelling

catheters and is not helpful in delineating colonization versus infection. Treatment of *Candida* UTI is only indicated in cases of persistent candiduria in patients who have symptoms consistent with UTI without an alternative etiology (ie, concurrent bacteriuria). Imaging such as renal ultrasound or CT abdomen/pelvis should also be obtained in the setting of persistent candiduria to assess for obstruction and need for urology consultation.

For candiduria in patients without indwelling catheters, the management approach is similar. First, a repeat clean-catch urine sample should be obtained (or a specimen from the catheter if clean catch is not feasible) to see if *Candida* is again isolated. If applicable, patients should also be assessed for the presence of concurrent vaginitis. For patients who reisolate *Candida* in urine, imaging is indicated to assess for obstruction; however, as with catheterized patients, treatment of candiduria is only indicated when patients have signs/symptoms consistent with UTI. Exceptions to this management approach include patients undergoing urologic procedures and neutropenic patients for which asymptomatic candiduria should be treated.

Review of Question 9

The patient in case 6 has evidence of a possible UTI with fever and a urine culture from an indwelling urinary catheter growing *C. albicans*. Though this could be consistent with fungal CAUTI causing fever, the isolation of *C. albicans* may also represent colonization of the catheter. Empiric treatment is not warranted at this stage. Replacement of the urinary catheter (if the catheter cannot be removed all together) followed by repeating the urine culture should be pursued. Unless *Candida* is reisolated or there is clinical evidence of an upper urinary tract obstruction, renal ultrasound is not necessary at this juncture. The answer is (b), replace the indwelling urinary catheter and repeat the urine culture.

Additional Reading

➢ Kauffman CA. Diagnosis and management of fungal urinary tract infection. *Infect Dis Clin North Am*. 2014;28(1):61-74. https://doi.org/10.1016/j.idc.2013.09.004 ★ESSENTIAL READING

Recurrent UTI

Case 7: *A 78-year-old woman comes to see her primary care doctor after her third episode of cystitis in the last 9 months. She notes that each episode was heralded by urinary frequency, urgency, and dysuria. She has no known other medical conditions except for well-controlled hypertension on a single medication and osteoarthritis of her knees. Her pelvic examination does not reveal a prolapse but does show changes consistent with atrophic vaginitis. Her laboratory results reveal normal kidney function and no evidence of diabetes. Her urinalysis on evaluation when she is asymptomatic is normal, without any cells in sediment. She asks for something to prevent further infections.*

Question 10: What advice would you give as an initial intervention to this patient?

(a) Prescribe continuous antibiotic prophylaxis with ciprofloxacin
(b) Start vaginal estrogen
(c) Recommend cranberry juice supplementation
(d) Initiate episodic antibiotic prophylaxis with intercourse
(e) Explain to her that there are no evidence-based methods to reduce the frequency of UTIs in postmenopausal women

For the answer to this question, see the following text.

Recurrent UTIs take many different forms. They can be precipitated by sexual intercourse most frequently in premenopausal women but also in postmenopausal women. Postmenopausal women are especially prone to recurrent UTIs due to the increased incidence of atrophic vaginitis and changes in the vaginal microbiome precipitated by lack of estrogenization of the tissues in the vaginal and lower urinary tracts. A detailed review of this pathophysiology is included in the recommended reading.

In general, recurrent UTIs in men are often associated with underlying structural issues leading to urinary retention or the presence of an indwelling catheter.

When undertaking the care of a patient with recurrent UTI, there is frequently no single intervention that "heals all." There are associations with recurrent UTIs related to sexual activity related to spermicidal contraceptives; if a woman is using this form of contraception, changing to a different agent may provide benefit. It is not clear that other behavior modifications such as early voiding after sexual intercourse or increased hydration to precipitate more frequent urination are effective in isolation, but certainly these are low-risk interventions that are easy to do.

For postmenopausal women, especially those in whom there may be associated incontinence, a pelvic examination to exclude pelvic floor dysfunction or prolapse is advised. If there is no correctable anatomic issue, then vaginal estrogens are a well-tolerated, low-risk intervention to undertake. Vaginal estrogens can be applied in many forms including vaginal rings, creams, and tablets and may take some careful feedback from the patient about her experiences to find the most favorable preparation. Utilization of supplements such as cranberry extracts and D-mannose have been tried, and some individuals may find benefit, but the data are mixed (as presented in a recent Cochrane review). Investigators are studying the use of vaginal probiotics, which may have efficacy in combination with estrogens.

For those who are unable to derive benefit from these interventions, antibiotic prophylaxis is often tried. Postcoital antibiotics can be effective in decreasing the incidence of UTI and the most well-studied agent is trimethoprim/sulfamethoxazole. Continuous prophylaxis has been shown to be effective in clinical trials, but the efficacy is lost once prophylaxis is stopped. Further, prophylaxis is not usually 100% effective, so UTIs will likely be less frequent but still present, and when they occur, the

organisms present are likely to have antimicrobial resistance to the class of prophylactic drug.

Review of Question 10

The patient described in case 7 does not appear to have an anatomic issue to which her recurrent UTIs can be ascribed. Further, she has changes on examination that are consistent with atrophic vaginitis. Based on the sentinel randomized controlled trial of vaginal estrogens versus placebo performed by Raz and Stamm and published in 1993, this patient will likely derive benefit from vaginal estrogens. This study not only demonstrated decreased antimicrobial use for UTI in the estrogen group over the follow-up period but also demonstrated other benefits such as decreased vaginal colonization with Enterobacterales with lower vaginal pH and recolonization with *Lactobacillus* spp (normal vaginal flora). Thus, the correct answer is (b), start vaginal estrogen as an initial intervention.

Additional Readings

- Albert X, Huertas I, Pereiro I, Sanfélix J, Gosalbes V, Perrotta C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev*. 2004;(3):CD001209. https://doi.org/10.1002/14651858.CD001209.pub2
- Cooper TE, Teng C, Howell M, Teixeira-Pinto A, Jaure A, Wong G. D-Mannose for preventing and treating urinary tract infections. *Cochrane Database Syst Rev*. 2022;(8):CD013608. https://doi.org/10.1002/14651858.CD013608.pub2
- Goldstein I, Dicks B, Kim NN, Hartzell R. Multidisciplinary overview of vaginal atrophy and associated genitourinary symptoms in postmenopausal women. *Sex Med*. 2013;1(2):44-53. https://doi.org/10.1002/sm2.17
- Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *New Engl J Med*. 1993;329(11):753-756. ★ESSENTIAL READING
- Sihra N, Goodman A, Zakri R, Sahai A and Malde S. Nonantibiotic prevention and management of recurrent urinary tract infections. *Nature Rev Urol*. 2018;15:750-776. https://doi.org/10.1038/s41585-018-0106-x

Conclusion

Urinary tract infections are common and diverse, as reviewed here. When approaching a patient with lower urinary tract symptoms, not all patients require evaluation with urinalysis and urine culture. Not infrequently, however, given the complexity of patients and the increasing incidence of drug-resistant bacteria, urinalysis and urine culture can be an invaluable tool for management. Relatedly, isolation of bacteria or *Candida* from urine is not always pathogenic, necessitating careful consideration of the reason for testing, the host, and any extenuating circumstances such as upcoming urologic procedures or pregnancy. Like urine testing, imaging to exclude upper tract involvement is not always necessary but in certain situations, as outlined previously, is essential to guide treatment decisions. Finally, UTIs may be recurrent. In these situations, careful evaluation for potential modifiable risk factors is beneficial. A number of pharmacologic interventions have been studied, some less rigorously than others, and a standard approach to treating such recurrent infections does not currently exist. As the world's population ages and as medical advancements continue to increase, additional study into better approaches to prevent UTIs is needed.

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