CLINICAL PRACTICE

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Acute Pyelonephritis in Adults

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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An otherwise healthy 35-year-old woman presents with urinary urgency, dysuria, fever, malaise, nausea, and flank pain. During a recent trip to India, she took a fluoroquinolone for diarrhea. On examination, the temperature is 38.6°C, the pulse 110 beats per minute, and the blood pressure 105/50 mm Hg; she has suprapubic and flank tenderness, without abdominal tenderness. The white-cell count is 16,500 per cubic millimeter, and the serum creatinine concentration 1.4 mg per deciliter (124 μmol per liter) (most recent measurement before presentation, 0.8 mg per deciliter [71 μmol per liter]). Urinalysis is positive for leukocyte esterase and nitrites. How would you evaluate and manage this case?

THE CLINICAL PROBLEM

ACUTE PYELONEPHRITIS[1] IS A SEVERE URINARY TRACT INFECTION (UTI) syndrome; other UTI syndromes include febrile UTI (UTI accompanied by fever, irrespective of the presence or absence of flank pain or tenderness[2,3]), acute prostatitis, and urinary-source bacteremia. These conditions can precipitate a dysregulated host response that results in sepsis or septic shock.[4]

The term pyelonephritis denotes inflammation of the renal pelvis and kidney. Such localization is usually inferred clinically from the presence of flank pain or tenderness. An infectious cause of pyelonephritis is supported by urinalysis that shows bacteriuria or pyuria (or both) and a urine culture that shows substantial concentrations of a uropathogen, usually *Escherichia coli* or other gram-negative bacilli.

Pyelonephritis typically manifests suddenly with signs and symptoms of both systemic inflammation (e.g., fever, chills, and malaise) and bladder inflammation (e.g., urinary frequency, urgency, and dysuria). However, consensus is lacking regarding diagnostic criteria.[5] Up to 20% of patients do not have bladder symptoms, and some patients do not have fever[5]; in addition, some studies of pyelonephritis did not require the presence of flank pain or tenderness as an enrollment criterion.[6,7] Clinical presentations and disease severity vary widely, from mild flank pain with low-grade or no fever to septic shock.[1,5,8] Rates of bacteremia vary widely across studies (ranging from <10 to >50%); rates depend on host factors and are higher among patients who are severely ill, those who are immunocompromised, those who have urinary tract obstruction, and those who are 65 years of age or older.[9,10]

The estimated annual incidence of pyelonephritis is 459,000 to 1,138,000 cases in the United States and 10.5 million to 25.9 million cases globally.[11,12] Generally, the percentage of patients who are hospitalized is lower than 20% among young

KEY CLINICAL POINTS

ACUTE PYELONEPHRITIS

- Acute pyelonephritis has the potential to cause sepsis, septic shock, and death.
- Urine culture is the cardinal confirmatory diagnostic test.
- Imaging is recommended at the time of presentation for patients with sepsis or septic shock, known or suspected urolithiasis, a urine pH of 7.0 or higher, or a new decrease in the glomerular filtration rate to 40 ml per minute or lower. Subsequent imaging is indicated in patients whose condition worsens or does not improve after 24 to 48 hours of therapy.
- The rising prevalence of *Escherichia coli* resistant to fluoroquinolones and trimethoprim–sulfamethoxazole complicates empirical oral therapy. In patients who receive oral treatment from the outset, depending on the likelihood of resistance, an initial dose of a supplemental, long-acting, parenteral antimicrobial agent (e.g., an aminoglycoside, ceftriaxone, or ertapenem) may be appropriate, and close follow-up is warranted.
- Assessment of illness severity, underlying host status, and the patient's psychosocial situation and estimation of the likelihood of pathogen resistance to relevant antimicrobial agents are critical in decisions regarding patient disposition and treatment.

women but higher among young children and adults older than 65 years of age. A total of 712 deaths were attributed to kidney infection in the U.S. National Vital Statistics Reports for 2014,[13] but 38,940 deaths were attributed to septicemia; on the basis of a conservative estimate that 10% of septicemia cases originate from pyelonephritis, there may be nearly 4000 deaths from pyelonephritis annually.[14] The total (direct and indirect) estimated cost related to pyelonephritis in the United States was $2.1 billion (in year 2000 dollars),[15] but the use of observation units has decreased the rate of admissions for pyelonephritis and presumably the costs.[16]

Risk factors for cystitis (e.g., sexual activity, new sexual partner, spermicide exposure, and personal history or maternal history of UTI) also confer a predisposition to pyelonephritis,[17] although 3% or less of cases of cystitis and asymptomatic bacteriuria progress to pyelonephritis.[18] Factors that impede urine flow (e.g., pregnancy or mechanical obstruction) increase this risk. Other risk factors probably include a genetic predisposition (e.g., altered innate immunity from low CXCR1 expression), a high microbial load, pathogen virulence attributes (e.g., adhesins such as P fimbriae), and possibly diabetes mellitus.[19]

Pyelonephritis usually occurs when enteric bacteria enter the bladder and ascend to the kidneys.[20] Rarely, organisms such as *Staphylococcus aureus* or candida seed the kidneys hematogenously.

Few data document the natural history of untreated pyelonephritis. In one study, among 14 women who received an antibiotic to which the pathogen was resistant, 5 (36%) had a clinical cure — a finding that suggests either spontaneous clearance or partial antibiotic effectiveness despite in vitro resistance.[21]

With appropriate care, clinical manifestations usually decrease progressively, as shown by a reduction in symptoms and downward trends in the fever curve and white-cell count; however, resolution may require up to 5 days.[22] Worsening or no improvement by 24 to 48 hours arouses concern for potential complications that may warrant urgent intervention. These complications include obstruction (more likely with urolithiasis, tumors, sickle cell disease, or diabetes), renal or perinephric abscess (often caused by obstruction), and emphysematous pyelonephritis (a rare, necrotizing, gas-forming infection associated with diabetes).[23]

Mild acute kidney injury from inflammation-related hemodynamic shifts is common and resolves quickly with treatment. Advanced renal failure is rare in the absence of coexisting urinary tract obstruction. Recurrent pyelonephritis is relatively uncommon (recurrence rate of <10%) and suggests a possible predisposing condition.[12]

PATHOGENS

Among young healthy women, specific virulent clones of *E. coli* account for more than 90% of pyelonephritis cases.[20] In contrast, among men, elderly women, and urologically compromised or institutionalized patients, less-virulent *E. coli* strains, non–*E. coli* gram-negative bacilli, gram-

positive organisms, and candida are more prevalent, although infections with *E. coli* still predominate.[1] Emerging antimicrobial resistance is attributable largely to the epidemic spread of highly successful *E. coli* clones, most notably the *H*30 subset within sequence type ST131.[24]

STRATEGIES AND EVIDENCE

DIAGNOSIS

In a patient with flank pain or tenderness (with or without fever) plus a urinalysis showing pyuria, bacteriuria, or both (with or without voiding symptoms), pyelonephritis is an appropriate presumptive diagnosis. Other causes of flank pain or tenderness, with or without fever, include acute cholecystitis, appendicitis, urolithiasis, paraspinous muscle disorders, renal-vein thrombosis, and pelvic inflammatory disease. In men, fever plus pyuria, bacteriuria, or both, but without flank pain or tenderness, suggests possible prostatitis.

The cardinal confirmatory test is the urine culture, which typically yields 10,000 or more colony-forming units of a uropathogen per milliliter of urine.[1,25] Lower counts may be present if the patient had received previous antimicrobial therapy, has extreme urine acidification, or has urinary tract obstruction.[26] Positive blood cultures may assist in establishing a diagnosis in ambiguous cases (e.g., in populations with a high prevalence of asymptomatic bacteriuria or in patients who have received previous antimicrobial therapy), but the presence of bacteremia rarely alters management.[9,27] Initial imaging to identify obstruction, abscess, or necrotizing infection is reserved for patients with sepsis or septic shock, known or suspected urolithiasis, a urine pH of 7.0 or higher, or a new decrease in the glomerular filtration rate to 40 ml per minute or lower (which is suggestive of obstruction).[10,28]

TREATMENT

Assessment of illness severity, coexisting medical conditions, and psychosocial status allows for initial triage to one of three disposition options (Table 1 and Fig. 1). One option is direct discharge to home (with or without a fluid bolus or a parenteral dose of a long-acting, broader-spectrum agent) (Table 2 and Fig. 2); this option is appropriate for mildly ill patients who have minimal nausea, no vomiting, stable coexisting medical conditions, a reliable psychosocial situation, and a suitable empirical oral antimicrobial option. A second option is extended care in the emergency department or observation unit for more extensive resuscitation and initial intravenous antimicrobial therapy; this option is appropriate for patients who are initially unable or unwilling to swallow an oral agent, seem too ill to go home immediately, or have clinically significant hypovolemia. This option allows deferral of hospital admission decisions, pending the outcome of initial therapy. Abundant evidence supports the suitability of such discharge-based strategies for appropriately selected patients.[29] In contrast, immediate hospital admission — the third option — is warranted for patients who have severe illness, unstable coexisting medical conditions, an unreliable psychosocial situation, or no acceptable oral therapy option.

The three pillars of pyelonephritis management are supportive care, antimicrobial therapy, and source control. Each is described in detail below.

SUPPORTIVE CARE

Fluid resuscitation can reduce malaise, nausea, and vomiting. Thus, patients who are discharged directly home may benefit from an initial intravenous fluid bolus, patients who are cared for initially in the emergency department warrant more extensive fluid therapy, and patients who are admitted to the hospital directly because of sepsis or septic shock should receive aggressive fluid resuscitation (e.g., 30 ml of isotonic crystalloid per kilogram of body weight within a 3-hour period) and possibly vasopressor drugs.[30] Medications to control symptoms, such as analgesics, antipyretics, and antinausea agents, should be used as needed.

INITIAL ANTIMICROBIAL THERAPY

Effective antimicrobial therapy should be initiated promptly. Efficacy is dependent on the delivery of a drug in adequate concentrations to the site of infection (renal tissue, blood, or both — not just the urine); the drug should be predictably active against the infecting organism, should have proven clinical efficacy for pyelonephritis, and should not be contraindicated by allergies or drug–drug interactions. Nitrofurantoin and oral fosfomycin attain adequate concentrations only in the urine and thus should be

Table 1. Triage and Management Considerations for Initial Disposition of Patients with Acute Pyelonephritis or Febrile Urinary Tract Infection.

Aspect of Care	Disposition of Patients		
	Immediate Discharge to Home	Initial Management in Emergency Department or Observation Unit	Immediate Hospital Admission
Triage			
Initial illness severity	Mild, no vomiting	Moderate, with or without vomiting	Sepsis or critical modifying factors*
Suitability of oral therapy	Yes; intravenous dose before discharge is optional	Yes, after initial intravenous dose or doses	No
Coexisting medical conditions*	None or stable	None or stable	Potentially unstable or critical*
Psychosocial situation*	Stable	Stable	Potentially unstable or critical*
Supportive care			
Fluid resuscitation	None or minor resuscitation	Moderate resuscitation, with or without maintenance	Vigorous resuscitation
Cardiopulmonary	None	None	May need one or more of the following: a vasopressor, supplemental oxygen, and invasive or noninvasive mechanical ventilation
Medications for symptoms†	Intravenous, oral, or both	Intravenous, oral, or both	Intravenous, oral, or both
Delivery of antimicrobial agent			
Oral	Prescription at or before discharge from the emergency department or observation unit	Before discharge from the emergency department or observation unit, if sent home	Defer until patient's condition is stabilized in hospital
Intravenous	Single dose, if needed	Immediate dose; can readminister in the emergency department or observation unit	Immediate administration; continue in hospital
Source control			
Imaging	None	If at risk for obstruction, abscess, or emphysematous pyelonephritis‡	If at risk for obstruction, abscess, or emphysematous pyelonephritis‡
Urologic evaluation or interventional radiology	None	If undrained focus discovered	Urgent, if undrained focus discovered

* Modifying factors include coexisting medical conditions and psychosocial situation. Hospital admission may be warranted even with mild or moderately severe illness if the patient has one or more unstable or severe coexisting conditions (e.g., cardiac, pulmonary, or psychiatric), an unreliable home situation, or other factors that reduce the likelihood of adherence to home therapy or of reaccessing care in case of clinical worsening at home.
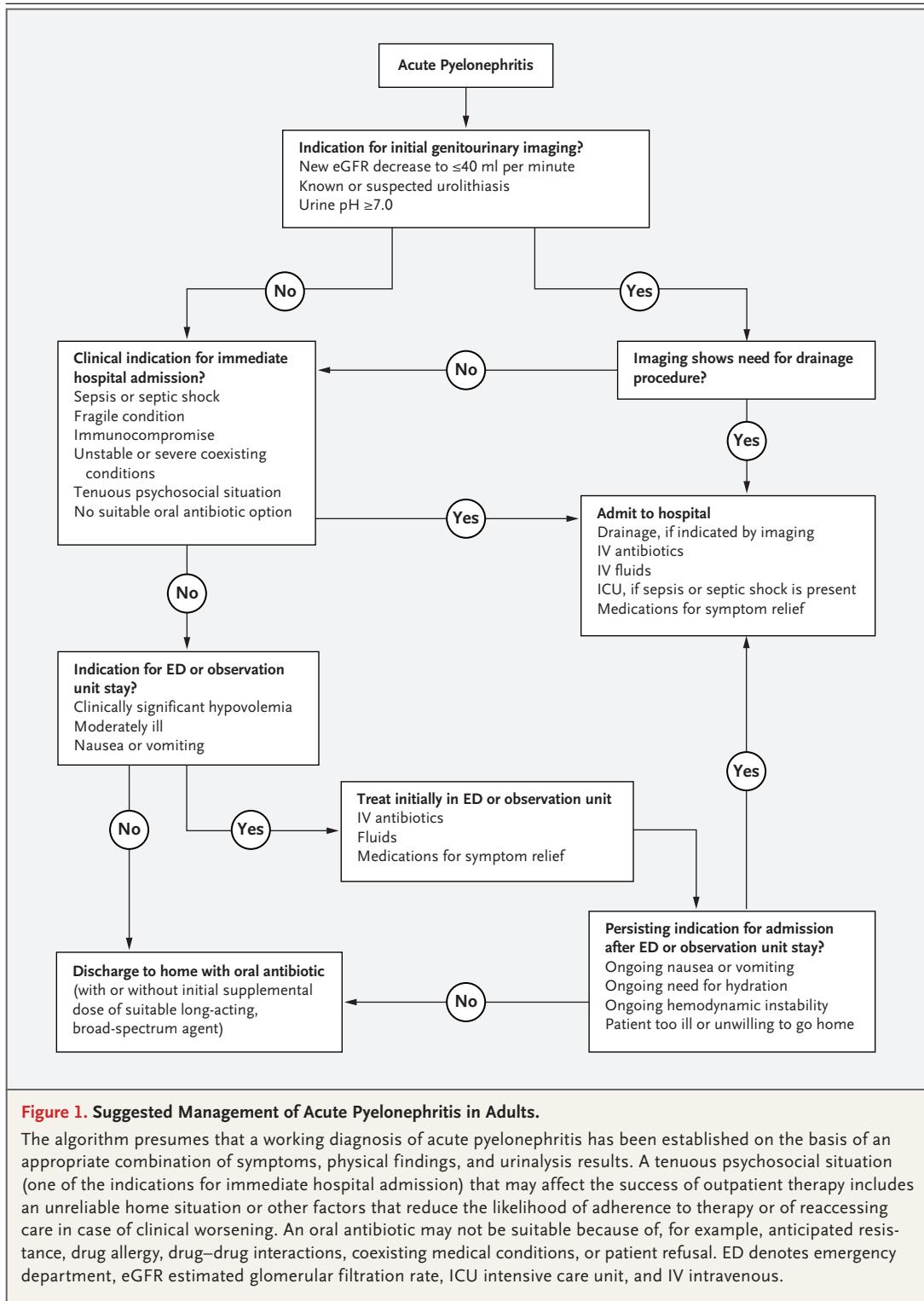† Medications for symptoms include antiemetics (e.g., prochlorperazine and ondansetron), analgesics (e.g., opiates and acetaminophen), anti-inflammatory drugs (e.g., ibuprofen), and urinary anesthetics (e.g., phenazopyridine).
‡ Risk factors for or predictors of urinary tract obstruction and renal or perinephric abscess include known or suspected urolithiasis, a urine pH of 7.0 or higher, a new decrease in the estimated glomerular filtration rate to 40 ml per minute or lower, unexplained oliguria, septic shock, worsening clinical status despite aggressive medical therapy, and sickle cell disease. Emphysematous pyelonephritis should be suspected if the patient has diabetes plus septic shock, worsening clinical status despite aggressive medical therapy, or known or suspected urinary tract obstruction.

avoided. In contrast, fluoroquinolones and trimethoprim–sulfamethoxazole, if active against the pathogen, are highly efficacious.[29] These agents attain high concentrations in the urine and renal tissue, have an acceptable side-effect profile, and have performed excellently (e.g., rate of clinical success, ≥90%) in clinical trials.[2,3,29,31]

The choice of empirical antibiotic therapy is guided by estimates of the likelihood of a resistant organism (as estimated on the basis of epidemiologic data and individual patient risk factors for resistance) and by an assessment of whether the patient will have an adverse outcome if the treatment is inadequate (temporarily) because of a resistant organism. Antimicrobial resistance is a growing problem; the prevalence of resistance to trimethoprim–sulfamethoxazole and fluoroquinolones among *E. coli* isolates exceeds 10% in most surveys.[1] The 2011 guidelines regarding pyelonephritis from the Infectious

Acute Pyelonephritis

Indication for initial genitourinary imaging?
New eGFR decrease to ≤40 ml per minute
Known or suspected urolithiasis
Urine pH ≥7.0

No → **Clinical indication for immediate hospital admission?**
Sepsis or septic shock
Fragile condition
Immunocompromise
Unstable or severe coexisting conditions
Tenuous psychosocial situation
No suitable oral antibiotic option

Yes → **Imaging shows need for drainage procedure?**
No → (Clinical indication for immediate hospital admission)
Yes → **Admit to hospital**

Admit to hospital
Drainage, if indicated by imaging
IV antibiotics
IV fluids
ICU, if sepsis or septic shock is present
Medications for symptom relief

Yes → (Admit to hospital)
No → **Indication for ED or observation unit stay?**
Clinically significant hypovolemia
Moderately ill
Nausea or vomiting

Yes → **Treat initially in ED or observation unit**
IV antibiotics
Fluids
Medications for symptom relief

No → **Discharge to home with oral antibiotic**
(with or without initial supplemental dose of suitable long-acting, broad-spectrum agent)

Persisting indication for admission after ED or observation unit stay?
Ongoing nausea or vomiting
Ongoing need for hydration
Ongoing hemodynamic instability
Patient too ill or unwilling to go home

Yes → (Admit to hospital)
No → (Discharge to home with oral antibiotic)

Figure 1. Suggested Management of Acute Pyelonephritis in Adults.
The algorithm presumes that a working diagnosis of acute pyelonephritis has been established on the basis of an appropriate combination of symptoms, physical findings, and urinalysis results. A tenuous psychosocial situation (one of the indications for immediate hospital admission) that may affect the success of outpatient therapy includes an unreliable home situation or other factors that reduce the likelihood of adherence to therapy or of reaccessing care in case of clinical worsening. An oral antibiotic may not be suitable because of, for example, anticipated resistance, drug allergy, drug–drug interactions, coexisting medical conditions, or patient refusal. ED denotes emergency department, eGFR estimated glomerular filtration rate, ICU intensive care unit, and IV intravenous.

Diseases Society of America (IDSA) recommend empirical therapy with a fluoroquinolone if the prevalence of resistance to fluoroquinolones among local uropathogens is less than 10%.[29] Unfortunately, local susceptibility data may be unavailable or may not be derived from a relevant

patient population (e.g., inpatients vs. outpatients). Moreover, certain patient-specific factors (e.g., recent hospitalization or antibiotic use) increase the risk of resistance (Fig. 2).[1] Furthermore, a resistance threshold of 10% or less, as recommended by the IDSA guidelines, may be too lenient if patients are critically ill, fragile (including having marginal or tenuous organ-system function), or immunocompromised or if they have a tenuous home situation, given the greater risk of bad outcomes if initial treatment is ineffective (Figs. 1 and 2). Under these circumstances, empirical monotherapy with a fluoroquinolone or trimethoprim–sulfamethoxazole is inadvisable. Conversely, for otherwise healthy patients with mild illness and a stable psychosocial situation, a higher resistance threshold could be acceptable, and empirical treatment with a fluoroquinolone or trimethoprim–sulfamethoxazole should be considered. Oral extended-spectrum cephalosporins (and, where available, pivmecillinam) may offer more reliable in vitro susceptibility than fluoroquinolones or trimethoprim–sulfamethozazole but have lower bioavailability, and evidence supporting their use for pyelonephritis is limited.[32-34]

Accordingly, patients who are discharged immediately home with instructions to take an empirical oral agent should receive an initial supplemental dose of a broader-spectrum, long-acting parenteral agent (e.g., ceftriaxone, gentamicin, amikacin, or ertapenem) (Table 2) if the anticipated likelihood of resistance to the oral agent (estimated on the basis of local susceptibility data, if available, and patient-specific factors) exceeds whatever resistance threshold best suits the individual patient (Fig. 2). For example, for an otherwise healthy woman with mild pyelonephritis, a suitable patient-specific resistance threshold might be 15% rather than 10%. If the patient's estimated likelihood of having a fluoroquinolone-resistant pathogen is 20% (which exceeds the 15% threshold) and fluoroquinolone therapy is planned, a long-acting supplemental drug should be given. Similarly, patients cared for initially in the observation unit or hospital should receive one or more of such broad-spectrum parenteral agents.

MONITORING OF EFFECTIVENESS OF THERAPY

Patients discharged with instructions to take an oral agent before the results of susceptibility testing are returned require close follow-up to confirm that their condition has improved. When culture results are available, resistance to the selected oral agent should prompt substitution of an active agent. When a suitable oral option is not available, outpatient intravenous therapy or hospital admission is appropriate. Hospitalized patients who are discharged after the results of susceptibility testing are returned can receive a suitable oral agent, if available, or intravenous therapy to be administered at home.[35]

Clinical worsening or lack of any improvement after 1 to 2 days of antibiotic therapy mandates repeat urine culture and imaging (see below) to identify whether an obstruction or other anatomical complication is the reason for the lack of clinical improvement. For patients who are cared for as outpatients, a lack of improvement over this time also warrants the administration (or readministration) of a broad-spectrum agent, including possibly intravenous therapy to be administered at home.[35]

DURATION OF THERAPY

Multiple trials of treatments in men and women support several conclusions regarding the duration of therapy. First, among women who have susceptible pathogens, the rates of clinical success are high (>90%) with a 5-to-7-day course of a fluoroquinolone or aminoglycoside or a 14-day course of trimethoprim–sulfamethoxazole.[2,6,21,29,31,36-39] Second, among women, in vitro resistance predicts an unacceptable failure rate.[21] Third, among men with febrile UTI (i.e., fever plus bacteriuria or pyuria, with or without flank pain or tenderness or overt prostatitis), one third of whom have clinical pyelonephritis,[3] the cure rates with ciprofloxacin among those with a susceptible pathogen are approximately as high with 14 days of therapy as with 28 days of therapy[3] and are only marginally lower with 7 days of therapy.[2] Fourth, on the basis of limited data from women with pyelonephritis, 10 to 14 days of therapy with extended-spectrum cephalosporins and mecillinam–pivmecillinam may suffice.[7,32-34,38,39] Data are lacking on the most effective treatment durations in cases involving severe disease, delayed treatment response, mechanical interventions (including those for hydroureter, stones, abscesses, or necrotizing infection), or other antimicrobial agents.

Table 2. Antimicrobial Agents Commonly Used for Treatment of Acute Pyelonephritis in Adults.
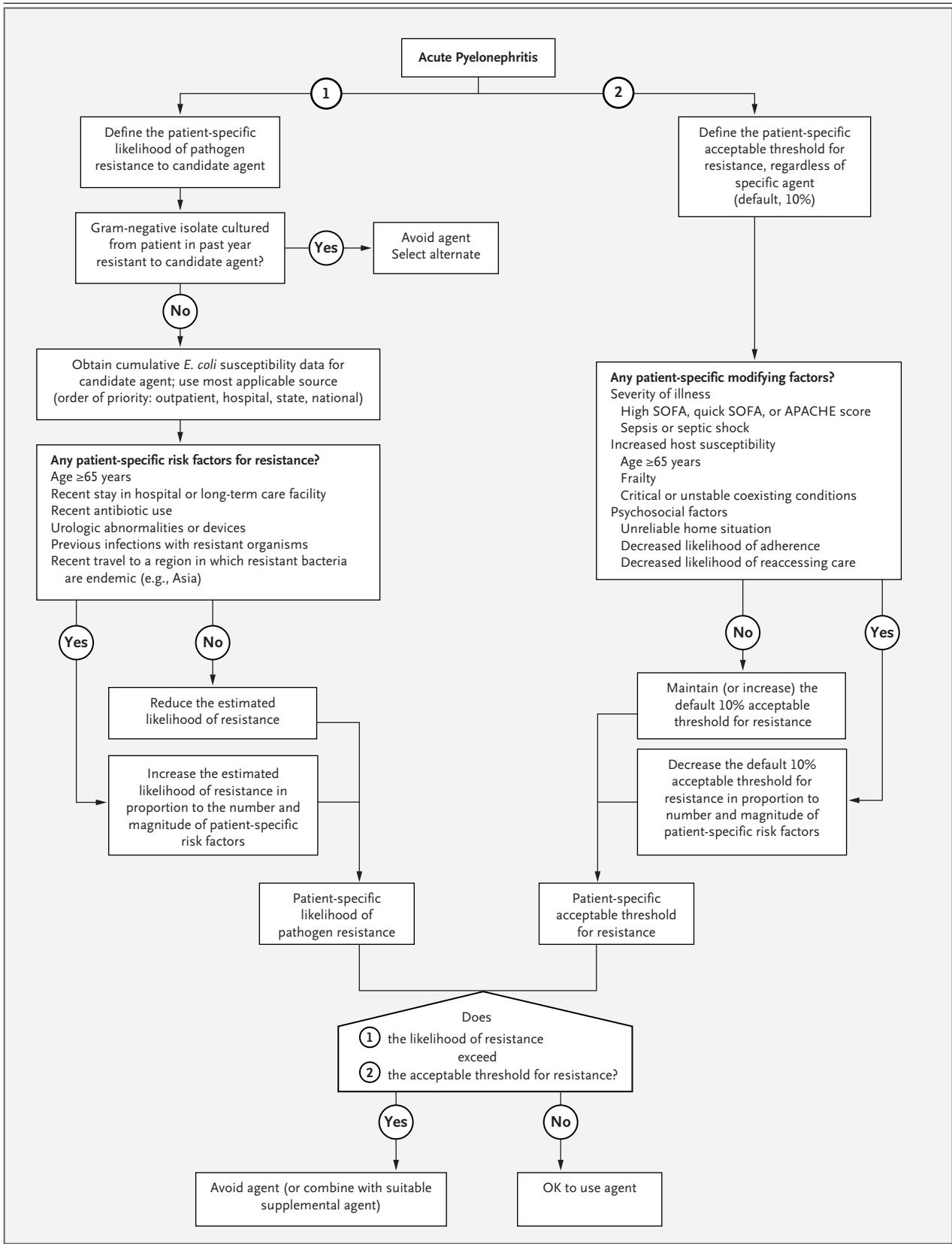
Route of Administration, Drug Class, and Drug and Dosage	Days of Treatment	Spectrum of Activity	Comment	Safety of Use during Pregnancy†
Oral*				
Fluoroquinolones				
Ciprofloxacin, 500 mg twice daily	7	Gram-negative bacilli	Because of possible resistance, initial intravenous administration of a supplemental drug is often warranted	C
Ciprofloxacin extended release, 1000 mg daily	7	Gram-negative bacilli	Because of possible resistance, initial intravenous administration of a supplemental drug is often warranted	C
Levofloxacin, 750 mg daily	5	Gram-negative bacilli	Because of possible resistance, initial intravenous administration of a supplemental drug is often warranted	C
Antifolate drugs				
Trimethoprim–sulfamethoxazole, 160 mg of trimethoprim and 800 mg of sulfamethoxazole, twice daily	10–14	Gram-negative bacilli	Because of possible resistance, initial intravenous administration of a supplemental drug is often warranted	C
Penicillins				
Amoxicillin–clavulanate, 875 mg of amoxicillin and 125 mg of clavulanate, 3 times daily	10–14	Enterococci, some gram-negative bacilli	Administer if the pathogen is likely to be enterococcus; not for empirical monotherapy	B
Pivmecillinam, 400 mg 2 times daily	10–14	Gram-negative bacilli	Unavailable in the United States	B
Cephalosporins				
Cefixime, 400 mg daily	10–14	Gram-negative bacilli	Active against many fluoroquinolone-resistant and trimethoprim–sulfamethoxazole-resistant gram-negative bacilli; little clinical evidence available	B
Cefpodoxime, 200 mg twice daily	10–14	Gram-negative bacilli	Active against many fluoroquinolone-resistant and trimethoprim–sulfamethoxazole-resistant gram-negative bacilli; little clinical evidence available	B
Intravenous*				
Penicillins				
Piperacillin–tazobactam, 3.375 g (3 g of piperacillin and 0.375 g of tazobactam) to 4.5 g (4 g of piperacillin and 0.5 g of taxobactam) every 6 hours	10–14	Gram-negative bacilli, enterococci	Active against some cephalosporin-resistant gram-negative bacilli	B

Drug and Dose	Days	Target Organisms	Comments	Category†
Mecillinam, 400 mg 3 times daily	10–14	Gram-negative bacilli	Unavailable in the United States	B
Cephalosporins				
Ceftriaxone, 1 g every 24 hours	7–10	Gram-negative bacilli, some gram-positive cocci‡	Administer alone or as a supplement to an oral drug; active against most fluoroquinolone-resistant gram-negative bacilli	B
Cefepime, 1–2 g every 8 to 12 hours	7–10	Gram-negative bacilli, some gram-positive cocci	Active against most fluoroquinolone-resistant and some ceftriaxone-resistant gram-negative bacilli	B
Ceftolozane–tazobactam, 1.5 g (1 g of ceftolozane and 0.5 g of tazobactam) every 8 hours	7	Resistant gram-negative bacilli	Active against most fluoroquinolone-resistant and ceftriaxone-resistant gram-negative bacilli (not active against New Delhi metallo-beta-lactamase‡)	B
Ceftazidime–avibactam, 2.5 g (2 g of ceftizidime and 0.5 g of avibactam) every 8 hours	7–14	Resistant gram-negative bacilli	Active against most fluoroquinolone-resistant and ceftriaxone-resistant gram-negative bacilli and many carbapenem-resistant gram-negative bacilli (not active against New Delhi metallo-beta-lactamase‡)	B
Carbapenems				
Ertapenem, 1 g every 24 hours	7–10	Resistant gram-negative bacilli	Administer alone or as a supplement to an oral drug; active against most fluoroquinolone-resistant and ceftriaxone-resistant gram-negative bacilli	B
Meropenem, 1 g every 8 hours	7–10	Resistant gram-negative bacilli	Active against most fluoroquinolone-resistant and ceftriaxone-resistant gram-negative bacilli	B
Aminoglycosides				
Gentamicin, 5.0–7.5 mg/kg of body weight every 24 hours	7–10	Gram-negative bacilli	Administer alone or as a supplement to an oral drug; active against most fluoroquinolone-resistant and ceftriaxone-resistant gram-negative bacilli	D
Amikacin, 15–20 mg/kg of body weight every 24 hours	7–10	Resistant gram-negative bacilli	Administer alone or as a supplement to an oral drug; active against many gentamicin-resistant gram-negative bacilli	D

* Oral treatment is administered as initial home therapy or as step-down therapy after initial inpatient intravenous therapy; intravenous treatment is administered as an initial supplement to home oral therapy or for inpatients.

† Safety of use during pregnancy was defined according to pre-2015 Food and Drug Administration categories (which have been replaced with narrative labeling). B indicates that no risk has been found in studies in nonhumans (no risk has been found in studies of animal reproduction, but there are no adequate studies in humans); C indicates that risk is not ruled out (some risk has been found in studies of animal reproduction, but there are no adequate studies in humans and the benefits may warrant the risk), and D indicates that there is positive evidence of risk (evidence of risk has been found in studies in humans, but the benefits may warrant the risk).

‡ New Delhi metallo-beta-lactamase (carbapenemase) is highly prevalent in the Indian subcontinent and is associated with extensive coresistance to many or most alternative agents, including gentamicin. Of the drugs listed in this table, amikacin is the most likely to remain active against such strains.

Acute Pyelonephritis

① ②

Define the patient-specific likelihood of pathogen resistance to candidate agent

Define the patient-specific acceptable threshold for resistance, regardless of specific agent (default, 10%)

Gram-negative isolate cultured from patient in past year resistant to candidate agent? → **Yes** → Avoid agent Select alternate

No

Obtain cumulative *E. coli* susceptibility data for candidate agent; use most applicable source (order of priority: outpatient, hospital, state, national)

Any patient-specific risk factors for resistance?
Age ≥65 years
Recent stay in hospital or long-term care facility
Recent antibiotic use
Urologic abnormalities or devices
Previous infections with resistant organisms
Recent travel to a region in which resistant bacteria are endemic (e.g., Asia)

Any patient-specific modifying factors?
Severity of illness
 High SOFA, quick SOFA, or APACHE score
 Sepsis or septic shock
Increased host susceptibility
 Age ≥65 years
 Frailty
 Critical or unstable coexisting conditions
Psychosocial factors
 Unreliable home situation
 Decreased likelihood of adherence
 Decreased likelihood of reaccessing care

Yes **No**

No **Yes**

Reduce the estimated likelihood of resistance

Increase the estimated likelihood of resistance in proportion to the number and magnitude of patient-specific risk factors

Maintain (or increase) the default 10% acceptable threshold for resistance

Decrease the default 10% acceptable threshold for resistance in proportion to number and magnitude of patient-specific risk factors

Patient-specific likelihood of pathogen resistance

Patient-specific acceptable threshold for resistance

Does
① the likelihood of resistance
exceed
② the acceptable threshold for resistance?

Yes **No**

Avoid agent (or combine with suitable supplemental agent)

OK to use agent

SOURCE CONTROL

Indications for initial and subsequent imaging (i.e., baseline risk factors and clinical worsening or lack of improvement after 24 to 48 hours of therapy) to assess for obstruction, abscess, or necrotizing infection are discussed above and elsewhere.[28,40] Ultrasonography is more sensitive than computed tomography (CT) for the diagnosis of hydronephrosis (and is also less expensive and available at the bedside), whereas contrast-enhanced CT is more sensitive for the diagnosis of abscesses, inflammation, and gas formation. However, contrast is contraindicated in patients with renal dysfunction and impairs the ability of CT to detect stones, making unenhanced CT the preferred method for this objective.[40] Treatment of hydronephrosis usually involves percutaneous or endourological drainage, and abscesses warrant drainage if they are sufficiently large or if the patient's condition is unstable. Treatment of emphysematous pyelonephritis (a rare complication) usually involves partial or total nephrectomy.[23,41]

SPECIAL POPULATIONS

Pyelonephritis during pregnancy can progress rapidly, causing life-threatening complications in both the mother and the fetus.[42] Accordingly, most pregnant women with pyelonephritis, especially during the third trimester, should be admitted to the hospital and administered treatment intravenously. Once their condition is clinically stable, such patients can safely complete therapy orally at home. Antimicrobial options during pregnancy are constrained by the potential toxicity for the fetus of aminoglycosides (during the first trimester), trimethoprim–sulfamethoxazole (near term), and fluoroquinolones (throughout pregnancy) (Table 2).[42] A meta-analysis of 14 randomized trials (involving a total of almost 2000 women) showed a significantly lower risk of pyelonephritis among women who received treatment for asymptomatic bacteriuria during pregnancy than among those who received placebo or no treatment; however, the studies were considered to be of low quality.[43]

Among renal transplant recipients, pyelonephritis may confer a predisposition to graft failure, along with the typical septic complications of pyelonephritis.[44] In the selection of an empirical antimicrobial agent for pyelonephritis, the patient's prophylactic antimicrobial regimen should be considered.

Pyelonephritis in patients who have urologic abnormalities should be managed medically in the same way as for pyelonephritis in patients who do not have urologic abnormalities.[45] Heightened vigilance is needed for atypical or misleading clinical presentations, a need for source control (e.g., drainage), polymicrobial infection, and multidrug-resistant organisms.

AREAS OF UNCERTAINTY

Uncertainties in management include which are the most cost-effective imaging strategies, what is the most appropriate treatment for patients with clinical pyelonephritis but nonconfirmatory urine cultures, what are the suitable empirical oral antimicrobial options for patients at risk for multidrug-resistant organisms, and what are the appropriate resistance thresholds in relation to patient status. Data are insufficient to guide appropriate treatment durations for pyelonephritis in men (especially in men who have indicators of prostatic involvement); patients treated with agents other than fluoroquinolones or trimethoprim–sulfamethoxazole; and patients with severe illness, a delayed clinical response, known predisposing factors, infectious complications, or febrile UTI. The role of rapid diagnostic tests[46] is undefined, as are ways to obtain patient-relevant (rather than generic) cumulative susceptibility data.

GUIDELINES

Practice guidelines from the IDSA and the European Society for Microbiology and Infectious

Diseases address only uncomplicated pyelonephritis in women.[29,47] Urine culture is recommended. Candidates for oral treatment are recommended to receive an initial supplemental dose of an aminoglycoside or ceftriaxone if, among local uropathogens, resistance to the selected oral agent (with a fluoroquinolone being the favored agent) exceeds a prevalence of 10%. On the basis of available clinical trial data, recommended treatment durations are 5 days (levofloxacin, 750 mg daily), 7 days (standard or high-dose extended-release ciprofloxacin), 14 days (trimethoprim–sulfamethoxazole), and 10 to 14 days (oral beta-lactams). The recommendations in this article are largely concordant with these treatment durations but suggest a patient-specific threshold for acceptable resistance prevalence.

CONCLUSIONS AND RECOMMENDATIONS

This patient has acute pyelonephritis. She would probably benefit from fluid resuscitation in the emergency department. Rapid improvement might allow her to be discharged home with instructions to take an empirical oral therapy (e.g., a fluoroquinolone or an extended-spectrum cephalosporin). However, because of her recent antibiotic use and her recent travel to an area in which extensively resistant bacteria are endemic, she should receive, before discharge from the emergency department, supplemental therapy that more predictably covers multiresistant *E. coli* (e.g., ertapenem or amikacin). If signs suggesting sepsis develop during her stay in the emergency department, hospital admission and a more reliably active antimicrobial regimen would be indicated (Table 2 and Figs. 1 and 2). In this instance, and others that potentially involve extensively resistant pathogens, prudence favors the initial use of a combination regimen that maximizes the likelihood that at least one agent will be active against the pathogen, pending the availability of susceptibility results. Infectious diseases consultation may be helpful. Once susceptibility results are known, therapy should be narrowed appropriately. When the patient's condition is clinically stable, she can be treated orally if a suitable agent is available. Regardless of the presence or absence of bacteremia, a 7-day course of a fluoroquinolone should suffice for a susceptible organism, whereas a 10-to-14-day course is preferable with trimethoprim–sulfamethoxazole or a beta-lactam. If the clinical course is uneventful, no follow-up testing is needed, whereas worsening or a lack of improvement after 1 to 2 days should prompt repeat cultures plus imaging.

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