CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Urinary Tract Infections in Older Men

Anthony J. Schaeffer, M.D., and Lindsay E. Nicolle, M.D.

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.*

From the Feinberg School of Medicine, Northwestern University, Chicago (A.J.S.); and the University of Manitoba, Winnipeg, Canada (L.E.N.). Address reprint requests to Dr. Schaeffer at the Feinberg School of Medicine, Northwestern University, 303 E. Chicago Ave., Tarry Bldg. 16-703, Chicago, IL 60611, or at ajschaeffer@northwestern.edu.

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A 79-year-old community-dwelling man presents with urinary frequency, dysuria, and fever. Culture reveals extended-spectrum beta-lactamase *Escherichia coli*. He had a similar infection several months ago, with the same organism isolated, and he had a response to nitrofurantoin treatment. How would you further evaluate and manage this case?

An audio version of this article is available at NEJM.org

THE CLINICAL PROBLEM

Urinary tract infection in men without indwelling catheters is uncommon among men younger than 60 years of age, but the incidence increases substantially among men 60 years of age or older.[1,2] The reported incidence in the community is 0.9 to 2.4 cases per 1000 men among those who are younger than 55 years of age and 7.7 cases per 1000 men among those who are 85 years of age or older.[3,4] The frequency of severe presentations leading to hospitalization also increases with age.[5] Urinary tract infection is the most common cause of bacteremia in older men,[6-8] although death that is directly attributed to urinary tract infection is infrequent.[5,8] Recurrent infection is also more common among older men than among younger men. Long-term sequelae, including impaired renal function, are rare in the absence of urinary tract obstruction. The incidence of all urinary tract infections among older men is approximately half that among older women,[3,5] but infection rates among men in the community who are older than 80 years of age approach those among women in the same age range.[3,4]

Asymptomatic bacteriuria is uncommon among younger men but is present in up to 10% of community-dwelling men who are older than 80 years of age[9] and in 15 to 40% of male residents of long-term care facilities.[1] Persons with asymptomatic bacteriuria are also more likely to have symptomatic infections than those without asymptomatic bacteriuria, presumably because the same biologic factors promote both conditions. Antimicrobial treatment of asymptomatic bacteriuria is not indicated and promotes resistance to antimicrobial agents.[10]

As men age, they acquire structural and functional abnormalities of the urinary tract that impair normal voiding; the most common is benign prostatic hyperplasia, which can cause urinary tract infection owing to obstruction and turbulent urine flow. Acute bacterial prostatitis (prostate infection) is a severe, potentially life-threatening systemic infection.[11,12] Chronic bacterial prostatitis may manifest as recurring urinary tract infections, usually with the same bacterial strain iso-

KEY CLINICAL POINTS

URINARY TRACT INFECTIONS IN OLDER MEN

- The prevalence of bacteriuria and the incidence of urinary tract infection are substantially higher among older men than among younger men.
- The majority of older men with urinary tract infection have underlying urologic abnormalities.
- Effective treatment of infection requires determining whether the site of infection is the kidney, bladder, or prostate.
- Effective management of symptomatic episodes requires selection of antimicrobial therapy on the basis of urine culture.
- Chronic bacterial prostatitis requires prolonged antimicrobial therapy (30 days).
- Men with recurrent episodes who do not have urologic abnormalities that can be corrected or identified may require long-term suppressive therapy with antimicrobial agents.

lated with each episode.[13,14] Bacteria that are established in the prostate may be impossible to eradicate owing to limited diffusion of antibiotic agents into the gland or to the presence of colonized prostate stones.[13,15,16]

Older populations often have coexisting conditions, such as diabetes mellitus, that are associated with an increased susceptibility to infection. Urologic coexisting conditions, such as incontinence or urinary retention, facilitate the acquisition of bacteriuria owing to an increased exposure to interventions such as catheterization.[17,18] However, prospective studies have not shown associations between postvoiding residual urine volume and bacteriuria[19,20] or symptomatic urinary tract infection in men.[21] The most consistent predictors of asymptomatic bacteriuria are markers of functional disability, including incontinence, immobility, and dementia.[22,23]

A gram-negative organism is isolated from 60 to 80% of samples from older men living in the community who have urinary tract infections.[24,25] *E. coli* is the most common organism; other Enterobacteriaceae such as *Klebsiella pneumoniae* and *Proteus mirabilis* are isolated less frequently. Enterococcus species are the most common gram-positive organisms. Specific *E. coli* strains and virulence traits correlate with clinical presentation.[26] Strains that are isolated from men with pyelonephritis or febrile urinary infection are the most virulent, followed by strains isolated from men with cystitis; colonizing fecal strains tend to be the least virulent. In men without indwelling urinary catheters who live in an institution and who have bacteriuria, *E. coli* is also the most common pathogen isolated, but *P. mirabilis*, *Pseudomonas aeruginosa*, and multidrug-resistant strains are increasingly frequent.[1] In a study conducted in Spain, men were more likely than women to have extended-spectrum beta-lactamase strains isolated from the urine; older age and nursing home residence were also associated with increased risk of these strains.[27]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

In community-dwelling populations, cystitis (bladder infection) characteristically occurs with irritative symptoms in the lower urinary tract, including dysuria, urinary frequency, urinary urgency, nocturia, suprapubic discomfort, and occasionally, gross hematuria. Pyelonephritis (kidney infection) is typically associated with fever, costovertebral-angle pain or tenderness, and varied lower urinary tract symptoms (e.g., irritative symptoms). A prospective study showed transient increases in the serum prostate-specific antigen level, prostate volume, or both in more than 90% of men (median age, 63 years) who presented with febrile urinary tract infection, although localization of bacterial infection to the prostate was not reported.[28] Acute bacterial prostatitis typically manifests as fever and symptoms of lower urinary tract infection and, occasionally, obstructive uropathy.[12,14] Chronic bacterial prostatitis may manifest as recurrent acute cystitis when bacteria persisting within the prostate reenter the urethra and bladder.[13,14] Although symptoms of these infections in persons without indwelling catheters who live in institutions are similar to those in persons in the general population, clinical evaluation of persons living in institutions is more difficult owing to compro-

mised functional status, impaired communication, and the high frequency of chronic urinary tract symptoms that are attributed to coexisting illnesses such as prostatism or incontinence that is associated with chronic neurologic diseases.[1,29,30]

Culture of a urine specimen is essential for the management of suspected urinary tract infection. To limit the overtreatment of asymptomatic bacteriuria, urine specimens should be obtained only from men who have symptoms or signs that are potentially attributable to urinary tract infection.[30] Specimens should always be obtained before the initiation of antimicrobial therapy. A voided midstream urinary specimen obtained while the patient retracts the foreskin and after the glans is wiped with a moist gauze pad is usually adequate.[16] For patients using external catheters, the foreskin should be cleaned and a clean external catheter applied for the collection of the specimen.[31] Specimens obtained from patients who are being treated with intermittent catheterization are acquired directly from the bladder.

Bacteriuria suggests urinary tract infection. Pyuria is a nonspecific finding that is frequent in older patients with or without bacteriuria[1] and is not diagnostic of symptomatic urinary tract infection or indicate a need for antimicrobial treatment. The absence of pyuria, however, has a negative predictive value of 95% or more to rule out infection.[2,30]

A quantitative urine culture revealing a bacterial count of at least 10^5 colony-forming units (CFUs) of a single organism per milliliter from a voided specimen confirms a microbiologic diagnosis of urinary tract infection.[1,2] The isolation of a single organism with a count of at least 10^3 CFUs per milliliter from a voided specimen or more than two organisms with counts of more than 10^5 CFUs per milliliter may also be consistent with symptomatic infection and should be interpreted on the basis of the clinical context.[16] For specimens obtained by means of ureteral catheterization, counts of 100 CFUs or more per milliliter are diagnostic of bacteriuria.[1,10] For patients with external catheters, the quantitative count of at least 10^5 CFUs per milliliter is appropriate.[31] Isolation of the same organism from blood and urine cultures usually supports a diagnosis of urosepsis.

For patients with a first urinary tract infection, evaluation of the upper and lower urinary tract is recommended (Fig. 1), given the high prevalence of urologic abnormalities among men who present with urinary tract infection.[14,32] Residual urine volume should be assessed by means of noninvasive ultrasonography. Although a residual urine volume of 100 ml or more is generally considered to be abnormal, the relevance needs to be interpreted on the basis of the clinical context, such as the severity and frequency of urinary tract infection.[19,20]

Patients with fever should have immediate assessment of the upper urinary tract by means of computed tomography (CT) with the use of contrast material or by means of renal ultrasonography to rule out obstruction or other abnormalities requiring source control. CT with the use of contrast material is the most sensitive imaging test, but ultrasonography may be more accessible in some clinical settings and will usually identify a clinically important obstruction. In a study conducted in Sweden, 15 of 85 men presenting with febrile urinary tract infection had previously unrecognized lesions of the urinary tract that required surgical intervention, including prostatic hypertrophy with obstruction, urethral stricture, bladder or renal stones, and bladder cancer.[33]

An identified abnormality is not necessarily the cause of infection, and further urologic evaluation may be required to determine its relevance. For example, in a patient with pyelonephritis, obstruction at the ureteral pelvic junction is likely to be a contributing factor.

Identification of the same strain in repeat infections suggests bacterial persistence within the urinary tract. An abnormality in the upper urinary tract, for example, a kidney stone, can be confirmed as the source of persistence by means of ureteral catheterization for urine culture. A source of persistence in the lower urinary tract may be either in the bladder (e.g., a stone) or the prostate.

A diagnosis of chronic bacterial prostatitis can be confirmed by means of culture of the prostatic fluid with the use of the classic four-glass Meares–Stamey test (Fig. 2).[34] The two-glass test (with urine specimens obtained before and after prostatic massage) may be used for screening and has a high (>95%) correlation with the four-

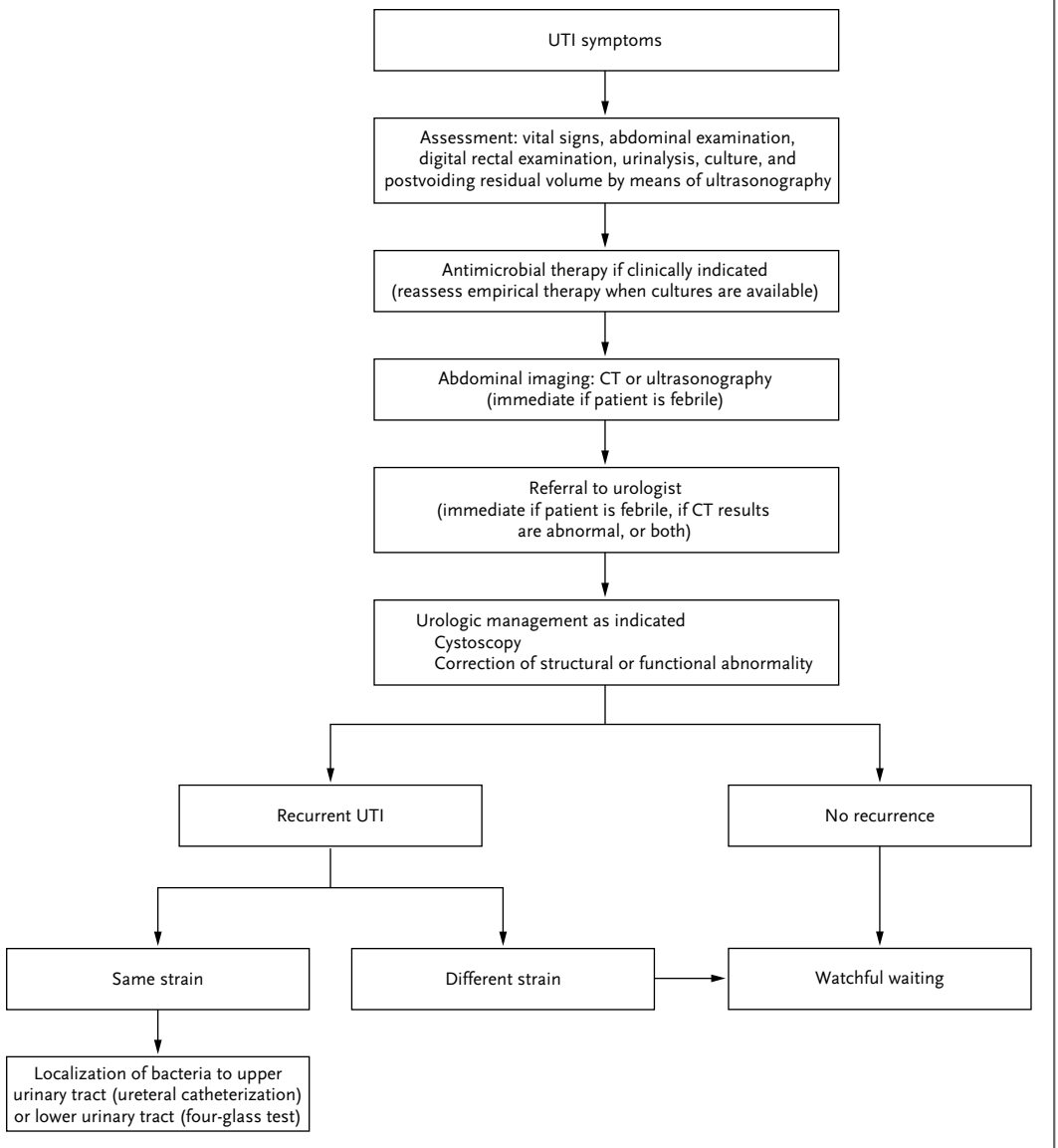

Figure 1. Evaluation and Treatment of Urinary Tract Infection in Older Men.
CT denotes computed tomography, and UTI urinary tract infection.

glass test (in which the first glass contains a urine specimen [first 10 ml] obtained before expressed prostatic secretion, the second contains a midstream urine sample obtained before expressed prostatic secretion, the third contains expressed prostatic secretion, and the fourth contains a urine specimen [first 10 ml] obtained after expressed prostatic secretion).[35] Identification of a uropathogen in specimens containing prostatic secretion at a value that is at least 10 times as great as the value in the expressed prostatic secretion or urine specimen obtained before prostatic massage is diagnostic of chronic bacterial prostatitis. If initial testing to localize the infection to the prostate is negative, repeat testing should be considered when suspicion is high, because in some cases the infection may indeed be in the prostate; the false negative rate

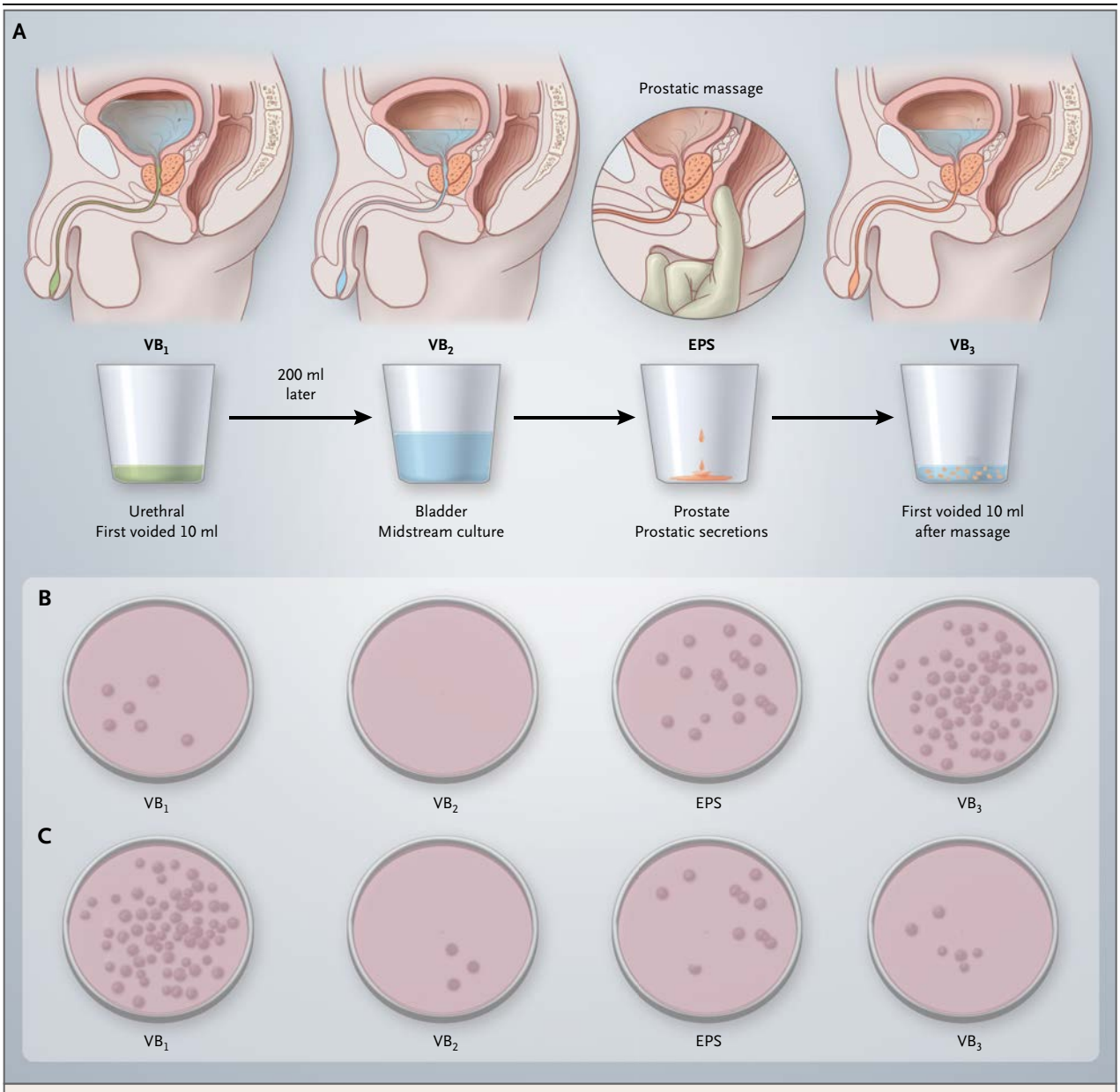

Figure 2. Four-Glass Test.

Adapted from Meares and Stamey.[34] In the four-glass test, the patient voids the first 10 ml of urine (the urethral specimen; VB_1) into a collection glass (Panel A). After the patient voids approximately 200 ml, a midstream specimen (bladder urine; VB_2) is collected. After the bladder is emptied, expressed prostatic secretions (EPS) are obtained after prostatic massage. The first 10 ml of urine that is voided after prostatic massage (VB_3) is considered to be prostatic washout. The presence of bacteria in the EPS and VB_3 samples when the VB_1 and VB_2 samples do not show growth (or a count of colony-forming units per milliliter that is 10 times as high in the EPS and VB_3 samples as in the VB_1 and VB_2 samples) is highly diagnostic of bacterial prostatitis (Panel B). Growth of gram-negative bacilli in the VB_1 specimen without substantial growth in the other samples is diagnostic of urethral colonization (Panel C). Gram-positive staphylococcal species frequently colonize the distal urethra and do not cause bacterial prostatitis.

is not well established.[34] Recurrent urinary tract infection that is attributed to chronic bacterial prostatitis may involve a new organism, which suggests that reinfection may occur.

MANAGEMENT

Antimicrobial treatment is selected on the basis of the clinical presentation, known or suspected infecting organism and susceptibilities, the side

effect profile of the medication, and renal function. Agents with high levels of urinary excretion should be used (Table 1). For cystitis, first-line therapies include nitrofurantoin, trimethoprim–sulfamethoxazole, and ciprofloxacin or levofloxacin, typically administered for 7 days. Nitrofurantoin is effective for the treatment of cystitis but has limited tissue penetration and is not effective for the treatment of pyelonephritis or bacterial prostatitis. Initial therapy of acute pyelonephritis is usually with ciprofloxacin or levofloxacin, ceftriaxone, or gentamicin. The duration of treatment is generally 7 to 14 days. If the bacteria that are subsequently isolated are resistant to empirical antimicrobial therapy, an alternative effective agent should be given, regardless of clinical response; initial clinical improvement, attributed to very high levels of antimicrobial agents in urine, may be observed despite antimicrobial resistance, but symptomatic relapse after treatment is likely. A follow-up urine culture is not recommended unless symptoms persist or recur after therapy.

Randomized trials involving both men and women have supported the efficacy of many antibiotics for the treatment of complicated urinary tract infection and pyelonephritis (Table 1).[36-41] Because outcomes are not stratified according to sex, the comparative efficacy of therapy in men versus women is uncertain. Despite the likelihood of prostatic infection, treatment outcomes in men presenting with febrile urinary tract infection are similar when treatment is administered for 2 weeks and for 4 weeks.[42,43]

Acute bacterial prostatitis should be treated empirically with broad-spectrum parenteral antibiotics such as extended-spectrum penicillins, ceftriaxone with or without the addition of an aminoglycoside, or a fluoroquinolone.[14] Inappropriate therapy can lead to rapid progression and even death.[11,12] Approximately one quarter of patients with acute bacterial prostatitis have bacteremia, and 5 to 10% may have associated abscesses in the prostate. Routine ultrasonography of the prostate that is performed to identify a potential prostatic abscess is not recommended for patients who have a prompt response to antimicrobial therapy. Difficulty with urinating is frequently present, and alpha-blocker therapy may be considered; some patients temporarily require catheterization. Therapy should be tailored to the specific organism that has been isolated and should be continued so that a 4-week course of therapy (that includes both the parenteral and oral therapies) is completed.[11,12] Data from randomized clinical trials are needed in order to compare therapies or define the effective duration of treatment. Chronic bacterial prostatitis develops after acute infection in approximately 5% of men.[15]

Chronic bacterial prostatitis is usually treated with a fluoroquinolone or trimethoprim–sulfamethoxazole for 30 days.[15,44] A fluoroquinolone is usually first-line therapy; levofloxacin and ciprofloxacin are equally effective.[45,46] In a trial comparing different regimens of levofloxacin (at a dose of 750 mg daily for 2 weeks, 750 mg daily for 3 weeks, or 500 mg daily for 4 weeks) in men with chronic prostatitis (median duration, approximately 8 years), the clinical efficacy was similar among the regimens immediately after therapy (63 to 69% of patients had a response), but at 6 months the response rate was significantly higher with the 4-week regimen (45%, vs. 28% with the 2-week regimen and 28% with the 3-week regimen).[47]

The selection of oral antimicrobial therapy for persons who cannot take standard therapies (because of adverse effects or antimicrobial resistance) is challenging because many antimicrobial agents do not reach effective levels in the prostate.[15] Macrolides,[48] fosfomycin,[49] and minocycline or other tetracyclines[15] may penetrate into the prostate and have been effective for susceptible organisms in some patients. If bacterial relapse occurs after 30 days of antimicrobial therapy, retreatment to ameliorate symptoms is indicated, but more prolonged courses of antimicrobial therapy are not usually recommended.

Patients with obstructive uropathy may consider transurethral resection to improve flow and, potentially, remove putatively infected tissue, but outcomes of this surgical approach have not been critically evaluated. Patients may be prescribed long-term suppressive therapy or antimicrobial therapy that can be self-initiated when symptoms develop. Although data from randomized trials are lacking to guide the use of suppressive therapy in this context, therapy is based on the infecting organism and adjusted to the minimal dose necessary to prevent symptoms. The specific regimen is determined on the

Table 1. Antimicrobial Therapy for the Treatment of Urinary Tract Infection and Prostatitis in Men.*

Antimicrobial Agent	Dose for Normal Renal Function	Clinical Use†	Adverse Effects and Contraindications
Oral			
Ciprofloxacin	500 mg twice daily	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Levofloxacin	500 mg or 750 mg daily	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Trimethoprim–sulfamethoxazole	160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily	First-line therapy for cystitis; second-line therapy for chronic prostatitis	Sulfa hypersensitivity; liver toxic effects
Trimethoprim	100 mg twice daily	First-line therapy for cystitis	
Nitrofurantoin monohydrate macrocrystals	100 mg twice daily	First-line therapy for cystitis only	Lung and liver toxic effects
Fosfomycin‡	3 g single dose	Cystitis	
Amoxicillin	500 mg three times daily	Cystitis	Beta-lactam hypersensitivity
Amoxicillin–clavulanate§	500 mg three times daily or 875 mg twice daily	Cystitis	Beta-lactam hypersensitivity
Cephalexin	500 mg four times daily	Cystitis	Beta-lactam hypersensitivity
Cefixime	400 mg once daily	For resistant organisms in cystitis or pyelonephritis	Beta-lactam hypersensitivity
Cefpodoxime proxetil	100–200 mg twice daily	Cystitis or pyelonephritis	Beta-lactam hypersensitivity
Parenteral			
Ceftriaxone	1–2 g every 24 hr	First-line therapy for pyelonephritis; use with gentamicin for acute prostatitis	Beta-lactam hypersensitivity
Ciprofloxacin	400 mg every 12 hr	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Levofloxacin	500–750 mg every 24 hr	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Gentamicin or tobramycin	5–7 mg/kg every 24 hr	First-line therapy for pyelonephritis; use with beta-lactam for acute prostatitis	Vestibulocochlear toxic effects; renal failure
Piperacillin–tazobactam§	3.375 g every 8 hr	For resistant organisms in cystitis, pyelonephritis, or acute prostatitis	Beta-lactam hypersensitivity
Ceftazidime	1 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Ceftazidime–avibactam§	2.5 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Ceftolozane–tazobactam§	1.5 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Meropenem	500 mg every 6 hr or 1 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams
Doripenem	500 mg every 6 hr	For resistant organisms in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams
Ertapenem	1 g once daily	For resistant organisms but not *Pseudomonas aeruginosa* in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams

* The data presented here are for commonly used agents and are not comprehensive. First-line therapy is selected on the basis of clinical presentation and the susceptibility of the infecting bacteria. When empirical therapy is initiated, the antimicrobial agent should be reassessed once culture results are available.

† The duration of therapy for cystitis is generally 7 days, and the duration of therapy for pyelonephritis is 7 to 14 days; 30 days of therapy is recommended for chronic prostatitis. Treatment for acute prostatitis is usually initiated with parenteral therapy and stepped down to oral therapy when clinically indicated to complete a 30-day course (that includes both the parenteral and oral therapies).

‡ A single dose of fosfomycin is indicated for the treatment of uncomplicated urinary infection. It may have a role in the treatment of resistant organisms in patients with other presentations of urinary infection, but the effective dose has not yet been determined.

§ The dose refers to the amount of the first noted agent in the combination.

basis of the individual patient but is often approximately one half the full therapeutic dose. When antimicrobial resistance precludes the use of fluoroquinolones or trimethoprim–sulfamethoxazole, nitrofurantoin, minocycline, or other tetracyclines may be effective in controlling the symptoms of cystitis that are attributable to bacterial relapse, even though nitrofurantoin does not penetrate the prostate. Potential adverse effects with long-term use, such as pulmonary or liver toxic effects with nitrofurantoin, should be considered. For self-initiated therapy, the patient is provided with an oral antimicrobial agent that is appropriate for the prior infecting organism. When symptoms occur, a urine culture is obtained and the duration of treatment is usually 7 days.

When the infection is not localized to the prostate and no other explanation for recurrent infection is apparent, a similar strategy of suppressive or self-initiated therapy can be considered for bacterial relapse. If recurring infection occurs with different strains isolated, treatment should address factors that increase susceptibility to reinfection. Such treatment may include alpha-blocker therapy or other interventions, such as transurethral resection of the prostate, to reduce residual urine volume.

AREAS OF UNCERTAINTY

The contribution of bacteria or viruses other than recognized uropathogens to urinary tract infections in men is not clear. Whether bacteria access the urinary tract transmucosally from the rectum or by retrograde urethral migration is also unknown. The most effective urologic evaluation of men with urinary tract infection is uncertain. The minimum duration of antimicrobial treatment for cystitis or pyelonephritis in men has not been determined. The benefits and risks of long-term suppressive therapy for chronic recurrent prostatitis require further study.

GUIDELINES

Guidelines for the diagnosis and treatment of chronic bacterial prostatitis have been published by Prostate Cancer UK[50] and for the management of asymptomatic bacteriuria by the Infectious Diseases Society of America.[10] The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette probably has chronic bacterial prostatitis with extended-spectrum beta-lactamase *E. coli* infection that manifests as acute episodes of febrile urinary tract infection. Imaging of the upper urinary tract and referral to a urologist for cultures to localize the infection to the prostate are recommended. If imaging of the upper urinary tract identifies any abnormalities, correction should be considered. If the testing to localize the infection to the prostate is positive and the organism is sensitive to a fluoroquinolone or trimethoprim–sulfamethoxazole, a 30-day course of treatment is indicated. If the bacteria are not susceptible to these preferred antimicrobial agents, alternative agents that penetrate the prostate,[48,49] as discussed in the Strategies and Evidence section, may be considered for a trial of therapy. If the initial therapy fails or relapse occurs, watchful waiting, intermittent self-initiated therapy, or suppressive therapy should be considered. Given the severity of recurrent infection and the lack of potentially curative antimicrobial agents, if the patient is prescribed long-term suppressive therapy, we would adjust the dose and frequency to a level that would be sufficient to prevent recurrent symptoms of urinary tract infection. Therefore, because of two febrile infections, we favor suppressive therapy. The patient should be aware of potential adverse effects of long-term antimicrobial therapy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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