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?

**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. 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. The frequency of severe presentations leading to hospitalization also increases with age. Urinary tract infection is the most common cause of bacteremia in older men, although death that is directly attributed to urinary tract infection is infrequent. 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, 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.

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 and in 15 to 40% of male residents of long-term care facilities. 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.

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. Chronic bacterial prostatitis may manifest as recurring urinary tract infections, usually with the same bacterial strain iso-
lated with each episode.\textsuperscript{13,14} Bacteria that are estab-
lished in the prostate may be impossible to
eradicate owing to limited diffusion of antibi-
otic agents into the gland or to the presence of
colonized prostate stones.\textsuperscript{13,15,16}

Older populations often have coexisting con-
ditions, such as diabetes mellitus, that are as-
associated with an increased susceptibility to in-
fection. Urologic coexisting conditions, such as
incontinence or urinary retention, facilitate the
acquisition of bacteriuria owing to an increased
exposure to interventions such as catheteriza-
tion.\textsuperscript{17,18} However, prospective studies have not
shown associations between postvoiding residu-
alar urine volume and bacteriuria\textsuperscript{19,20} or symptoma-
tic urinary tract infection in men.\textsuperscript{21} The most
consistent predictors of asymptomatic bacteri-
uria are markers of functional disability, includ-
ing incontinence, immobility, and dementia.\textsuperscript{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.\textsuperscript{24,25}
\textit{E. coli} is the most common organism; other
Enterobacteriaceae such as \textit{Klebsiella pneumoniae}
and \textit{Proteus mirabilis} are isolated less frequently.
Enterococcus species are the most common
gram-positive organisms. Specific \textit{E. coli} strains
and virulence traits correlate with clinical pre-
sentation.\textsuperscript{26} Strains that are isolated from men
with pyelonephritis or febrile urinary infection
are the most virulent, followed by strains iso-
lated 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, \textit{E. coli} is
also the most common pathogen isolated, but
\textit{P. mirabilis}, \textit{Pseudomonas aeruginosa}, and multidrug-
resistant strains are increasingly frequent.\textsuperscript{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 as-
associated with increased risk of these strains.\textsuperscript{27}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Diagnosis of Urinary Tract Infection}
\end{figure}

\section*{Strategies and Evidence}

\textbf{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.\textsuperscript{28} Acute bacterial
prostatitis typically manifests as fever and symp-
toms of lower urinary tract infection and, occa-
sionally, obstructive uropathy.\textsuperscript{12,14} Chronic bacte-
rial prostatitis may manifest as recurrent acute
cystitis when bacteria persisting within the pros-
tate reenter the urethra and bladder.\textsuperscript{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 popu-
lation, clinical evaluation of persons living in
institutions is more difficult owing to compro-

\begin{table}
\centering
\caption{Key Clinical Points}
\begin{tabular}{|l|}
\hline
\textbf{Urinary Tract Infections in Older Men} \\
\hline
- 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. \\
\hline
\end{tabular}
\end{table}
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. 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. 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 bacteriuria1 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 10^5 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.21 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). 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-
The four-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). 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...
is not well established. 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 of therapy on patients with acute bacterial prostatitis. 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. Macrolides, fosfomycin, and minocycline or other tetracyclines 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.*  

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

* 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 and for the management of asymptomatic bacteriuria by the Infectious Diseases Society of America. The recommendations in this article are generally concordant with these guidelines.

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, 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.

Dr. Schaeffer reports receiving fees for serving on advisory boards and travel support from Boehringer Ingelheim and Melinta Therapeutics, consulting fees from Quadrant HealthCom, ClearView Healthcare Partners, Navigant Consulting, Hollister, and KJJ Associates, author contribution fees from Advanstar Communications, fees for moderating a webinar from Cipla, and an honorarium and travel expenses from WebMD for video discussion on the treatment of complicated urinary tract infections. No other potential conflict of interest relevant to this article was reported.

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