CME CREDIT

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'Telephone treatment' of uncomplicated acute cystitis

ABSTRACT

Acute cystitis in women is typically uncomplicated and amenable to empiric antimicrobial therapy. We advocate a simple approach, in which women with uncomplicated cases are treated over the telephone. Such a program has been in place at the Cleveland Clinic since 1992, and has yielded good results.

KEY POINTS

Most young, otherwise-healthy women can be treated empirically with trimethoprim-sulfamethoxazole for 3 days without laboratory evaluation or scheduled follow-up, provided they are screened carefully.

Because of a high rate of bacterial resistance, ampicillin or amoxicillin should not be routinely used in treating UTIs.

Young, otherwise-healthy men with a single episode can be treated with culture-directed antimicrobial therapy without the need for further evaluation.

PATIENT INFORMATION
Urinary tract infections, page 502

A 26-YEAR-OLD WOMAN calls your office complaining of burning during urination. The problem began approximately 2 days ago. She has no significant past medical history. She reports minimal suprapubic pain and no symptoms of nausea, vomiting, fever, or chills. She says she has no vaginal discharge. Her last menstrual period was 1 week ago. Her last urinary tract infection (UTI) was about 2 years ago, and she recalls having a total of three UTIs in her entire life. She has never had symptoms or treatment suggestive of pyelonephritis and has never had kidney stones. She has no allergies and is taking birth control pills.

How would you manage this patient?

WHY NOT TREAT EMPIRICALLY?

This woman appears to have an uncomplicated case of acute cystitis. Her treatment should be easy. Yet, 137 physicians gave 82 different answers, when given a case much like this one in a 1991 survey[1]—a remarkable diversity of opinion for a commonplace disorder.

The true incidence is hard to determine (because many women treat themselves or get better spontaneously[2]), but one estimate is that up to 50% of women have at least one UTI in their lifetime.[3] A survey of college students found an even higher incidence: 0.7 UTIs per woman per year.[4]

Being so common, UTIs are costly to society in both dollars and productivity.[5] Evaluation and treatment costs approximately $1 billion per year.[6,7] One survey found that young women lost an average of 1.2 days of work or school per UTI.[8]

Given that UTIs in women are common

TABLE 1

Protocol for telephone treatment of acute cystitis in women

Inclusion criteria—at least two of the following:

- Dysuria
- Increased frequency
- Urgency
- Nocturia
- Incomplete emptying of bladder

Exclusion criteria—the patient must come for an appointment if she has any of the following:

- Pregnancy
- Flank pain
- Fever
- Chills
- Kidney infection or kidney stones
- Vaginal discharge with itching, burning, or pain
- Diabetes
- Hematuria (in a patient older than 50 years)
- Bladder infection in the past 2 months or five in the past year

Treatment by telephone

If no history of sulfa allergies, give:

Trimethoprim 160 mg and sulfamethoxazole 800 mg (Bactrim DS or Septra DS, 1 tablet) twice a day for 3 days

If allergic to sulfa, give:

Nitrofurantoin (Macrobid) 100 mg one tablet twice a day for 3 days; or

Ciprofloxacin (Cipro) 100 mg two tablets twice a day

To relieve burning, give:

Phenazopyridine (Pyridium) 95 mg three times a day for 2 days as needed (Tell the patient the drug will discolor urine and will stain fabric and that she should therefore wear a panty liner)

Tell the patient:

This treatment cures approximately 80% of cases

If symptoms persist longer than 3 days or get worse, she should make an appointment to see her doctor

She should drink six 8-ounce glasses of water every day for the next 3 days

and their diagnosis and treatment are straightforward, some experts believe physicians could save time and money by following simple, empiric algorithms, and still provide good care.[9,10] We agree.

One health maintenance organization decreased its cost of treating acute cystitis by 35% by following an algorithm by which eligible women were treated with antibiotics for 3 days, without a urine culture.[9] Use of the recommended 3-day antibiotic regimen increased by 24%, and use of urine cultures decreased from 70% to 37%. Another study[10] also found that empiric therapy was associated with better quality of life, lower cost, and better outcomes than was a strategy based on urine cultures.

Most women know when they have a UTI: In a survey of women with recurrent UTIs, 92% correctly diagnosed themselves as having a UTI, as confirmed by a positive urine culture.[11] Why not deal with the problem over the phone and save everybody's time?

CLEVELAND CLINIC EXPERIENCE WITH TELEPHONE MANAGEMENT OF UTIs

The Cleveland Clinic internal medicine department has used nurse-directed telephone screening questionnaires since 1992. The nurse asks a set of questions, and if the history supports the diagnosis of UTI and no contraindications are identified, empiric antibiotic treatment is given. We recommend 3 days of treatment with trimethoprim-sulfamethoxazole or trimethoprim alone (TABLE 1).

Most patients preferred telephone management

More than 700 patients have been treated with this protocol. In 1993, we interviewed 50 of the 123 women treated at that point. Most had received trimethoprim-sulfamethoxazole, and of those, 83% said their symptoms had cleared up and 92% said they were satisfied with telephone management (C. Betz, unpublished data, 1993). In December 1997, we repeated the survey, working backward until 50 more patients had been interviewed. This time, 94% said their symptoms resolved, and *all* of them were sat-

isfied. Two women did not complete their treatment. One discovered that she was pregnant and stopped taking her medication; her symptoms resolved anyway. The other patient also improved spontaneously. In three women, symptoms did not resolve with the original regimen. Two came in for an office visit and were given an additional antibiotic, which cleared up their symptoms. The third was given additional antibiotic treatment without an office evaluation; her symptoms also resolved.

The complication rate was low. One patient suffered from a headache and one patient felt that the antibiotic worsened her symptoms.

When given a choice of office vs telephone management, one patient said she would have preferred an office visit (she did not complete her treatment but had resolution of symptoms) and one patient had no preference. The rest said they preferred treatment by telephone.

CRITERIA FOR INCLUDING AND EXCLUDING PATIENTS FROM EMPIRIC TREATMENT

Do presenting symptoms indicate complications?

The symptoms of an acute UTI are straightforward in women:

- Dysuria
- Increased frequency
- Urgency
- Mild suprapubic tenderness (although this was present in only 10% of cases in one study[12])

However, one must be sure that the patient has only an uncomplicated case. Therefore, she should *not* have:

- Flank pain
- Significant abdominal pain
- Fever or chills[6]
- An ill appearance
- Diabetes[13]
- Pregnancy[14]
- Any immunocompromising disease, including AIDS[15,16]
- Recent instrumentation, ie, catheterization, cystoscopy[17]
- Use of immune-modifying drugs[15]
- A known structural abnormality of the urinary tract[18]
- Recurrent UTIs[18]
- A history of pyelonephritis[11]
- Known nephrolithiasis[18]
- Known renal disease[18]
- A solitary kidney or transplanted kidney[15]
- Recent surgery[19]
- Vaginal discharge[19]
- Gross hematuria[6]
- Present or recent use of antibiotics.[6]

Few prospective studies broke down the symptom profile as it pertains to the likelihood of infection, but complaints of acute onset of dysuria without fever or complicating factors probably represent acute cystitis.[6,20]

Is UTI the cause of acute dysuria?

Conditions other than urinary tract infection that can cause acute dysuria include:

Acute urethritis due to infection with *Chlamydia trachomatis*, *Neisseria gonorrhea*, herpes simplex, or other pathogens.

Vaginitis secondary to bacterial vaginosis, candidiasis, or trichomoniasis.[6,19,21]

Interstitial cystitis, which may cause suprapubic discomfort, increased urinary frequency, and often hematuria. This condition should be considered if symptoms persist despite treatment for acute cystitis.[6,22]

If symptoms persist despite treatment, consider interstitial cystitis

Are laboratory tests indicated?

Urine cultures need not be obtained routinely in the evaluation of acute cystitis, but they should be obtained from patients for whom empiric antibiotic treatment fails. Many practitioners obtain either a urine dipstick analysis or a urine culture or both. If the history suggests a sexually transmitted disease, a pelvic examination with appropriate cultures and microscopy is recommended.

Urine culture is the gold standard. In studies in 1956, Kass and Findland defined a bacterial count of $\geq 10^5$/mL as a discriminating value between true infection vs contamination. However, this value was found to have a sensitivity as low as 50% in young women. At present, most experts agree that UTIs can occur with bacterial counts as low as 100/mL.[6,23–26]

TABLE 2

Cost of antimicrobial therapy for acute cystitis in women

AGENT	DOSAGE*	COST*
Trimethoprim	100 mg twice a day	$4.86
Trimethoprim-sulfamethoxazole	160/800 mg twice a day	$0.33
Norfloxacin	400 mg twice a day	$13.68
Ofloxacin	200 mg twice a day	$14.10
Cefuroxime	250 mg twice a day	$15.18
Nitrofurantoin	100 mg four times a day	$3.20

*Three-day course; costs are wholesale costs to Cleveland Clinic pharmacy

***E coli* accounts for 80% of UTIs**

Low-count urine cultures should be requested in patients with recurrent symptoms and prior negative urine cultures, in which case special instructions to the laboratory may be needed.

Dipstick tests. One dipstick test uses indoxylcarboxic acid to detect esterase, an enzyme present in white blood cells. Using an arbitrary value of 10 white blood cells or more per high-power field as a standard, this test has a reported sensitivity ranging from 75% to 96% and a specificity ranging from 94% to 98%.[6]

Another dipstick test detects nitrite. Used by itself, this test has a relatively low sensitivity because not all urinary pathogens can reduce nitrate to nitrite. Used concomitantly however, the nitrite and leukocyte esterase tests have a sensitivity of 88% to 92% and a specificity of 66% to 76%, (using $\geq 10^5$ microorganisms per mL as a standard).[23] Of note: these data were collected in research settings, and the sensitivity and specificity of these tests may differ in an office setting. Both of the above tests are available on the same strip.

Pathogens seen in acute cystitis are predictable. *Escherichia coli* accounts for approximately 80% of cases; *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus, is found in 5% to 15%.[6,27] Other pathogens include *Proteus mirabilis*, *Klebsiella pneumoniae*, and other gram-negative enteric bacteria.

Urine samples often are contaminated with periurethral and perivaginal microorganisms. Lactobacilli, anaerobic streptococci, diphtheroids, and coagulase-negative staphylococci other than *S saprophyticus* are likely to represent contamination.[10]

Drug treatment

Many empiric regimens have been evaluated. A treatment duration of 3 days is currently recommended.

Trimethoprim-sulfamethoxazole is bacteriolytic and comparatively inexpensive (TABLE 2) and provides reliable coverage for *E coli*. For these reasons, several authorities recommend it as first-line therapy.[6,17,28,29]

Most of the side effects and allergic reactions to this combination are due to the sulfur component in sulfamethoxazole. Trimethoprim alone provides coverage comparable to that of the combination and greater renal tissue drug levels than does sulfamethoxazole.[30] Therefore, trimethoprim is often used alone.

Fluoroquinolones (eg, norfloxacin, ofloxacin) are acceptable alternatives to trimethoprim-sulfamethoxazole.[31] They provide excellent coverage and cause few adverse reactions.[31] However, they are generally more expensive than other commonly used agents (TABLE 2). Since widespread use of fluoroquinolones will likely lead to antimicrobial resistance, some experts reserve them for use in complicated infections.[30,32]

Cephalosporins (eg, cefuroxime) are also active against the common pathogens in acute cystitis, but are also relatively expensive. Their side effects are similar to those of the aminopenicillins.

Nitrofurantoin provides good coverage for typical uropathogens. It is commonly used in prophylactic regimens for recurrent UTIs. A drawback to nitrofurantoin is that on rare occasions it can cause pulmonary reactions and hepatitis, more likely with chronic suppressive use.

Methenamine hippurate is used to acidify the urine, primarily as a prophylactic agent. Methenamine and sulfonamides precipitate in urine, and their concomitant use should therefore be avoided.

Oral aminopenicillins (eg, ampicillin, amoxicillin) are *not* recommended, because *E coli* is gaining resistance to these agents.[6,30,32] Resistance to amoxicillin-clavulanate is only slightly lower than to amoxicillin alone. Resistance is often independent of beta-lactamase activity.[30]

Phenazopyridine, a urinary analgesic, is sometimes useful in dysuric patients. However, it should not be used routinely, as its side effects include hepatitis, acute renal failure, and hemolytic anemia.[33] Patients should be warned about the expected change in urine color and the fabric staining associated with phenazopyridine.

Follow-up

As with any algorithmic approach to medicine, the key is surveillance. Patients should be asked to call back if symptoms worsen or persist. Urine culturing in all patients with refractory symptoms will provide surveillance of uropathogens and identify patterns of sensitivity and resistance. No laboratory confirmation or follow-up is needed unless symptoms persist or worsen. Telephone management with empiric therapy appears to be cost-effective, but the data must be interpreted with caution. Prospective studies are needed. An office visit with empiric treatment is an acceptable alternative.

Preventive strategies

Women have control over some of the factors that predispose to UTIs, such as diaphragm use,[34,35] infrequent voiding, wearing of tight underclothing,[36] and sexual intercourse (the last perhaps due to trauma, transfer of enteric bacteria to the urethra, transfer of pathogens between partners, or vaginal intercourse after anal intercourse).[4,8,37]

Patient education is advisable

We should encourage awareness and education about acute cystitis. Several books[38,39] and Web sites offer reliable information about UTIs to the general public. (See the Cleveland Clinic's patient education web site at http://www.ccf.org/education/pated and also the patient information page "urinary tract infections," accompanying this article on page 502.)

TABLE 3

Symptom profile from 38 male patients with urinary tract infections

SYMPTOM	FREQUENCY (%)
Dysuria	76
Increased frequency	53
Gross hematuria	42
Malaise	34
Fever	37
Tenesmus	21
Loin pain	18
Urethral discharge	16
Urinary odor	8

UTIs IN YOUNG, OTHERWISE-HEALTHY MEN

UTIs are much less common in young, otherwise-healthy men than in women of the same age. A study in university men in the United States estimated the incidence at 4.9 UTIs per 10,000 men per year,[40] while a study in a similar population in Norway found a rate of 4.9 per 10,000 per year.[41] This low incidence is attributed to the length of the urethra, the distance between the urethra and the anus, and the antibacterial properties of prostatic fluid.[42]

Historically, UTI in men was considered indicative of an underlying anatomic defect, but in recent years this concept has been questioned. True, the incidence is slightly higher in newborns, infants, and elderly men,[43] all of whom are more likely to have anatomic defects of the urinary tract. Lack of circumcision in the young[44] and prostatic hypertrophy in the elderly[27] are anatomical variations that contribute to the increased incidence of UTI.

Nevertheless, other factors contribute. Case reports demonstrate identical uropathogens among sexual partners and conclude that sexual transmission may contribute to UTI in men and women.[37,45] Also, homosexuality has been identified as a risk for UTI.[46] The trauma and direct inoculation of the urethra with enteric bacteria during anal coitus in homosexual men may overcome the protective barriers normally provided. Heterosexual anal coitus may be a contributing factor to the occurrence of UTI in young,

See the patient information handout on page 502

otherwise-healthy males.

Although lack of circumcision has been linked to an increased risk of UTI in young men,[44] in a recent study 87% of the men found to have acute cystitis were circumcised.[40]

Presenting symptoms

The presenting symptoms of acute cystitis in young men differ from those in young women (TABLE 3). In a recent study, gross hematuria and fever were common findings in young men; in contrast, gross hematuria and fever are uncommon in women.[6,29]

Differential diagnosis

If the history or physical findings suggest urethritis, you must exclude the presence of gonorrhea or chlamydial infection. Prostatitis may mimic or occur concomitantly with acute cystitis. Extraurogenital signs and symptoms should be identified to exclude systemic disease such as Reiter syndrome.

Laboratory tests

A urine culture should be obtained in all men suspected of having a UTI and telephone treatment is not recommended. A midstream voided sample is adequate. In a study that compared urine cultures obtained by voiding, urethral catheterization, and suprapubic aspiration, a bacterial count of 10^3 or more colony-forming units per mL of voided urine was found to be the most sensitive and specific indicator of UTI.[42] The Infectious Diseases Society of America consensus panel recommends that a count of 10^4 or more colony-forming units per mL be used for the study of UTI in men.[27,42]

Telephone treatment is not recommended for men suspected of having a UTI

If the history or physical suggests a sexually transmitted disease, appropriate culture samples and microscopy are recommended. Epididymitis and prostatitis should be included in the differential diagnosis and should be searched for during the physical examination.[30,47] Routine radiologic evaluation for anatomic defects is no longer indicated.[6,48,49] If the patient looks ill, or if you suspect pyelonephritis, or if culture-directed antimicrobial therapy has failed, an anatomic evaluation should be considered. Urologic evaluation should include either renal ultrasonography or computed tomography.[48,50]

Pathogens

The causative microorganisms in young men with UTIs are similar to those in women.[6,40,43] In a recent study, 37 (93%) of 40 UTIs were caused by *E coli*.[40] As in women, ascending migration of urovirulent coliforms likely contributes to the development of acute cystitis.

Treatment

Acute cystitis in young, otherwise-healthy men can be treated with a 7-day course of sensitivity-directed antibiotic therapy without the need for further evaluation. Sulfamethoxazole-trimethoprim is a reasonable empiric antimicrobial choice. If the symptoms resolve, no further evaluation is needed. If culture-directed therapy fails, a repeat urine culture and further evaluation are suggested. If culture-directed antimicrobial therapy fails, a fluoroquinolone is suggested while awaiting repeat culture results.

Antibiotic therapy should be directed by culture sensitivity. Pending the culture report, trimethoprim-sulfamethoxazole can be given as empiric treatment. The duration of treatment should be at least 7 days. A posttreatment urine culture is not suggested if the symptoms resolve. If culture-directed therapy fails, a repeat urine culture and further investigation are recommended. A fluoroquinolone is suggested while awaiting further workup and repeat culture results.[10,29]

Cost

The cost of evaluating and treating a male patient with acute cystitis is more than for a female patient. However, the incidence rate is so much lower in male patients that the cost to the health care system is negligible. In the past, intravenous pyelography, computed tomography scans, ultrasound, cystoscopy, and functional bladder testing accounted for the bulk of the cost of evaluating UTIs in adult men. At present, a workup to rule out an anatomic or neurologic defect is not routinely recommended.[6,40]

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