Management of Urinary Tract Infections in the Era of Increasing Antimicrobial Resistance

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KEYWORDS
- Urinary tract infection • Acute cystitis • Resistance • Fosfomycin
- Trimethoprim-sulfamethoxazole • Nitrofurantoin • Recurrent UTI

KEY POINTS
- Antimicrobial resistance in common urinary pathogens is increasing at an alarming rate, as a result of overuse and misuse of antibiotics. Resistance patterns vary by geographic location, but are rising nationwide and globally.
- In the properly selected woman with suspected uncomplicated cystitis, evaluation by a symptom-based approach is both cost-effective and may improve patient satisfaction.
- Acute, uncomplicated urinary tract infections (UTIs) should be treated with fosfomycin, nitrofurantoin, or trimethoprim-sulfamethoxazole. Fluoroquinolones are no longer recommended as first-line therapy for uncomplicated UTI.
- Recurrent UTIs are common. Risk factors include recent intercourse, new sexual partner, and contraceptive type.
- Prevention of recurrent UTIs should begin with a history-based approach to identify associated factors. Antimicrobial prophylaxis should be reserved for use when all other considerations have failed.

INTRODUCTION

A previously healthy 32-year-old woman presents to primary care with dysuria and urinary frequency of 2 days’ duration. She denies fevers, chills, or flank pain. You have seen her for this reason 3 times in the last 2 years.

This scenario is frustratingly common in modern medicine. The problem is becoming more complex. Despite the availability of oral antibiotics (in fact, because of that
availability), antimicrobial-resistant gram-negative rods are becoming increasingly important for patients and physicians alike. This article provides an update and practical strategies for the prevention, diagnosis, and treatment of urinary tract infections (UTI) in the contemporary era.

INCIDENCE AND IMPACT

Acute uncomplicated bacterial cystitis is a frequent problem in the American outpatient setting, with an estimated 8.6 million cases annually, accounting for 1.6 billion dollars in health care expenditures. Acute cystitis is associated with an average of 6.1 days of symptoms and 1.2 productive days lost because of illness. Of patients with acute cystitis, an estimated 59% present to primary care and 23% to emergency departments.1

MICROBIOLOGY, RESISTANCE MECHANISMS, AND RISK FACTORS

Staphylococcus saprophyticus and any member of the Enterobacteriaceae family (including Escherichia coli, Klebsiella pneumonia and Proteus mirabilis) and can cause cystitis. However, E coli remains the most common cause, responsible for an estimated 65% to 95% of cases. Because of the predominance of this bacteria, E coli resistance is often a focus of epidemiologic resistance studies.4–6

The most recent Infectious Disease Society of America (IDSA) guidelines for treatment of uncomplicated cystitis and pyelonephritis focused on the resistance of organisms responsible for uncomplicated cystitis.7 The guidelines describe the association between antimicrobial prescribing and resistance development as collateral damage. For example, areas with high rates of fluoroquinolone prescribing for all reasons, in particular sinopulmonary infections, show higher E coli fluoroquinolone resistance compared with areas with lower prescription rates.8 Despite clinical practice guidelines for a wide variety of common infections, studies continue to document improper antibiotic prescribing patterns, both in the hospital and in the ambulatory setting.9,10

Microbes have developed multiple antimicrobial resistance mechanisms, including alterations of the drug target, enhanced drug efflux, and limitation of drug influx.11 Many resistance elements are chromosomal point mutations that provide a survival advantage in the setting of selective drug pressure.12 In contrast, plasmid-mediated genes provide a highly mobile alternative mode of resistance of increasing prevalence. Microbes can exchange plasmids between members of the same or different species. Examples of plasmid-mediated resistance include carbapenem resistance of Klebsiella pneumoniae and fluoroquinolone resistance of Enterobacteriaceae. Resistant bacteria have increased survivorship under antibiotic selection, leading to increased prevalence.11,12 Furthermore, plasmids often contain genes encoding for resistance against multiple drugs, and thus bacteria resistant to 1 antimicrobial agent are more likely to also be resistant to others.5,6

Resistance caused by extended spectrum β-lactamases (ESBL) deserve special mention. ESBLs are a family of plasmid-borne hydrolytic enzymes that inactivate penicillins and cephalosporins. Original descriptions of ESBL involved E coli and K pneumoniae, but the plasmids have been detected in a variety of gram-negative rods since then. The current frequency of ESBL expression probably varies substantially from region to region, although national and international numbers are difficult to come by. It is clear that these plasmids are seen routinely in areas where they were previously not found; for example, resistance increased from undetectable to detectable in 8 years’ surveillance in Europe, although the overall frequency was low as of
2012. Although penicillins and cephalosporins are rendered inactive by ESBLs, carbapenems are still generally active against them.

However, carbapenem-resistant Enterobacteriaceae are also on the increase, thanks to the expression of carbapenemases. Like ESBLs, these are β-lactamases, but they have activity against carbapenems in addition to penicillins and cephalosporins. Two of the most clinically important carbapenemases are the Klebsiella pneumoniae carbapenemase (KPC) and the New Delhi metallo-β-lactamase-1 (NDM-1).

KPC expression has been detected in many Enterobacteriaceae including E coli and Proteus, as well as non-Enterobacteriaceae such as Pseudomonas aeruginosa. It was first identified in North Carolina in 2001, and since then, has become endemic in many hospitals in the North Eastern United States. In addition to β-lactams, cephalosporins, and carbapenems, these bacteria typically show resistance to quinolones and aminoglycosides. KPC resistance was believed to be isolated to the United States until it was identified in France in 2005 (in a patient recently hospitalized in the United States). This enzyme is encoded by a transposon capable of insertion into diverse plasmids, thereby providing rapid and interspecies transmission. Another worrisome realization is that resistance detection by standard methods is not reliable. Sensitivity testing to meropenem and imipenem is inadequate to evaluate for in vitro carbapenem resistance, because some carrier organisms remain in the susceptible range by in vitro testing. Ertapenem testing has shown better sensitivity than the other carbapenems. Those with increased minimum inhibitory concentrations (MICs) to carbapenems should be tested using the modified Hodge test for further resistance characterization. However, this specialized technique is challenging to perform, and it is possible that many laboratories do not detect KPC expression.

NDM-1 was first recognized in a patient hospitalized in New Delhi, India in 2007. Most cases since that time have been linked in some way to the Indian subcontinent, where prevalence estimates range from 5% to 18%. By August 2010, the resistance was found worldwide, with the exception of Central and South America. By June 2012, a total of 13 cases had been reported in the United States. Organisms with NDM-1 expression are usually sensitive to colistin and may be sensitive to tigecycline and fosfomycin. The NDM-1 gene is transmitted on a variety of plasmids, some highly mobile, even between distantly related gram-negative organisms. Bacterium with NDM resistance can colonize hosts and contaminate water and environmental surfaces.

Regardless of the mechanisms involved, resistance patterns continue to change, in patterns that are geographically distinct and dynamic. For example, overall E coli drug resistance is higher in Portugal and Spain when compared with Northern European nations and Canada. There is a pressing need for a unified national American drug resistance surveillance system. One effort, the National Antimicrobial Resistance Monitoring System (available at http://www.NARMS.com), a coalition between the US Centers for Disease Control, Food and Drug Administration (FDA), and Department of Agriculture, monitors the resistance patterns of enteric bacteria cultured from humans and animals. However, this group is largely focused on food-borne illness, and is underfunded to investigate patterns of gram-negative resistance as they pertain to UTI.

Defining one’s local resistance patterns is even more difficult. Many hospitals monitor resistance of organisms cultured in their microbiology laboratory. These data may reflect drug-exposed, hospital-acquired organisms more than community-acquired, outpatient-based illnesses. Thus, hospital antibiograms likely overestimate community resistance patterns. However, the IDSA recommends avoiding antimicrobial agents when local resistance exceeds 20%, implying that primary care
providers should be familiar with local outpatient resistance patterns. We hope that local health departments will collaborate with outpatient providers and their laboratories to create local ambulatory antibiograms.

**EVALUATION**

*Your patient is calling on Friday afternoon with her usual UTI symptoms. She does not have fevers, back pain, nausea or vomiting. Can empirical treatment be started? Should you obtain a urinalysis or culture before treatment?*

Urine culture remains the gold standard to confirm suspected UTI, but bacterial colony count and resistance patterns require more than 24 hours of analysis, and therefore a probable diagnosis must be made by history, examination, and point-of-care diagnostics. Symptoms of dysuria, frequency, hematuria, nocturia, and urgency all increase the probability of UTI, with likelihood ratios between 1.10 and 1.72, whereas vaginal discharge decreases the likelihood of UTI (**Table 1**).\(^2\)

Dipstick analysis is a quick and cheap diagnostic tool. But is it reliable? The positive predictive value is substantial in the setting of both positive leukocyte esterase (LE) and nitrite, but these tests are limited by low sensitivity, and therefore a low negative predictive value as well (**Table 2**).\(^2\) For example, not all uropathogens can convert nitrate into nitrite. With limited negative predictive values, UTI may be difficult to rule out even when all features are negative.\(^2\) Dipstick-positive hematuria has been shown to increase the likelihood for UTI and is additive with a positive nitrite.\(^2\) Symptom-based evaluation provides only modest positive predictive value, whereas urine dipstick analysis is unable to effectively rule out UTI when there is moderate clinical suspicion.

Definitive diagnosis of cystitis can be made only with clinical symptoms and bacteriuria. IDSA guidelines recommend a colony-forming unit level of \(10^5\) or greater as diagnostic of UTI.\(^7\) However, colony counts of \(10^2\) have shown improved sensitivity and retained specificity among symptomatic women.\(^2\)

In some settings, empirical treatment has been found to be cost-effective and to reduce overall symptom duration when compared with dipstick and culture evaluations.\(^2\) Guidelines have been proposed to help providers reduce expense and inconvenience to patients. **Fig. 1** represents 1 such guideline modified to reflect concerns regarding resistance. These guidelines have reduced the use of urinalysis, cultures,

<table>
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<th>Table 1</th>
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<tr>
<td><strong>The accuracy of symptoms for diagnosis of UTI</strong></td>
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<tr>
<td><strong>Symptom</strong></td>
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<tr>
<td>Dysuria</td>
</tr>
<tr>
<td>Frequency</td>
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<tr>
<td>Urgency</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Vaginal discharge(^a)</td>
</tr>
<tr>
<td>Hematuria(^b)</td>
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</table>

\(a\) Based on \(\geq 10^2\) CFU/mL.

\(b\) Based on \(\geq 10^3\) CFU/mL.

Table 2
The accuracy of dipstick for diagnosis of UTI

<table>
<thead>
<tr>
<th>Dipstick</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive LE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.62</td>
<td>0.70</td>
<td>2.01</td>
<td>0.54</td>
</tr>
<tr>
<td>Positive nitrite&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.50</td>
<td>0.82</td>
<td>2.78</td>
<td>0.61</td>
</tr>
<tr>
<td>Positive LE or nitrate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.75</td>
<td>0.70</td>
<td>2.50</td>
<td>0.36</td>
</tr>
<tr>
<td>Both LE and nitrate positive&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.45</td>
<td>0.99</td>
<td>45</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Likelihood ratios calculated from published data.
<sup>a</sup> Nonurologic population.
<sup>b</sup> General population.


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Eligible woman telephones or presents to clinic with predominant symptoms of dysuria or urgency

Patient is triaged to a primary care consulting nurse

Patient offered the choice of either an office visit with a healthcare provider or telephone management. Does the patient request an office visit?

Any risk factor for complicated UTI?
- Resistance Factors (see Table 3)
- Age <18 or > 55?
- History of uro/gyn surgery or procedure within 6 months?
- Urinary catheter?
- Fever, chills, back pain?
- Nausea, vomiting?

Allergies or intolerance prevent recommended regimen?

Review local resistance. Avoid antibiotics with local resistance > 20%. Prescribe one of the following:
1. Trimethoprim-sulfamethoxazole 1DS tab PO BID x 3 days OR
2. Nitrofurantoin 100 mg QID x 3 days OR
3. Fosfomycin 3 gm PO Once

Schedule visit with provider

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*Fig. 1. Evaluation and management of acute, uncomplicated UTI. (Adapted and modified from* Sanjay S, Scholes D, Fihn SD, et al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. Am J Med 1999;106(6):638.*)
and office visits and have increased use of recommended antibiotics. Cystitis is one of the few, if not the only, infectious diseases in which telephone triage antibiotic prescribing has been shown to be an acceptable option. In indeterminate cases, dipstick or culture should be used to assist with making the diagnosis and reducing antibiotic use for inappropriate cases. Culture is recommended if pyelonephritis is suspected or if the individual patient is at higher risk for resistance.

In cases in which the diagnosis remains unclear, it may be appropriate to delay initiation of antibiotics. In this scenario, the patient submits a urine culture, which is monitored for 48 hours. If positive, a prescription is provided. In a randomized, controlled trial evaluating this approach, patients in the delayed antibiotics arm received antibiotics less often, although those who ruled in for UTI had symptoms for 37% longer than those in the immediate arm. The severity of symptoms was not of significant increased severity in either arm, and there was no increased progression to pyelonephritis among those in the delayed arm.

Because geographic resistance is difficult to estimate, many studies have examined individual factors believed to be predictive for development of resistant UTI. These factors include age older than 60 years, recent international travel, previous history of a UTI, chronic medical conditions, recent hospitalization, and any recent antibiotic course (with more recent treatment portraying a higher risk of resistance). Risk factors should be considered when using empirical treatment guidelines and when they are present, urine culture should be considered before antibiotic start.

TREATMENT: RECOMMENDED DRUG AND COURSE

In choosing the best antimicrobial agent for uncomplicated cystitis, prescribers must take into account a patient’s treatment history, allergies or intolerances, pregnancy or breastfeeding status, insurance coverage, and drug interactions. Because side effects vary by agent, these should be taken into account as applicable. Please see Table 3.

Nitrofurantoin

Nitrofurantoin is an inactive antiseptic that is largely activated in the urine by microbes. It is produced in 3 formulations that vary by crystal preparation. The smaller crystalline form of nitrofurantoin (Furadatin), is rapidly absorbed, leading to gastrointestinal (GI) upset, and thus it is rarely used. Macrocristalline nitrofurantoin (Macrobid), is composed of

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Risk factors for UTI caused by a resistant organism</th>
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<tbody>
<tr>
<td><strong>Risk Factors for Antimicrobial Resistance</strong></td>
<td></td>
</tr>
<tr>
<td>• Age older than 60 years</td>
<td></td>
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<tr>
<td>• Previous history of UTI</td>
<td></td>
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<tr>
<td>• Chronic medical conditions</td>
<td></td>
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<tr>
<td>• Recent hospitalization</td>
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</tr>
<tr>
<td>• Any recent antibiotic treatment</td>
<td></td>
</tr>
<tr>
<td>• Recent travel abroad</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosing</td>
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<td>-----------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>100 mg by mouth twice a day × 5 d</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1 double strength tablet by mouth twice a day × 3 d</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3 g by mouth × 1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250 mg by mouth twice a day × 3 d</td>
</tr>
</tbody>
</table>

<sup>a</sup> Contraindicated at term.

<sup>b</sup> American College of Obstetricians and Gynecologists recommends using during first trimester only if no other options.<sup>36</sup>

approximately 75% nitrofurantoin monohydrate and 25% macrocrystal, which produce a slow-release preparation by forming a gel matrix in the stomach.\textsuperscript{34} The bioavailability is increased when taken with food.\textsuperscript{34}

As a result of brisk renal excretion, blood levels rarely reach a therapeutic level, thus reducing effectiveness and making this drug not suitable in pyelonephritis, perinephric abscess, or prostatitis. The rate of clearance is proportional to the creatinine clearance, and dose adjustments are necessary with renal impairment.\textsuperscript{35} The urinary excretion of modified-release nitrofurantoin is similar to that of macrocrystalline nitrofurantoin.\textsuperscript{34}

The most common adverse effects of using nitrofurantoin are GI in origin, including nausea, vomiting, and diarrhea\textsuperscript{35}; the macrocrystalline preparations are better tolerated.\textsuperscript{33,35} Nitrofurantoin may color the urine brown. Less common side effects include several hypersensitivity reactions characterized by chills, fever, blood cell dyscrasias, and hepatitis, all of which are treated by discontinuation of the drug. Nerve effects have been reported, with neuropathies being most common in patients with chronic kidney disease. Acute pneumonitis is reported as a rare effect also treated by drug removal.\textsuperscript{35}

Chronic nitrofurantoin pulmonary toxicity rates are difficult to estimate but are believed to be rare. For example, chronic lung reactions related to nitrofurantoin were 2.0%, 5.3%, and 3.4% of all adverse reactions reported in the United Kingdom, Sweden, and Holland, respectively, over approximately 3 decades.\textsuperscript{36} In a Mayo Clinic retrospective review of cases believed to be secondary to nitrofurantoin, most subjects were women (94%), older (median age of 72 years), and patients who had received a prolonged preventative dosing exposure (median interval of 23 months).\textsuperscript{37}

Nitrofurantoin has been associated with a variety of fetal malformations when used in the first trimester. The American College of Obstetricians and Gynecologists recommends using a different agent during this time if an alternative is available.\textsuperscript{38} It is also recommended to avoid nitrofurantoin use between 38 weeks’ gestation and delivery because of the possibility of hemolytic anemia.\textsuperscript{34} Data are limited, but use seems safe for breastfeeding infants older than 1 month and without glucose-6-phosphate dehydrogenase deficiency.\textsuperscript{39}

Nitrofurantoin has few drug interactions, probably because of reliance on microbial activation. However, an alternative therapy should be considered when fluconazole is used, because of reports of hepatic and pulmonary toxicity.\textsuperscript{40} Antacids containing magnesium may also reduce absorption and subsequent urinary secretion.\textsuperscript{34}

Microbes rarely produce new resistance to nitrofurantoin, making this an excellent choice when considering emerging resistance. However, the less common \textit{Proteus}, \textit{Pseudomonas}, \textit{Enterobacter}, and \textit{Klebsiella} species are usually inherently resistant.\textsuperscript{35}

The efficacy of nitrofurantoin compared with other antimicrobials has been studied. When compared with 3 days of low-dose ciprofloxacin, ciprofloxacin showed higher bladder eradication rates but similar rates of clinical resolution.\textsuperscript{41} No difference in outcomes was found when a 5-day course of nitrofurantoin was compared with a 7-day course of trimethoprim-sulfamethoxazole.\textsuperscript{42}

\textbf{Trimethoprim-Sulfamethoxazole}

Trimethoprim-sulfamethoxazole (cotrimoxazole, Bactrim, Septra) was first introduced as a combination drug in the 1970s. It inhibits bacterial production of folate at 2 separate steps, causing a bacteriostatic effect. Trimethoprim-sulfamethoxazole is readily absorbed from the GI tract, has a half-life of approximately 10 hours, and is renally excreted between 25% and 60% in the first 24 hours.\textsuperscript{35}
Adverse effects of trimethoprim-sulfamethoxazole are variable, but most commonly include GI upset and rash, which vary from transient eruptions to fixed drug reactions to catastrophic exfoliative syndromes (Stevens-Johnson syndrome and toxic epidermal necrolysis). Trimethoprim-sulfamethoxazole can cause a variety of anemias, some related to folate deficiency, as well as thrombocytopenia and rarely methemoglobinemia. 35

Hyperkalemia may be a concern when prescribing trimethoprim-sulfamethoxazole. It is caused by a reduction in potassium elimination from the distal nephron and is potentiated by reduction in glomerular filtration rate, concomitant use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone blockers. 43 Elderly individuals are at greatest risk for hyperkalemia caused by trimethoprim-sulfamethoxazole. Severe hyperkalemia (>5.5 mmol/L) was found in 21% of treated hospitalized patients, 44 but less often in a prospective controlled trial of outpatients, among whom only 6% developed severe hyperkalemia after a 5-day course. 45

Trimethoprim-sulfamethoxazole deserves special mention with regards to drug interactions. Both components inhibit separate P450 enzymes, leading to multiple interactions. The drug inhibits warfarin metabolism and is associated with a 3-fold higher risk of GI bleeding when used in combination with warfarin compared with use of other antibiotics. 46 Other interactions include sulfonylureas (hypoglycemia), 35,43 methotrexate (pancytopenia), and anticonvulsants (toxicity). 35

When used in the first trimester of pregnancy, trimethoprim-sulfamethoxazole has been shown to be associated with rare cases of neural tube, cardiovascular, and possibly oral cleft palate and urinary system defects. After 32 weeks’ gestation, a theoretic risk of fetal kernicterus exists and so the drug should be avoided if possible. 43 It seems to be safe during breastfeeding. 43,47

Resistance mechanisms can occur by chromosomal mutation and selection but are largely based on plasmids, likely leading to the known distinct regional resistance patterns. 35 For example, in the ECO-SENS study evaluating European E coli resistance, trimethoprim-sulfamethoxazole resistance was found in 26.7% of uncomplicated UTIs in Portugal but only in 9.5% in Austria. 4

Trials comparing trimethoprim-sulfamethoxazole with other antimicrobials for UTI treatment have shown similar efficacy to nitrofurantoin, 41 ciprofloxacin, 41 and fosfomycin. 48

Fosfomycin

Fosfomycin is an inhibitor of cell wall synthesis, structurally unrelated to any other antibiotic, 49 and is active against most urinary tract pathogens. 21 It is approximately 40% bioavailable with a 4-hour half-life. The active drug is renally excreted, with excellent urinary concentrations, exceeding most MICs for pathogens. 49,50

Fosfomycin is approved for a single 3-g dose in uncomplicated UTI. 49,51 With such dosing, no dose adjustment is needed for patients with renal or hepatic dysfunction. 52 Side effects of single 3-g dosing are typically mild and resolve within 1 to 2 days, and include diarrhea, nausea, abdominal pain, headache, dizziness, and vaginitis. 51 In a review of more than 800 patients, 53 side effects occurred in only 6.1% of patients and none was considered severe. Patients should be counseled that urinary symptoms slowly improve over 2 to 3 days, even after a single dose, and that this is not necessarily a sign of failure. 54

Drug interactions are few, but include balsalazide and metoclopramide, the latter of which when used with fosfomycin may decrease fosfomycin serum and urinary concentrations. 52
Fosfomycin is safe in pregnancy. The drug is likely excreted in low levels in breast milk, but limited data suggest safety with breastfeeding.

Resistance to fosfomycin is rare, but when present, it is caused by decreased drug transport into the bacterium and enzymatic modification of the drug. Furthermore, many species resistant to other antibiotics, including ESBL-producing \textit{E coli}, are susceptible to fosfomycin.

Single-dose fosfomycin has been compared with a 7-day course of nitrofurantoin and a 5-day course of trimethoprim-sulfamethoxazole. Clinical efficacy was similar between trimethoprim-sulfamethoxazole and single-dose fosfomycin. When fosfomycin was compared with nitrofurantoin, rates of clinical cure (resolution of symptoms) were similar for both treatments. Despite similar early clinical response rates, the microbiological cure rates (resolution of bacteriuria) at the first follow-up visit were lower for fosfomycin (78%) than nitrofurantoin (86%). The drug costs about $80 for treatment course, which is more expensive than the other first-line agents (trimethoprim-sulfamethoxazole and nitrofurantoin). It is also not so easily available, because many pharmacy chains do not carry it.

\textbf{Fluoroquinolones}

Ciprofloxacin and levofloxacin, both fluorinated quinolones, are commonly (and often inappropriately) used for empirical UTI treatment. The bactericidal effects of the drugs come from targeting DNA gyrase and topoisomerase IV. Fluoroquinolones are well absorbed orally, have a half-life of about 4 hours, and are time-dependent and concentration-dependent agents. Given this pharmacokinetic picture, once-daily extended release formations of ciprofloxacin have been found to be equally efficacious to twice-daily dosing, but at an increased price. Ciprofloxacin is largely renally excreted and can lead to increased urinary concentrations.

Side effects are most commonly GI in origin, with up to 17% of patients having nausea or other form of discomfort. Of the fluoroquinolones, ciprofloxacin is the most likely to cause \textit{Clostridium difficile} colitis. Other common side effects include those of the central nervous system (mild headache to rarely seizure, usually when used with theophylline or nonsteroidal antiinflammatory drugs) and rash. Corrected QT interval (QTc) prolongation is usually associated with other drugs in the same class, but should probably be avoided in patients using other prolonging agents or with a history of QTc disorder.

Fluoroquinolones have long been known to cause tendon rupture. However, this effect is rare. In a case control study, it occurred in approximately 3.2 cases per 1000 and only in patients older than 60 years. Use of corticosteroids was found to be a risk factor for rupture. It is advisable to counsel all patients regarding this risk and to ask them to discontinue treatment and contact their physician with any unexpected tendon or joint pain, especially at the Achilles tendon. Ciprofloxacin is contraindicated in pregnancy because of the risk of fetal arthropathy. A review performed by the American Academy of Pediatrics found no evidence for adverse outcome with breastfeeding.

The main drug interaction to recall is that ciprofloxacin can lead to an increase in theophylline levels and subsequent toxicity. It can also lead to increases in international normalized ratio in patients on warfarin.

Resistance to fluoroquinolones occurs secondary to changes in the drug target or to increased drug efflux. Resistance may be mediated by acquisition of genes via plasmids. The increase in fluoroquinolone resistance in \textit{E coli} has occurred at an alarming rate in relation to increased prescribing practices. For example, in the Denver Health System, when the preferred antibiotic for UTI was changed from
trimethoprim-sulfamethoxazole to levofloxacin because of baseline trimethoprim-sulfamethoxazole resistance, the rate of levofloxacin-resistant isolates increased from 1% to 9% in 6 years.8

OTHER ANTIBIOTICS

Cefpodoxime has been used for treatment of UTI, given its tolerability and twice-daily dosing. However, cefpodoxime has been found to be inferior to ciprofloxacin60 and equivalent to trimethoprim-sulfamethoxazole in a study with limited power,61 questioning overall efficacy. Amoxicillin-clavulanate was compared with ciprofloxacin and found to be inferior, even in cases in which strains were sensitive to amoxicillin-clavulanate. As recommended by the IDSA guidelines, β-lactams should be avoided if possible to avoid resistance and reduce collateral damage.7

ORAL CONTRACEPTIVES AND ANTIBIOTICS

Patients with UTI are often women of childbearing age, many of whom rely on oral contraceptive pills (OCPs) for birth control, and so the question of antibiotic interactions with OCPs should be addressed openly. Although more than 200 articles have been published on this question, it is difficult to establish a firm interaction in most cases. Although certain antibiotics that heavily inhibit cytochrome 3A4 (in particular, rifampin) may be expected to increase OCP metabolism, these drugs are virtually never used for UTI. However, based on the serious nature of the consequences, and in light of some continued uncertainty, it is customary to counsel patients to consider using an alternative method of birth control in addition to continuing OCPs until 1 menstrual cycle has completed after antibiotic treatment.62,63

PREVENTION AND OTHER CONSIDERATIONS

Another patient recalls that she has had 3 UTIs in the last 12 months and asks about preventative methods, including continuous antibiotics, cranberry juice, and probiotics.

Recurrent UTIs

An estimated 26.6% of women with initial UTI have a recurrence within 6 months.64 Women with a history of recurrent UTI have an average of 2.6 episodes per patient-year (varying from 0.3–7.6 episodes).65 Recurrent episodes seem to cluster in time, with the highest risk of recurrence immediately after a previous event.65

At first diagnosis, hematuria and urgency may be strong predictors of recurrent UTI.64 These investigators propose that this finding may indicate that the initial causal bacterium was particularly virulent. Compared with other organisms, when E coli caused a first UTI, recurrence was more likely.66

Risks for recurrent UTI are similar to those of first UTI. These risks include recent sexual intercourse,66–68 new sexual partner,67 and use of diaphragm, cervical cap, or spermicide.66,69 Other risk factors include age younger than 15 years at the time of first UTI,67 mother or family with history of UTI,67,70 and history of previous UTI.68,71

Anatomic factors have been implicated. Women with a shorter urethra-anus distance have more frequent UTIs compared with those with longer measurements.72 Studies have also looked at individual genetic variables, including Lewis blood group73 and toll-like receptor polymorphisms74 for further understanding of recurrent UTI susceptibility. These factors remain unproved and are not modifiable.
Behavior and Habits

Evidence of the relationship between habits and recurrent UTI is limited. Habits not associated with a change in recurrence rates include voiding after sexual intercourse, delayed voiding, wiping patterns, douching, use of hot tubs, or pantyhose. Caution should be exercised when interpreting these data, because in such small trials, a small effect may not be realized until larger studies are performed.

Mode of Contraception

Contraception method is related to acquisition of UTI. Recent condom use, both lubricated and nonlubricated, with or without spermicidal cream or gel, was found to strongly increase the risk of a first and recurrent UTI. Diaphragm use is also highly associated with both first and recurrent UTI.

Spermicide

Spermicide use is associated with increased frequency of first and recurrent UTI. Nonoxynol-9, the most commonly used spermicide, is toxic to lactobacilli, and in particular hydrogen peroxide (H₂O₂)-producing lactobacilli including Lactobacillus crispatus. The toxic effect to lactobacilli is greater than its toxic effect to *E coli* and may enhance *E coli* attachment to urogenital epithelial cells, with spermicide users more likely to be colonized with *E coli* than nonusers. Unless there are no other options, spermicides should be avoided.

Probiotics

The use of probiotics has become popular in the age of increasing antimicrobial use and resistance; however, no probiotic agent has been approved for therapeutic use by the FDA. *Lactobacillus* has been shown to be safe in studies of generally immunocompetent hosts. Evidence for the use of probiotics is diverse and inconsistent, but the proposed mechanisms for prevention of urogenital infection by probiotics include modulating host immunity, preventing adherence of pathogenic organisms to the urogenital epithelium, and modulating growth/colonization of these pathogens. When comparing patients with recurrent UTI with those without UTIs, patients with recurrent UTIs were less likely to be colonized with H₂O₂-producing strains of lactobacilli and more likely to have *E coli* introital colonization, even when controlling for use of spermicide. However, in a 2008 review that evaluated 4 studies looking at the efficacy of *Lactobacillus* for prevention of UTI, only 1 study reported a positive effect (reduction in rate of recurrent UTI), but many were underpowered and used a variety of *Lactobacillus* strains, including those not shown to produce H₂O₂. Most recently, Lactin-V, a product containing an H₂O₂-producing strain of *Lactobacillus crispatus*, was evaluated in a phase 2 clinical study. When used vaginally once per week after antibiotic treatment of UTI, a relative risk reduction of 50% (95% confidence interval, 0.2–1.2) was shown, but the study included only 100 participants, and was likely underpowered to see a statistically significant benefit. In a randomized trial comparing low-H₂O₂-producing *Lactobacillus* and trimethoprim-sulfamethoxazole prophylaxis, the *Lactobacillus* was shown to be inferior to trimethoprim-sulfamethoxazole. Until further evidence is available in larger, randomized trials, using *L crispatus*, probiotics cannot be conclusively recommended. However, they are unlikely to be harmful and may provide benefit to individual patients.

Cranberries

Cranberries are often used for UTI treatment and prevention. Cranberry extract has been shown both ex vivo and in vivo to interfere with *E coli* adherence to the
uroepithelium. Many trials have studied the use of cranberry in various forms and concentrations, but with mixed results. A 2012 Cochrane review, limited because of article diversity, calculated a risk reduction of 0.62, with women, children, and consumers of cranberry juice having the most observed benefit. Most recently, a randomized controlled trial comparing cranberry juice and placebo found no difference in time to UTI; however, this study did note reduction of infections with P-fimbriated E coli strains in the cranberry group. Cranberry has been shown to be inferior when compared with trimethoprim-sulfamethoxazole for prophylaxis. Results are discouraging, although patients may safely choose to try cranberry; those who cannot tolerate the sugar and acidity of juice might try extract capsules instead, although again the supporting evidence has been underwhelming.

**Urinary Additives**

Methenamine salts are proposed to prevent UTI by producing formaldehyde from hexamine, leading to urinary acidification, and thus making the bladder more hostile to microbial invasion. Few large trials have evaluated the efficacy of these additives. The salts come in 2 forms: methenamine hippurate and methanamine mandelate; the latter is not widely available. Typically well tolerated, methenamine salts were examined by a Cochrane review in 2012. With great study heterogeneity, subgroup analysis showed a relative risk (RR) of 0.24 when used by patients without renal tract abnormalities, a finding not shown in patients with such abnormalities. Furthermore, treatment duration of 1 week showed an RR of recurrent UTI of 0.14. These medications are generally well tolerated, although some women discontinued use because of a sensation of urethral burning caused by chemical irritation.

**Estrogen for Postmenopausal Women**

After menopause, women are believed to lose the UTI-protective benefits of estrogen, with resultant increases in vaginal pH and decrease in introital *Lactobacillus* colonization, among other effects. Investigations of estrogens to prevent recurrent UTI have varied by dose, route (oral vs vaginal), and control group (placebo vs antimicrobial). In a 2008 Cochrane review, oral estrogen replacement was not found to reduce recurrent UTI, whereas vaginal estrogens showed a reduced risk (RR of 0.25 and 0.64 in 2 trials). Studies comparing estrogen replacement with prophylactic antibiotics were again heterogeneous in design and showed conflicting results. Topical estrogen treatment could be considered in motivated, postmenopausal women with recurrent UTIs, especially when the risk of prophylactic antibiotic use is high.

**Evaluation of Recurrent UTIs**

The purpose of recurrent UTI workup is to evaluate and eliminate any cause that might predispose the patient to morbidity related to recurrent UTIs. The workup should start with a thorough history, including possible predisposing factors, such as temporal relationship to intercourse and method of contraception. Symptoms such as vaginal discharge or odor may point toward an alternative diagnosis. The physical examination should focus on vaginal and urethral disease, and in particular uterine or rectal prolapse. Residual urinary volume should be measured with either bladder ultrasonography or catheterization to rule out retention (Fig. 2). After these tests are completed, imaging may be considered, although in many cases, it yields no information to change management. Cystoscopic or radiologic evaluation should be considered in patients with complicated, persistent, or febrile infections. Patients without fever, flank pain, or hematuria can usually be managed without imaging. In a prospective study of 100 patients referred for urologic work
up in the setting of UTI, the usefulness of imaging and subsequent findings was evaluated. Abdominal radiographs were performed in all 100 patients without an abnormal finding in any case. Renal ultrasonography was performed in 90 cases, with 5 abnormalities found, and in 16 intravenous urograms, 2 were abnormal. In total, 6 abnormalities were found, but only 1 was considered related to recurrent UTIs.97 Those with pyelonephritis caused by urea-splitting organisms such as Proteus vulgaris should be considered for ultrasonography or plain radiography to rule out nephrolithiasis, because of the association between these bacteria and struvite calculi.96

Cystoscopy has been used in the evaluation of recurrent UTI to evaluate for structural abnormalities not found with imaging, such as urethral stricture, bladder calculus, or colovesical fistula. In a study of 118 patients with recurrent UTI undergoing cystoscopy, all of whom had some form of previous imaging, only 8% of the women had a significant abnormality detected radiographically. Most of these abnormalities were in women older than 50 years. Furthermore, negative imaging before cystoscopy carried a negative predictive value of 99% for finding an abnormality.98 Given these findings, in women without risk factors for structural abnormalities and with negative imaging, cystoscopy can usually be deferred. Furthermore, given the association of

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**Fig. 2.** Recommended management of women with recurrent cystitis.
abnormal findings with age, it is likely not necessary to evaluate women younger than 40 years with cystoscopy.\textsuperscript{97,98}

**Antibiotic Prevention**

When conservative, nonantimicrobial measures fail to prevent recurrent UTI, antibiotics are relied on. In a recent Cochrane review,\textsuperscript{99} the effectiveness, safety and administration schemes of antibiotic prophylaxis were reviewed. This database defined recurrent UTI as 3 or more episodes within 1 year or 2 or more episodes within 6 months. Antibiotic prophylaxis prevented recurrence after treated UTIs with an RR of 0.21 and a number needed to treat to prevent 1 recurrence of 1.85. As expected, the rate of side effects was higher in the treatment group (RR 1.58 for severe side effects), with high dropout overall (exceeding 20% in some studies). Dropout was highest amongst the nitrofurantoin groups. After prophylaxis was discontinued, the protective effect was no longer evident. However, the investigators were unable to pose a best antibiotic, duration, or other mode because of the heterogeneity of the studies.

Prophylactic regimens are used in many schedules, including daily, weekly, monthly, and postcoital. With the pressure of antibiotic resistance, regimens with limited duration offer the benefit of less exposure. Postcoital administration of trimethoprim-sulfamethoxazole was more effective than placebo at preventing UTI (0.3 events per patient-year compared with 3.6 events per patient-year), although this was a small study,\textsuperscript{100} and postcoital ciprofloxacin showed similar efficacy compared with daily administration in another study.\textsuperscript{101} Patient-initiated regimens have also been studied. In a randomized trial in 2011,\textsuperscript{102} patients were randomized to continuous prophylaxis or patient-initiated treatment. The patient-initiated arm was instructed to take a single dose after an event known to be associated with recurrence in the individual’s circumstance (eg, intercourse, delayed micturition, diarrhea). Groups had similar efficacy but fewer side effects in the patient-initiated arm (9.1%) compared with the continuous group (30%). Limitations of this study included inclusion of only postmenopausal women and a rotation of the continuous antibiotic every 2 to 4 weeks. Because recurrence is known to cluster near the time of initial UTI,\textsuperscript{64,65} duration of prophylaxis might continue for 6 to 12 months, regardless of the method chosen.\textsuperscript{99}

**SUMMARY**

In the era of increasing microbial resistance, caution should be taken when prescribing both for the individual patient’s risk of resistant infection and for reducing community antimicrobial resistance. Practice guidelines have been shown to reduce cost and increase the rate of appropriate antibiotic use. Antibiotics with less potential for promoting resistance (nitrofurantoin, fosfomycin) should be used preferentially. Trimethoprim-sulfamethoxazole remains an important first-line agent in most settings. Fluoroquinolones and broad-spectrum antibiotics should be reserved as second-line agents. Some host factors may be modified to reduce risk of recurrence. Prophylactic antibiotics should be minimized and (if needed) used in a patient-initiated scheme.

**REFERENCES**


Vaginal infections update

Jane Mashburn, CNM, MN

Vaginal symptoms are one of the leading reasons that women visit their health care providers. Women often self-diagnose and may treat themselves inappropriately. This article describes the etiology, risk factors, symptoms, diagnosis, and treatment of the 3 most common vaginal infections: bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis.


Keywords: bacterial vaginosis, trichomoniasis, vaginitis, vulvovaginal candidiasis

INTRODUCTION

Symptoms of vaginal problems, such as discharge, itching, and odor, occur in most women during their lifetimes. These symptoms can cause distress and embarrassment and are the leading cause for women to seek care from a health care provider. In the United States, it is estimated that 10 million office visits per year are for vaginal symptoms. These symptoms are usually caused by one of 3 infections: bacterial vaginosis (BV), trichomoniasis, or vulvovaginal candidiasis (VVC). This article reviews clinical findings, diagnosis, and management, including management of recurrences, for these 3 infections.

BACTERIAL VAGINOSIS

Etiology

Bacterial vaginosis is the most common cause of vaginal discharge in women of reproductive age and is the most common vaginal infection in the world. The etiology of BV is not completely understood but is associated with the replacement of normally occurring Lactobacillus bacteria in the vagina with other bacteria such as Gardnerella vaginalis, Ureaplasma, Mycoplasma, Prevotella, and Mobiluncus as well as other fastidious and uncultivated anaerobes. These normally occurring lactobacilli produce lactic acid, hydrogen peroxide, and bacteriocins that help to maintain an acidic pH in the vagina that is thought to protect against other infectious organisms. The bacteria responsible for BV produce enzymes that degrade the gel layer protection of the cervical and vaginal epithelium. These anaerobes are also known to produce inflammatory proteins that are associated with complications of pregnancy (eg, preterm labor and birth), pelvic inflammatory disease, endometritis, infections after gynecologic surgery, and increased susceptibility to HIV type 1, herpes simplex virus type 2, Neisseria gonorrhoeae, and Chlamydia trachomatis.

Risk Factors

Bacterial vaginosis is not considered a sexually transmitted infection (STI), but the risk profile associated with it resembles that of other STIs such as trichomoniasis, gonorrhea, and chlamydia. Risk factors include douching, use of an intrauterine device, having male partners who have sex with other women, increasing lifetime partners, having a new partner, having sex with women, inconsistent condom use, black ethnicity, and cigarette smoking. In a study to access douching as a risk factor, 3,602 women had a total of 13,517 visits, including an initial visit, followed by 4 quarterly visits up to one year for assessment of BV and douching. After adjusting for demographics and sexual activity, douching was associated with BV (odds ratio for weekly or greater douching vs never douching = 1.17; 95% confidence interval, 1.09-1.27). Oral contraceptive use has an inverse relationship to acquiring BV.

Clinical Presentation and Findings

Vaginal discharge and foul odor are the 2 most frequently reported symptoms; however, as many as 60% of women with BV do not report symptoms. Physical examination findings include a homogenous, thin, grayish vaginal discharge that coats the vaginal walls and a fishy vaginal odor. It is unknown whether asymptomatic BV resolves, remains stable, or becomes symptomatic.

Diagnosis

The Gram stain is the criterion standard for the diagnosis of BV. Using Nugent scoring, which examines the number of various bacteria per oil-immersion field of the Gram stain, a score of 0 to 3 is considered normal flora, and a score of 7 to 10 is overt BV. The intermediate scores between 3 and 7 are not clearly identified abnormal or normal. Ison scoring of the Gram stain does recognize partial BV in addition to overt BV. This partial BV, an intermediate form of abnormal flora, describes the presence of lactobacilli and BV-like flora together. The Ison intermediate BV is different from the Nugent intermediate flora. If the Gram stain is used to diagnose BV, the Ison score, which more correctly describes the total vaginal flora than the Nugent score, should be used.

Another method for making a clinical diagnosis of BV is using Amsel criteria. Three of the following are considered diagnostic for BV: homogenous gray-white vaginal discharge, fishy odor of discharge either with or without 10% potassium base.
hydroxide (KOH), vaginal pH greater than 4.5, or clue cells on saline wet mount (>20% clue cells).

Three other tests are currently being used to diagnose BV. Affirm VP III (Becton Dickinson, Sparks, Maryland) is a DNA probe-based test that measures for high levels of G vaginalis. BVBLUE (Gryphus Diagnostics, Knoxville, Tennessee) is a rapid point-of-care test with a reagent that will turn blue when mixed with a vaginal swab if there is an elevation of sialidase activity produced by bacterial pathogens associated with BV. The Pip Activity TestCard (Quidel Corporation, San Diego, California) is another rapid test for confirming suspicion of BV by identifying an enzyme produced by G vaginalis. All 3 of these tests have been shown to perform similarly to the Gram stain.1,3

Although some clinicians treat BV based on results of the Papanicolaou (Pap) test, studies comparing the Pap test findings with clinical diagnosis of BV have not been consistent.14 According to the Centers for Disease Control and Prevention (CDC), “Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity.”

Treatment

Treatment of symptomatic women is recommended by the CDC. The recommended treatment is either metronidazole orally, metronidazole gel intravaginally, or clindamycin cream intravaginally. Alternative treatment is either tinidazole orally, clindamycin orally, or clindamycin ovules intravaginally (Table 1). Providers should discuss treatment options with patients, including side effects, when deciding the route and type of medication. The recommended treatment of women with HIV is the same as for women who do not have HIV. Treatment of asymptomatic women is not recommended.1

Pregnancy

Even though BV is associated with complications in pregnancy such as premature rupture of membranes, preterm labor, preterm birth, and postpartum endometritis, the CDC recommends only treating pregnant women with symptoms. Studies have not demonstrated any teratogenic effects from metronidazole use at any time during pregnancy. Therefore, the treatment recommended for pregnant women is either metronidazole or clindamycin orally (Table 1). Clindamycin cream has been associated with adverse pregnancy outcomes, such as low birth weight and neonatal infections, when used between 16 and 32 weeks’ gestation. Therefore, the CDC advises that the practitioner be aware of these findings prior to prescribing clindamycin cream during pregnancy.1

Studies comparing the reduction of preterm birth rates in asymptomatic pregnant women with BV who were treated versus those who were not treated are inconclusive, regardless of whether they were at high risk or low risk for preterm birth.1 The US Preventive Services Task Force has recommended against screening asymptomatic women for BV even though one study demonstrated a 40% reduction rate of preterm birth in women at low risk for preterm birth who were treated with oral clindamycin.1

Recurrent Bacterial Vaginosis

Recurrences of BV are common. In one study, the recurrence rate was 69% in the women who were treated with the recommended regimen of oral metronidazole.16 The pathophysiology of recurrence is not fully understood although it does seem to occur just after menstruation. This would be a time of lowered estrogen and higher vaginal pH.17 Risk factors for recurrence include past history of BV, regular sex partners, sex with women, and new sex partners. In a study of 358 women, those who harbored Atopobium vaginae as well as G vaginalis had higher recurrence rates than those women who had G vaginalis only.16

Various treatments for recurrent BV have been studied.5,18,19 No treatment regimens have been identified as superior. Several treatment options are discussed in the newest CDC STI Treatment Guidelines, but no specific treatment is recommended.1 The use of metronidazole gel 2 times per week for 4 to 6 months has been shown to reduce recurrences. In addition, treatment with oral metronidazole for 7 days followed by 21 days of treatment with 600 mg of intravaginal boric acid showed a cure rate of 88% to 92%.5 Use of probiotics to reduce recurrences has been studied with inconclusive results. Acidification of the vagina with a variety of products has also been studied. To date, no well-designed randomized control trials have been reported, so the efficacy of acidification has not been established.17

TRICHRONOMIASIS

Trichomonas vaginalis is the most common nonviral, curable STI worldwide.20–22 Although it was accepted as a cause

Table 1. Treatment of Bacterial Vaginosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Duration, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg orally twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Metronidazole gel</td>
<td>One applicator</td>
<td>5</td>
</tr>
<tr>
<td>0.75%</td>
<td>intravaginally daily</td>
<td></td>
</tr>
<tr>
<td>Clindamycin cream</td>
<td>One applicator</td>
<td>7</td>
</tr>
<tr>
<td>2%</td>
<td>intravaginally daily</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinidazole</td>
<td>2 g orally once daily</td>
<td>2</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>1 g orally once daily</td>
<td>5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>300 mg orally twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Clindamycin ovules</td>
<td>100 g intravaginally daily</td>
<td>3</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg orally twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>250 mg orally 3 times daily</td>
<td>7</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>300 mg orally twice daily</td>
<td>7</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention1
of vaginal discharge in the 1940s, sexual transmission of the infection was demonstrated in the 1950s. For years, having the infection represented that one had risky sexual behaviors, but this garnered little attention. With the addition of newer diagnostic modalities, awareness of the magnitude of the infection has more recently received more attention. There are an estimated 7.4 million cases of trichomoniasis per year in the United States, which is more than twice the cases of chlamydia and more than 7 times the cases of gonorrhea. Trichomoniasis has been reported in 3% to 54% of young, sexually active women and 32% of incarcerated women.

**Etiology**

Trichomoniasis is caused by a parasitic, pear-shaped, motile protozoan. It adheres to the vaginal epithelium and releases cytotoxic substances that cause inflammation and breaks in the epithelium. _T. vaginalis_ does not need cervical cells for growth like _C. trachomatis_ and _N. gonorrhoeae_; it is a vaginal pathogen, and the whole vagina is at risk for being infected.

**Risk Factors**

Socioeconomic status, ethnicity, lower education level, and douching have been identified as risk factors for acquiring _T. vaginalis_. In addition, having concurrent STIs (eg, chlamydia, human papillomavirus, herpes, HIV) and multiple sexual partners have been identified as risk factors.

**Clinical Presentation and Findings**

Women may present with an increased amount of malodorous, yellow-green vaginal discharge and vaginal irritation. Many women with _T. vaginalis_ have very little or no symptoms. The vaginal walls and cervix may have tiny petechiae, often called "strawberry spots," and the cervix may bleed easily with contact.

**Diagnosis**

As with other STIs, culture is the criterion standard for diagnosing trichomoniasis. The culture method has been available since 1997 but is used infrequently in the clinic setting because of equipment needed to perform the test and the delay in results. The CDC recommends using the culture method for detection when trichomoniasis is suspected but not confirmed by wet mount microscopy. The method used most often for diagnosing trichomoniasis in the office setting has traditionally been microscopic examination of a saline wet mount for motile trichomonads. This method has a sensitivity of 50% to 66%, even when performed by experienced clinicians. More recent methods for diagnosing trichomoniasis include a nucleic acid probe, AffirmVP III (Becton Dickson, Sparks, Maryland) that evaluates for _G. vaginalis_ in addition to _T. vaginalis_. The sensitivity of this test is 80% to 90%, and the specificity is 99%. Another method for diagnosing is the rapid antigen test, OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, Massachusetts). When the vaginal collection swab is in contact with specific reagents, a blue color is produced if there is evidence of trichomonads. This test has an 83% to 90% sensitivity rate and 100% specificity rate. The results of the OSOM Trichomonas Rapid Test are available within 10 minutes of testing, and the AffirmVP III results are available within 45 minutes. Amplicor by Roche Diagnostic Corp is a polymerase chain reaction assay originally developed for confirmation of gonorrhea and chlamydia either in vaginal secretions or urine. It also has been approved to detect _T. vaginalis_ with 88% to 97% sensitivity and 98% to 99% specificity. Any of these newer tests can be added to the wet mount microscopy to confirm the diagnosis of trichomoniasis.

**Treatment**

The only FDA-approved drugs in the United States for treating _T. vaginalis_ are metronidazole and tinidazole (Table 2). When taken as recommended, the cure rate is 90% to 95% for metronidazole and 86% to 100% for tinidazole. Treatment of all sex partners of women with trichomoniasis is recommended.

**Pregnancy**

The CDC recommends that all symptomatic pregnant women with trichomoniasis be considered for treatment at any gestational age because no data support that metronidazole is teratogenic. The safety of tinidazole use during pregnancy has not been studied. Risks for increased prematurity or low-birth-weight neonates after treatment with metronidazole have been reported in the literature. In addition, pregnant women with trichomoniasis have been reported to have more adverse outcomes such as preterm rupture of membranes and preterm birth. These studies have limitations, so the CDC suggests that women be counseled about the risks and benefits of treatment and be given the option of treatment after 37 weeks’ gestation. The CDC-recommended treatment is metronidazole 2 g by mouth in one dose. Women also need to be counseled about getting partners treated and using condoms to prevent reinfection.

**Follow-up**

Follow-up of sexually active patients with trichomoniasis has not been accurately studied, although the CDC suggests that clinicians consider rescreening sexually active women 3 months after the initial infection. Most recurrent infections are caused by reinfection. A small percentage of women (2%-5%) are resistant to metronidazole. It is recommended that these women take a higher dose of metronidazole,

**Table 2. Treatment of Trichomoniasis**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>2 g orally</td>
<td>Single dose</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>2 g orally</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention
Pattullo and colleagues described a stepwise approach to prevention and control of trichomoniasis. They suggest obtaining 2 to 3 vaginal swabs and performing a wet mount of one swab. If the wet mount is negative, perform a rapid antigen test of the second swab. If this is also negative, and the prevalence of *T. vaginalis* is high in the patient population, they suggest that a culture be performed using the third swab.

**VULVOVAGINAL CANDIDIASIS**

Vulvovaginal candidiasis is the second most common cause of vaginitis in the United States after that caused by anaerobic bacteria. One episode of VVC occurs in approximately 75% of healthy women during their reproductive years, and it is estimated that 40% to 45% will have recurrent episodes.\(^1\)\(^,\)\(^2\)\(^7\) Vulvovaginal candidiasis is classified as either uncomplicated or complicated, based on frequency of episodes and host factors (Table 3).\(^1\)

**Etiology**

The majority of vaginal yeast cases are caused by the *Candida albicans* strain. The majority of non-albicans cases are caused by the *Candida glabrata* strain.\(^2\)\(^8\) The non-albicans fungi are more resistant to treatment than the albicans species. The organism also may be present in asymptomatic women.\(^2\)\(^9\)

**Risk Factors**

It is well known that recent antibiotic use is a significant risk factor for acquiring VVC in most women. Other risk factors include having some type of immunosuppressive illness, such as diabetes mellitus or HIV/AIDS.\(^9\)\(^,\)\(^2\)\(^9\) Wearing a wet swimsuit for long periods of time and frequent douching also may increase risk.

**Clinical Presentation and Findings**

The most common symptoms of VVC are vulvar and vaginal itching, pain, burning, and soreness. Physical examination may reveal a thick curd-like vaginal discharge as well as vulvar erythema.\(^1\)\(^,\)\(^2\)\(^7\) These symptoms are not specific to VVC. Many women report having a “yeast” infection, when in fact their discomfort is caused by either BV or trichomoniasis.

**Diagnosis**

Many cases of VVC are self-diagnosed, although this method has a sensitivity of only 35%.\(^3\)\(^0\) Typically VVC is diagnosed in the office by the clinical symptoms of increased vaginal discharge, vaginal itching, and irritation plus microscopy. This technique for diagnosis requires microscopic examination of the vaginal discharge to identify yeast hyphae or yeast buds, which are most easily visualized in a wet mount with 10% KOH. This diagnostic method is dependent on a working microscope as well as the clinical experience of the provider and detects 40% to 70% of cases when compared to culture.\(^3\)\(^1\) Culture (Sabouraud agar) of the vaginal discharge is considered the criterion standard for diagnosis. This method is expensive and requires several days to obtain results.\(^3\)\(^1\)\(^,\)\(^3\)\(^2\) More recently, rapid screening tests have been developed.\(^2\)\(^7\)\(^,\)\(^3\)\(^0\)\(^,\)\(^3\)\(^1\) Matsui et al\(^3\)\(^1\) developed an immunochromatographic method that detects *Candida* infection within 30 minutes. There is an over-the-counter rapid detection test (Savvycheck, Savyon Diagnostics, Israel) that Guar et al\(^3\)\(^0\) reported would be a 16% savings for patients when compared to visiting their providers for diagnosis and treatment of VVC. This test detects *Candida* antigens in vaginal secretions and has a sensitivity of 77%.\(^3\)\(^0\) The woman can perform this test at home by collecting a vaginal swab of discharge and placing the swab in the provided solution.

**Table 3. Classification of Vulvovaginal Candidiasis**

<table>
<thead>
<tr>
<th>Uncomplicated Vulvovaginal Candidiasis</th>
<th>Complicated Vulvovaginal Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic or infrequent vulvovaginal candidiasis</td>
<td>Recurrent vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Mild to moderate vulvovaginal candidiasis</td>
<td>Severe vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Etiology likely to be <em>Candida albicans</em></td>
<td>Non-albicans candidiasis</td>
</tr>
<tr>
<td>Non-immunocompromised women</td>
<td>Women with uncontrolled diabetes, debilitation, or immunosuppression or those who are pregnant</td>
</tr>
</tbody>
</table>

Source: Centers for Control and Disease Prevention\(^1\)

**Treatment**

Treatment of VVC depends on whether it is categorized as uncomplicated or complicated. The classification is dependent on frequency and severity of the infection as well as the causative organism and whether or not the woman is immunocompromised (Table 3). The CDC recommends short-course treatment with topical agents for uncomplicated VVC (Table 4). Many of these recommended treatments are available over the counter. Many are also oil-based creams and suppositories, which means they may weaken latex condoms and diaphragms. Patients should be educated about this interaction. If recommended treatment does not alleviate symptoms or if symptoms recur within 2 months, the patient should be evaluated by her health care provider.\(^1\) Treatment for
complicated VVC includes culturing the vaginal specimen for an explicit causative organism. Long-term therapy usually is warranted in these cases, with 7 to 14 days of topical therapy or 3 doses of oral fluconazole (dose of 100 mg, 150 mg, or 200 mg on days 1, 4, and 7). The recommended maintenance dose is oral fluconazole weekly for 6 months.

Severe VVC is characterized by vulvar erythema, swelling, excoriation, and fissure formation. It is treated with 7 to 14 days of topical azole therapy or 2 sequential doses of 150 mg of oral fluconazole. Treatment of partners of women with uncomplicated VVC is not recommended, and whether to treat partners of women with recurrent VVC is controversial.

The treatment of non-albicans VVC is also the longer duration of oral or topical azole. If there is recurrence, a 600-mg boric acid capsule is administered intravaginally daily for 2 weeks. In a study of 18 women with non-albicans VVC, Hetticarachchi et al. found that treatment with amphotericin 100 mg and fluocytosine 1 g aqua gel intravaginally nightly for 14 nights cured all cases of VVC.

### Table 4. Vulvovaginal Candidiasis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravaginal agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butoconazole 2% cream</td>
<td>5 g nightly</td>
<td>3 days&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Butoconazole 2%</td>
<td>5 g nightly</td>
<td>Single dose</td>
</tr>
<tr>
<td>sustained release cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole 1% cream</td>
<td>5 g nightly</td>
<td>7-14 days&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clotrimazole 2% cream</td>
<td>5 g nightly</td>
<td>3 days</td>
</tr>
<tr>
<td>Miconazole 2% cream</td>
<td>5 g nightly</td>
<td>7 days&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Miconazole 4% cream</td>
<td>5 g nightly</td>
<td>3 days</td>
</tr>
<tr>
<td>Miconazole 100 mg suppository</td>
<td>100 mg nightly</td>
<td>7 days&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Miconazole 200 mg suppository</td>
<td>200 mg nightly</td>
<td>3 days&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Miconazole 1,200 mg suppository</td>
<td>1200 mg nightly</td>
<td>Single dose</td>
</tr>
<tr>
<td>Nystatin 100,000 unit vaginal tab</td>
<td>1 tab nightly</td>
<td>14 days</td>
</tr>
<tr>
<td>Ticonazole 6.5% ointment</td>
<td>5 g</td>
<td>Single dose</td>
</tr>
<tr>
<td>Terconazole 0.4% cream</td>
<td>5 g nightly</td>
<td>7 days&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Terconazole 0.8% cream</td>
<td>5 g nightly</td>
<td>3 days</td>
</tr>
<tr>
<td>Terconazole 80 mg suppository</td>
<td>1 suppository nightly</td>
<td>3 days</td>
</tr>
<tr>
<td>Oral agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td>150 mg tablet</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

<sup>a</sup>Available over the counter.

<sup>b</sup>Recommended in pregnancy.

Source: Centers for Disease Control and Disease Prevention

Pregnancy

The VVC treatment advised for pregnant women is the same as the recommended treatment for nonpregnant women.

### CONCLUSION

Vaginal symptoms are a major reason that women seek services from their health care providers. Many of these symptoms are caused by BV, trichomoniasis, or VVC. It is important for the health care provider to make the correct diagnosis so that infection-specific treatment can be provided. Treatment recommendations for BV, trichomoniasis, and VVC should be based on current CDC guidelines.

### AUTHOR

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### CONFLICT OF INTEREST

The author has no conflicts of interest to disclose.

### REFERENCES


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