

Trimethoprim-Sulfamethoxazole Revisited

Philip A. Masters, MD; Thomas A. O'Bryan, MD; John Zurlo, MD; Debra Q. Miller, MD; Nirmal Joshi, MD

During the past 3 decades, the combination of trimethoprim and sulfamethoxazole has occupied a central role in the treatment of various commonly encountered infections and has also been particularly useful for several specific clinical conditions. However, changing resistance patterns and the introduction of newer broad-spectrum antibiotics have led to the need to carefully redefine the appropriate use of this agent in clinical practice. While trimethoprim-sulfamethoxazole's traditional role as empirical therapy for several infections has been modified by increasing resistance, it remains a highly useful alternative to the new generation of expanded-spectrum agents if resistance patterns and other clinical variables are carefully considered. It also seems to have an increasing role as a cost-effective pathogen-directed therapy with the potential to decrease or delay development of resistance to newer antibiotics used for empirical treatment. In addition, trimethoprim-sulfamethoxazole continues to be the drug of choice for several clinical indications.

Arch Intern Med. 2003;163:402-410

Many new antibiotics offer an expanded spectrum of *in vitro* antimicrobial susceptibility and an improved toxicity profile compared with older agents. However, the threat of development of resistant organisms from selection pressure and the high cost of these drugs raise significant concerns about their widespread use. Furthermore, in many instances, less expensive conventional antibiotics may be therapeutically equivalent in clinical practice. With a renewed interest in appropriate antibiotic use for common infections¹ and the current focus on providing cost-conscious health care, this article examines the combination of trimethoprim and sulfamethoxazole to redefine its therapeutic role in relation to newer antimicrobial agents in the face of resistance trends and adverse effect profiles.

MECHANISM OF ACTION

The concept of using the fixed combination of trimethoprim and sulfamethoxazole resulted from the recognition that bacteria are obligate folic acid synthesizers, while humans obtain folate through dietary sources.

Trimethoprim and sulfamethoxazole inhibit bacterial synthesis of tetrahydrofolic acid, the physiologically active form of

folic acid and a necessary cofactor in the synthesis of thymidine, purines, and bacterial DNA (**Figure**). Sulfamethoxazole, a sulfonamide drug, is a structural analogue of para-aminobenzoic acid and inhibits synthesis of the intermediary dihydrofolic acid from its precursors. Trimethoprim is a structural analogue of the pteridine portion of dihydrofolic acid that competitively inhibits dihydrofolate reductase and, consequently, the production of tetrahydrofolic acid from dihydrofolic acid. This sequential blockade of 2 enzymes in one pathway results in an effective bactericidal action.

The drug was introduced in the late 1960s based on several potential advantages of the combination of these 2 components over each one individually. The sequential blockade of the bacterial folate synthesis pathway produces *in vitro* synergism,²⁻⁴ and it was postulated that such synergy would occur *in vivo*. It was also hoped that the use of 2 agents in a single pathway would prevent the development of bacterial resistance to either component alone.⁴

However, the clinical relevance of synergy has been questioned by studies^{5,6} of urinary tract infections (UTIs) and respiratory tract infections in which trimethoprim alone seems to be as efficacious as the combination product. In addition, emerging sulfonamide resistance and the finding that the activity of the trimethoprim component is the strongest determinant of efficacy of the antibiotic⁷ call into question the pro-

From the Divisions of General Internal Medicine (Drs Masters, O'Bryan, Miller, and Joshi) and Infectious Diseases (Dr Zurlo), The Pennsylvania State University College of Medicine, Hershey.

tection from resistance provided by the combination product.⁸

Despite these concerns, situations exist in which there is variable antimicrobial susceptibility to both components. In these cases, synergy and the ability of the combination product to potentially decrease the development of resistance may be important factors in determining the clinical efficacy of the drug.⁸

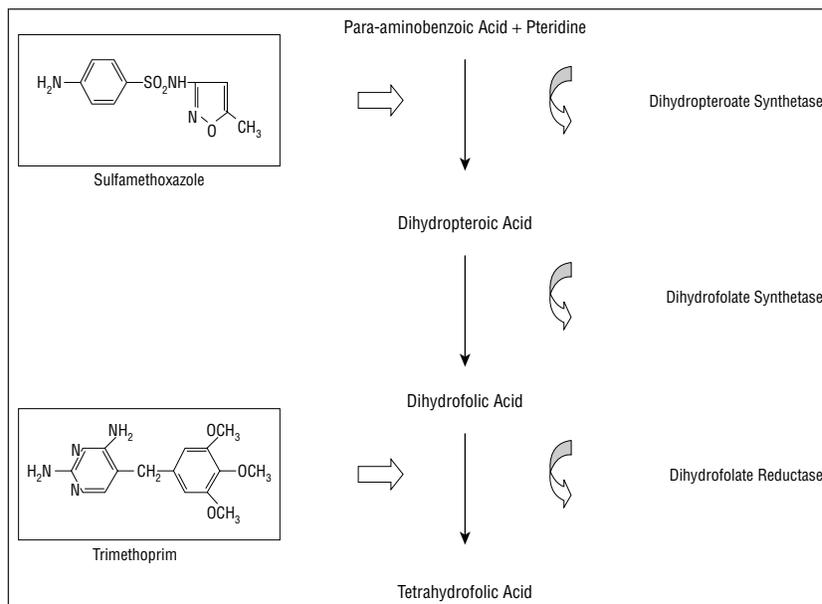
PHARMACOLOGICAL CHARACTERISTICS

The optimal ratio of the concentration of the 2 drugs for potential synergy has been determined to be 20 parts of sulfamethoxazole to 1 part of trimethoprim.³ Thus, available preparations are manufactured in a 1:5 fixed ratio of trimethoprim to sulfamethoxazole that results in peak serum concentrations of both drugs at levels in the desired synergistic ratio.

Trimethoprim-sulfamethoxazole is available in oral and intravenous preparations. The standard single-strength tablet contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole, and the more clinically used double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole.

When taken orally, both components are well absorbed from the gastrointestinal (GI) tract and may be administered without regard to food or other medications. However, trimethoprim is absorbed more rapidly than sulfamethoxazole, and is more widely distributed throughout the body.⁹ Because of this unequal distribution, a wide range of concentrations is achieved in different tissues and body fluids. High concentrations of both drugs are found in the sputum, cerebrospinal fluid, prostatic fluid, and bile.

Trimethoprim is excreted mostly unchanged in the urine, with approximately 10% to 30% metabolized to an inactive form. Sulfamethoxazole is primarily metabolized in the liver, with approximately 30% excreted unchanged in the urine. In otherwise healthy individuals, the approximate half-lives of both agents in the 8- to 14-hour range require twice-daily dosing. Because most drug excretion occurs via



Folate synthesis pathway and sites of action of trimethoprim and sulfamethoxazole.

the kidney, renal insufficiency may increase the half-lives of both agents up to 30 hours or more. Therefore, the dosage of trimethoprim-sulfamethoxazole should be adjusted for a creatinine clearance of less than 30 mL/min (<0.50 mL/s).¹⁰

Both components cross the placenta and appear in breast milk, with detectable concentrations found in fetal serum in patients undergoing therapy.¹¹ Trimethoprim-sulfamethoxazole is listed in Pregnancy Category C by the US Food and Drug Administration.

DRUG INTERACTIONS

Through various mechanisms, both components of the trimethoprim-sulfamethoxazole combination product may significantly influence the metabolism of several drugs frequently used concurrently with the antibiotic, requiring consideration of potential risks in treating patients taking these medications. The major drug interactions noted with trimethoprim-sulfamethoxazole and the proposed mechanisms are listed in **Table 1**.

TOXICITY AND ADVERSE EFFECTS

Trimethoprim-sulfamethoxazole is a generally safe medication with a well-defined adverse effect profile in immunocompetent patients (**Table 2**).

However, clinicians need to be aware of several uncommon, but potentially serious, adverse effects associated with trimethoprim and the sulfamethoxazole component of the combination product.

Gastrointestinal and cutaneous symptoms are the most commonly encountered adverse effects and have generally been attributed to the sulfonamide portion of the drug.^{6,32} These reactions tend to be mild, dose related, and reversible, and often do not require discontinuation of therapy.^{7,22,33} Although difficult to establish, rates of severe or life-threatening reactions seem to be low in immunocompetent patients.^{29,34}

A quantitative comparison of overall adverse effect rates between different antibiotics is difficult; however, multiple studies³⁵⁻³⁷ suggest that trimethoprim-sulfamethoxazole has a 2 to 3 times increased incidence of adverse effects relative to newer antibiotics, such as the fluoroquinolones, for the treatment of similar infections.

Gastrointestinal

Gastrointestinal intolerance occurs in approximately 3% to 8% of patients.^{22,23} Symptoms commonly include nausea, vomiting, and anorexia. Diarrhea, glossitis, and stomatitis are much less frequent. Hepatotoxicity, a known but rare complication of sulfonamide

Table 1. Major Drug Interactions With Trimethoprim-Sulfamethoxazole

Medication	Mechanism (Responsible Component)	References
Warfarin sodium	Potentiates an anticoagulant effect (sulfamethoxazole)	12, 13
Methotrexate	Increases the free serum methotrexate fraction (unclear, possibly sulfamethoxazole)	14, 15
Phenytoin	Increases the elimination half-life, increasing serum levels (trimethoprim)	16, 17
Digoxin	Increases the elimination half-life, increasing serum levels (trimethoprim)	17
Sulfonylureas	May mimic or potentiate the effect of sulfonylureas, particularly in high doses, with increased insulin output and, rarely, hypoglycemia (sulfamethoxazole)	18, 19
Procainamide hydrochloride	Decreases renal tubular secretion of procainamide and its active metabolite, <i>N</i> -acetylprocainamide, increasing serum levels (trimethoprim)	20
Oral contraceptives	Induces metabolism of contraceptive agents, leading to decreased effectiveness (unclear)	21

Table 2. Adverse Effects With Trimethoprim-Sulfamethoxazole in Immunocompetent Patients

Reaction	Estimated Frequency of Occurrence	References
Gastrointestinal	3%-8%	7, 22, 23
Dermatological	3%-4% (severe or life-threatening reactions rare)	7, 22-24
Renal	May cause a mild (~10%) elevation of the serum creatinine level at standard doses without decreasing the glomerular filtration rate	7, 25
	May lead to hyperkalemia at high doses and at standard doses in patients with existing renal failure or concurrent use of other medications known to increase the serum potassium level	26-28
Hematological	Rare, but occasionally severe; comparable to other sulfonamides	7, 29
Psychiatric	Uncommon; delirium and psychosis reported	30, 31

treatment, seems uncommon with trimethoprim-sulfamethoxazole treatment, and the risk is considered comparable to other antimicrobial agents.²⁹

Dermatological

Skin reactions occur in 3% to 4% of the general population treated with trimethoprim-sulfamethoxazole.²²⁻²⁴ Multiple skin reactions have been described, including a maculopapular rash, urticaria, diffuse erythema, morbilliform lesions, erythema multiforme, purpura, and photosensitivity. Severe reactions, including the Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported and fortunately occur only rarely, although sulfonamides seem to impart a large increase in risk for these types of reactions relative to other antibiotics.^{38,39}

Renal

Trimethoprim is known to decrease the tubular secretion of creatinine and may interfere with certain serum creatinine assays, leading to mild elevations of the serum creatinine level without true diminution of the glomerular filtration rate.^{25,40-42} These increases tend to be mild (approximately 10%), and reverse with drug discontinuation. Trimethoprim-sulfamethoxazole has only rarely been associated with direct nephrotoxicity.⁷

Recent observations^{25,26} of hyperkalemia occurring in patients treated with high-dose trimethoprim-sulfamethoxazole led to the elucidation of a mechanism whereby trimethoprim decreases potassium excretion by alteration of the transepithelial voltage in the distal renal tubule. Subsequent studies²⁸ have documented

that hyperkalemia may occur in association with the drug at lower doses used to treat routine infections, even in older patients with clinically normal renal function. Caution, thus, needs to be exercised when using trimethoprim-sulfamethoxazole in patients with preexisting renal dysfunction or in those taking concurrent medications (such as angiotensin-converting enzyme inhibitors and potassium-sparing diuretics) that may exacerbate this hyperkalemic effect to potentially dangerous levels.

Hematological

Although trimethoprim inhibits dihydrofolate reductase in bacteria, it is estimated that an approximately 50 000 times increased concentration of the drug is required to inhibit the human form of this enzyme.⁴³ Consequently, despite the theoretical potential to do so, trimethoprim does not seem to lead to megaloblastic changes when used in the treatment of routine infections, although patients with known low folate stores undergoing long-term treatment should be followed up for such changes.⁸

Sulfonamides have been associated with various other hematological disorders, including multiple forms of anemia, granulocytopenia, agranulocytosis, and thrombocytopenia. These reactions have also been reported with trimethoprim-sulfamethoxazole, although only rarely and at rates considered similar to other sulfonamides.⁷

Psychiatric

Delirium and psychosis have been rarely reported with trimethoprim-sulfamethoxazole use, particularly in elderly persons.^{30,31}

Adverse Reactions in Human Immunodeficiency Virus (HIV)-Infected Patients

Adverse reactions to trimethoprim-sulfamethoxazole seem to be particularly common in HIV-infected individuals, occurring in as many as 65% of those receiving the agent.⁴⁴⁻⁴⁶ These effects are seen when the medication is used for prophylaxis and treatment of *Pneumocystis cari-*

nii pneumonia (PCP). Unfortunately, up to 50% of patients may require discontinuation of trimethoprim-sulfamethoxazole owing to its toxicity.

Adverse events generally are divided into hypersensitivity reactions and all others. Hypersensitivity reactions are most common, and include a rash and fever that develop 8 to 12 days after the initiation of therapy, usually at doses of trimethoprim-sulfamethoxazole used to treat acute PCP.⁴⁷⁻⁴⁹ The rash is commonly a generalized maculopapular eruption that becomes pruritic. Other reactions include nausea and vomiting, diarrhea, neutropenia, thrombocytopenia, anemia, transaminase elevations, cholestatic jaundice, and azotemia.^{44,46-49} Less common adverse reactions include hyperkalemia, hyponatremia, resting tremor, aseptic meningitis, rhabdomyolysis, the Stevens-Johnson syndrome, and toxic epidermal necrolysis.^{47,50-54} Some adverse reactions seem to be dose related (rash, fever, liver enzyme abnormalities, and GI disturbances), while others seem to be independent of dose (neutropenia, anemia, and azotemia).⁴⁹

The treatment of HIV-infected patients with drug-associated hypersensitivity reactions remains controversial, with symptomatic treatment through the reaction^{45,55} and gradual reintroduction of the drug (desensitization)^{56,57} proving to be successful strategies.

ANTIMICROBIAL ACTIVITY AND CLINICAL USE IN THE ERA OF EMERGING RESISTANCE

In the early 1970s, trimethoprim-sulfamethoxazole demonstrated a wide spectrum of activity against aerobic bacteria.^{3,58} Its antimicrobial efficacy and inexpensive cost rapidly garnered global popularity for its use in the treatment of UTIs, respiratory tract infections, and GI tract infections. However, increasing rates of resistance among clinically important pathogens have been reported worldwide during the past few decades.

Bacteria may become resistant to trimethoprim and sulfamethoxazole by several mechanisms, includ-

ing the development of permeability barriers, efflux pumps, naturally insensitive target enzymes, and genetic alterations or dysregulation in the genes encoding target enzymes.⁵⁹ Resistance to trimethoprim and sulfamethoxazole is transferable.⁵⁹ A plasmid-encoded alteration in dihydrofolate reductase resulting in trimethoprim insensitivity against a background of high sulfonamide resistance is increasingly prevalent among bacterial pathogens.⁶⁰

Certain organisms demonstrate marked geographic variation in resistance to trimethoprim-sulfamethoxazole, with a higher incidence typically found in developing countries. In addition, resistant gram-negative organisms are readily transmitted by person-to-person contact and spread by travelers.⁶⁰

Urinary Tract Infections

Trimethoprim-sulfamethoxazole is active against many Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, accounting for its widespread use in those with UTIs. In the United States, it has been the drug of choice for empirical therapy for uncomplicated UTIs in women.⁶¹

Unfortunately, the prevalence of resistant coliforms is increasing.^{59,62-70} In the 1980s, trimethoprim resistance in *E coli* isolates from outpatient urine samples often reached 15% to 20%.⁷¹ Trimethoprim resistance among enteric organisms is more prevalent in developing countries, with reported levels as high as 68% in South America, Asia, and Africa.⁶⁰ In the United States and Europe, recent use of antibiotics, hospitalization, and immunosuppression have been implicated as factors contributing to trimethoprim-sulfamethoxazole resistance among urinary tract isolates.⁶⁶⁻⁶⁸ The San Francisco General Hospital, San Francisco, Calif, reported a sharp increase of trimethoprim-sulfamethoxazole resistance in clinical isolates of *Staphylococcus aureus* and 7 genera of Enterobacteriaceae, including *E coli*, from 1988 to 1995.⁶⁵ Increases in resistance were most dramatic in isolates from HIV-infected patients and temporally associated with use of tri-

methoprim-sulfamethoxazole for prophylaxis against PCP.⁶⁵ Furthermore, a recent study⁷² of a small number of resistant *E coli* isolates from women with community-acquired UTI in 3 separate US states suggested that a single clonal group accounted for nearly half of such strains. Such findings increase the concern for widespread transmission from a contaminated food source, leading to intestinal colonization.⁷²

It is unclear if increased trimethoprim-sulfamethoxazole resistance among uropathogens correlates with treatment failure because a high urinary drug concentration may override in vitro insensitivity. A few studies⁷³ limited by a small sample size suggest a higher rate of clinical failure with trimethoprim-sulfamethoxazole among resistant organisms. The Infectious Diseases Society of America⁷⁴ has recommended that trimethoprim-sulfamethoxazole remain standard therapy for uncomplicated cystitis in women unless the prevalence of local resistance to the drug is greater than 10% to 20%. Patient factors favorable to the use of trimethoprim-sulfamethoxazole include no recent antimicrobial use, hospitalization, or recurrent UTI in the past year.⁷³

Superior clinical success rates with fluoroquinolones have led to a preference for their use for acute and chronic prostate infections, although trimethoprim-sulfamethoxazole retains a role as an effective second-line treatment.⁷⁵

Respiratory Tract Infections

Trimethoprim-sulfamethoxazole has been useful in the treatment of community-acquired upper and lower respiratory tract infections because of its activity against the major pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Several studies⁷⁶⁻⁷⁸ in the 1980s showed trimethoprim-sulfamethoxazole to be an effective treatment for otitis media, including infections caused by ampicillin-resistant strains of *H influenzae*.⁷⁹ It has also been a useful agent for acute bacterial sinusitis,⁸⁰ short-term exacerbations of chronic bronchitis,⁸¹⁻⁸⁵ and prophylaxis of recurrent otitis media.^{86,87} Un-

til recently, trimethoprim-sulfamethoxazole has been considered a reasonable alternative to β -lactam antibiotics for the empirical treatment of mild to moderate severity community-acquired pneumonia.⁸⁸

Emerging resistance among respiratory pathogens has raised serious concerns regarding the role of trimethoprim-sulfamethoxazole in the treatment of respiratory tract infections. The drug is not effective against most intermediate- and higher-level penicillin-resistant strains of *S pneumoniae*.⁸⁹ The SENTRY Antimicrobial Surveillance Program⁸⁹ recently reported a 15% to 20% frequency of trimethoprim-sulfamethoxazole resistance among *S pneumoniae* and *H influenzae* in the United States, Canada, and Europe. Higher rates of resistant respiratory pathogens were observed in Latin America and the Asian-Pacific region.⁸⁹

Consequently, treatment guidelines by the Sinus and Allergy Health Partnership⁹⁰ recommend trimethoprim-sulfamethoxazole only as an alternative in β -lactam-allergic patients for the treatment of mild acute bacterial sinusitis in adults and children who have not received antibiotics in the previous 4 to 6 weeks.

The American Thoracic Society's recommendations for the empirical treatment of community-acquired pneumonia, released in 1993, considered trimethoprim-sulfamethoxazole an option for initial outpatient management in adults with a comorbidity or in those 60 years or older. However, the more recent treatment guidelines for community-acquired pneumonia by the American Thoracic Society⁹¹ and the Infectious Diseases Society of America⁹² do not include trimethoprim-sulfamethoxazole among recommendations for empirical therapy.

Thus, trimethoprim-sulfamethoxazole as a treatment for upper and lower respiratory tract infections requires consideration of local resistance patterns and individual patient factors, such as severity of disease, when deciding the appropriateness of use.

GI Tract Infections

Salmonella and *Shigella* species and enterotoxigenic *E coli* were widely

susceptible to trimethoprim-sulfamethoxazole in the 1970s. This agent was frequently used as successful therapy and prophylaxis for bacterial enteric infections.⁹³

Resistant strains of *Shigella* species rapidly increased in developing countries and subsequently spread worldwide.^{59,94} Trimethoprim-sulfamethoxazole is no longer considered appropriate treatment of shigellosis in most parts of the world. Emerging resistance among *Salmonella* isolates has been slower and more geographically variable than with *Shigella* species.⁶⁰ In the United States, the incidence of infections due to *Salmonella typhi* has been stable since the mid 1960s; however, the proportion of cases acquired abroad has increased steadily.⁹⁵ Multidrug-resistant *S typhi* isolated in the United States from individuals with symptomatic typhoid fever was strongly associated with recent travel to the Indian subcontinent or to Vietnam.⁹⁵ Most strains from apparent domestically acquired infections remained sensitive to trimethoprim-sulfamethoxazole.⁹⁵

Trimethoprim-sulfamethoxazole seems to remain efficacious in the treatment of enterotoxigenic *E coli* in the interior of Mexico,⁹⁶ but resistance levels are high in other parts of the world.⁹⁷ *Yersinia enterocolitica*,⁹⁸ *Vibrio cholerae*,⁹⁹ and *Aeromonas hydrophila*¹⁰⁰ are bacterial causes of diarrheal infections that are usually susceptible.

Among travelers to many developing countries, fluoroquinolones have replaced trimethoprim-sulfamethoxazole as chemoprophylaxis.⁹³ The role of trimethoprim-sulfamethoxazole in the treatment and prevention of infectious diarrhea in travelers is restricted to certain locations (such as noncoastal Mexico)^{96,101} or when treatment is directed at specific pathogens.⁹³

Skin-Associated Infections

Many isolates of *S aureus* and *Staphylococcus epidermidis* remain susceptible to trimethoprim-sulfamethoxazole. However, resistant strains have been widely reported among both species, especially methicillin sodium-resistant organisms.

In a surveillance¹⁰² of international strains, most methicillin-

resistant coagulase-negative staphylococcal isolates were resistant to trimethoprim-sulfamethoxazole. *Streptococcus pyogenes* is variably susceptible.¹⁰³ Several antimicrobial agents are more effective and reliable for the treatment of skin, soft tissue, and other staphylococcal infections.

Clinical Use in HIV-Infected Patients

Treatment of Active Infections. Because it was previously recognized as an effective agent for the treatment of PCP in immunosuppressed individuals,¹⁰⁴ trimethoprim-sulfamethoxazole became the preferred treatment for PCP as the acquired immunodeficiency syndrome epidemic unfolded in the early 1980s. It was subsequently shown to be more effective and better tolerated than the other major parenterally active agent, pentamidine.⁴⁵

It remains the treatment of choice for HIV-infected patients with severe PCP (PO_2 , <70 mm Hg; or alveolar to arterial gradient of oxygen, >35 mm Hg [at presentation]). In these patients, the drug is usually administered intravenously, with prednisone given as adjunctive therapy.

For mild to moderate PCP, orally administered trimethoprim-sulfamethoxazole is also considered the agent of choice, although other oral drug combinations (trimethoprim and dapsone and primaquine phosphate and clindamycin) are equally effective.^{47,105-107}

Approximately 10% to 20% of patients with PCP fail to respond to trimethoprim-sulfamethoxazole as a first-line therapy. Although treatment failure is likely multifactorial, drug resistance likely plays a major role. Mutations in the *P carinii* dihydropteroate synthase gene have been identified more commonly in isolates from patients who have received trimethoprim-sulfamethoxazole or dapsone prophylaxis.¹⁰⁸

Trimethoprim-sulfamethoxazole is an effective treatment for infections due to the coccidian protozoal parasites *Isospora* and *Cyclospora*.^{109,110}

The drug has activity in the treatment of cerebral toxoplasmosis in patients with the acquired immunodeficiency syndrome,^{111,112} al-

though its use for this infection is not recommended because of the improved efficacy of other regimens.

Prophylaxis. Trimethoprim-sulfamethoxazole is the recommended agent for the prevention of first-episode and recurrent PCP.¹¹³ Indications for primary prophylaxis include a CD4 cell count of less than 200/ μ L or the presence of oropharyngeal candidiasis.¹¹³ Doses as low as 1 double-strength tablet 3 times weekly have been highly effective in preventing PCP.¹¹⁴ Trimethoprim-sulfamethoxazole has been superior to aerosolized pentamidine for the prevention of primary and recurrent episodes of PCP,^{115,116} and is equivalent overall when compared with dapsone-based regimens.¹¹⁶

One double-strength tablet daily has been effective for the primary prophylaxis of toxoplasmosis in patients with the acquired immunodeficiency syndrome,¹¹⁷ and is the agent of choice.¹¹³ When used prophylactically, trimethoprim-sulfamethoxazole also has been effective in preventing other concurrent bacterial infections.^{115,118-120}

Other Uses

Trimethoprim-sulfamethoxazole has proved beneficial for prophylaxis against opportunistic infections and for reduction in the occurrence of routine infections in patients receiving immunosuppressive therapy for organ transplantation.^{121,122} It is also commonly used prophylactically in afebrile neutropenic individuals, although the effectiveness of this practice has been questioned.¹²³ It is no longer considered an acceptable empirical treatment for febrile patients with neutropenia.¹²⁴

Nonfermentative gram-negative bacilli are important infectious agents among hospitalized and immunocompromised patients. *Stenotrophomonas (Xanthomonas) maltophilia* is typically resistant to several classes of broad-spectrum antibiotics, but commonly is inhibited by trimethoprim-sulfamethoxazole.^{125,126} Other nonfermentative organisms, including *Burkholderia (Pseudomonas) cepacia*, *Acinetobacter*, and *Alcaligenes*, are frequently susceptible.¹²⁵

Trimethoprim-sulfamethoxazole may have a place in therapy for meningitis caused by cephalosporin-resistant nonfermentative gram-negative bacilli and for *Listeria monocytogenes* infections in patients allergic to penicillin.¹²⁷⁻¹²⁹

Trimethoprim-sulfamethoxazole is frequently used to treat *Nocardia* infections,¹³⁰ and is efficacious in the treatment of Whipple disease, a multisystem illness caused by the bacillus *Tropheryma whippelii*.^{131,132}

Selected patients with Wegener granulomatosis may benefit from treatment with trimethoprim-sulfamethoxazole, although the mechanism of action and degree of clinical efficacy in patients with this disorder is uncertain.¹³³

CONCLUSIONS

Since its introduction more than 3 decades ago, trimethoprim-sulfamethoxazole has played a key role in the treatment of a wide variety of clinical infections. However, worldwide changes in resistance patterns and the introduction of newer agents with different pharmacological and antimicrobial characteristics are rapidly changing the manner in which this agent is appropriately used.

Emerging resistance has required modification of trimethoprim-sulfamethoxazole's role as empirical or first-line therapy for several infections for

which it traditionally had widespread use. With attention to local, regional, and worldwide resistance patterns, trimethoprim-sulfamethoxazole may retain its usefulness as a primary agent for selected indications in carefully assessed patients (eg, for the prophylaxis and treatment of PCP and for the primary prophylaxis for *Toxoplasma gondii* in HIV-infected patients). It continues to be a second-line or alternative antibiotic for various infections, particularly in penicillin-allergic patients or other situations in which newer antibiotics cannot be used (eg, for uncomplicated UTIs, short-term exacerbations of chronic bronchitis, acute otitis media, acute sinusitis, and acute and chronic prostatitis).

A clearly emerging role for the drug seems to be its use as a pathogen-directed therapy for organisms identified as sensitive to trimethoprim-sulfamethoxazole (eg, organisms causing community-acquired and nosocomial pneumonia, GI tract infections, staphylococcal infections, and sexually transmitted diseases). Increasing resistance may require the use of newer expanded-spectrum agents and even multiple-antibiotic regimens for the empirical treatment of many infections. For those pathogens found to be sensitive, however, trimethoprim-sulfamethoxazole remains an efficacious and cost-effective alternative (**Table 3**) with a well-defined adverse effect profile that may help preserve the usefulness of the broader-

Table 3. Comparative Cost of Trimethoprim-Sulfamethoxazole vs Selected Antibiotics*

Antibiotic†	Adult Dosing	Cost, \$‡
Trimethoprim-sulfamethoxazole	1 double-strength tablet every 12 h	28.57
Amoxicillin	500 mg every 12 h	14.84
Amoxicillin-clavulanic acid	500 mg every 8 h	81.63
	875 mg every 12 h	107.63
Azithromycin	500 mg once, then 250 mg/d for 4 d	45.84§
Cefuroxime axetil	500 mg twice daily	164.73
Cefixime	400 mg/d	89.38
Ciprofloxacin	500 mg twice daily	97.44
Clarithromycin	500 mg every 12 h	82.99
Doxycycline	100 mg twice daily	33.72
Erythromycin	333 mg every 8 h	15.12
Gatifloxacin	400 mg/d	90.21
Levofloxacin	500 mg/d	92.75
Moxifloxacin	400 mg/d	94.61

*Data from *Red Book Updates*.¹³⁴

†Generic drugs were used for comparison, if available.

‡Given for a 10-day course of therapy, based on the average wholesale price plus a \$4 dispensing fee.

§Denotes a 5-day therapy plan.

spectrum drugs used for empirical therapy. Proper use in this manner requires greater diligence by the clinician in seeking a microbial diagnosis and a concerted effort at focusing treatment once a diagnosis has been made.

Trimethoprim-sulfamethoxazole certainly retains a special role in the prophylaxis and treatment of certain HIV-associated infections, and as first-line therapy for various less common infections (organisms affected include *P carinii*, *S [X] maltophilia* and other nonfermentative gram-negative bacilli, *Isospora*, *Cyclospora*, *Nocardia*, and *T whippelii*).

The judicious use of trimethoprim-sulfamethoxazole may ultimately serve as a model for the future appropriate use of broad-spectrum antibiotics in the setting of increasing antimicrobial resistance pressure and cost-conscious medical practice.

Accepted for publication June 13, 2002.

Corresponding author and reprints: Philip A. Masters, MD, Division of General Internal Medicine, The Pennsylvania State University College of Medicine, 500 University Dr, Suite 4100, Hershey, PA 17033 (e-mail: pmasters@psu.edu).

REFERENCES

- Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. *Ann Intern Med.* 2001;134:479-486.
- Bushby SRM, Hitchings GH. Trimethoprim, a sulfonamide potentiator. *Br J Pharmacol.* 1968;33:72-90.
- Bushby SRM. Trimethoprim-sulfamethoxazole: in vitro microbiological aspects. *J Infect Dis.* 1973;128(suppl):S442-S462.
- Darrell JH, Garrod LP, Waterworth PM. Trimethoprim: laboratory and clinical studies. *J Clin Pathol.* 1968;21:202-209.
- Brumfitt W, Hamilton-Miller JM, Havard CW, Tansley H. Trimethoprim alone compared to cotrimoxazole in lower respiratory infections: pharmacokinetics and clinical effectiveness. *Scand J Infect Dis.* 1985;17:99-105.
- Lacey RW, Lord VL, Gunasekera HK, Leiberman PJ, Luxton DE. Comparison of trimethoprim alone with trimethoprim-sulfamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. *Lancet.* 1980;1:1270-1273.
- Rubin R, Swartz M. Trimethoprim-sulfamethoxazole. *N Engl J Med.* 1980;303:426-432.
- Howe R, Spencer R. Cotrimoxazole: rationale for re-examining its indications for use. *Drug Saf.* 1996;14:213-218.
- Brumfitt W, Pursell R. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women. *J Infect Dis.* 1973;128(suppl):657-665.
- Smilack JD. Trimethoprim-sulfamethoxazole. *Mayo Clin Proc.* 1999;74:730-734.
- Wormser GP, Keusch GT. Trimethoprim-sulfamethoxazole in the United States. *Ann Intern Med.* 1979;91:420-429.
- O'Reilly R, Motley C. Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. *Ann Intern Med.* 1979;91:34-36.
- O'Reilly R. Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. *N Engl J Med.* 1980;302:33-35.
- van Meerten E, Verweij J, Schellens J. Antineoplastic agents: drug interactions of clinical significance. *Drug Saf.* 1995;12:168-182.
- Tett S, Triggs E. Use of methotrexate in older patients: a risk-benefit assessment. *Drugs Aging.* 1996;9:458-471.
- Hansen JM, Kampmann JP, Siersbaek-Nielsen K, et al. The effect of different sulfonamides on phenytoin metabolism in man. *Acta Med Scand Suppl.* 1979;624:106-110.
- Brumfitt W, Hamilton-Miller J. Limitations of and indications for the use of co-trimoxazole. *J Chemother.* 1994;6:3-11.
- Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DiCP.* 1990;24:250-251.
- Chan J, Cockram C, Critchley J. Drug-induced disorders of glucose metabolism: mechanisms and management. *Drug Saf.* 1996;15:135-157.
- Kosoglou T, Rocci M, Vlasses P. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther.* 1988;44:467-477.
- Abramowicz M, ed. Oral contraceptives. *Med Lett Drugs Ther.* 2000;42:42-44.
- Lawson D, Jick H. Adverse reactions to cotrimoxazole in hospitalized medical patients. *Am J Med Sci.* 1978;275:53-57.
- Lawson D, MacDonald S. Antibacterial therapy in general medical wards. *Postgrad Med J.* 1977;53:306-309.
- Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis.* 1982;4:426-428.
- Ducharme M, Smythe M, Strohs G. Drug-induced alterations in serum creatinine concentrations. *Ann Pharmacother.* 1993;27:622-633.
- Choi MJ, Fernandez PC, Patnaik A, et al. Brief report: trimethoprim-induced hyperkalemia in a patient with AIDS. *N Engl J Med.* 1993;328:703-706.
- Velazquez H, Perazella M, Wright F, Ellison D. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med.* 1993;119:296-301.
- Marinella M. Trimethoprim-induced hyperkalemia: an analysis of reported cases. *Gerontology.* 1999;45:209-212.
- Jick H, Derby L. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy.* 1995;15:428-432.
- Amramowicz M, ed. Drugs that may cause psychiatric symptoms. *Med Lett Drugs Ther.* 2000;44:59-62.
- McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. *Am J Med.* 1991;90:528-529.
- Brumfitt W, Pursell R. Double-blind trial to compare ampicillin, cephalexin, co-trimoxazole and trimethoprim in treatment of urinary infections. *BMJ.* 1972;2:673-676.
- Frisch JM. Clinical experience with adverse reactions to trimethoprim-sulfamethoxazole. *J Infect Dis.* 1973;128(suppl):S607-S611.
- Gleckman R, Alvarez S, Joubert DW. Drug therapy reviews: trimethoprim-sulfamethoxazole. *Am J Hosp Pharm.* 1979;36:893-906.
- Boye NP, Gaustad P. Double-blind comparative study of ofloxacin and trimethoprim-sulfamethoxazole in the treatment of patients with acute exacerbations of chronic bronchitis and chronic obstructive lung disease. *Infection.* 1991;19(suppl 7):S388-S390.
- Grubbs NC, Schultz HJ, Henry NK, Ilstrup DM, Muller SM, Wilson WR. Ciprofloxacin versus trimethoprim-sulfamethoxazole: treatment of community-acquired urinary tract infections in a prospective, controlled, double-blind comparison. *Mayo Clin Proc.* 1992;67:1163-1168.
- Heck J, Staneck JL, Cohen MB, et al. Prevention of travelers' diarrhea: ciprofloxacin versus trimethoprim/sulfamethoxazole in adult volunteers working in Latin America and the Caribbean. *J Travel Med.* 1994;1:136-142.
- Roujeau J, Kelly J, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333:1600-1607.
- Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol.* 1999;40:458-461.
- Berglund F, Killander J, Pompeius R. Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. *J Urol.* 1975;114:802-808.
- Bye A. Drug interference with creatinine assay. *Clin Chem.* 1976;22:283-284.
- Shouval D, Ligumsky M, Ben-Ishay D. Effect of co-trimoxazole on normal creatinine clearance. *Lancet.* 1978;1:244-245.
- Burchall JJ, Hitchings GH. Inhibitor binding analysis of dihydrofolate reductases from various species. *Mol Pharmacol.* 1965;1:126-136.
- Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med.* 1984;100:663-671.
- Sattler FR, Cowan R, Nielsen DM, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a prospective, noncrossover study. *Ann Intern Med.* 1988;109:280-287.
- Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. *AIDS.* 1992;6:301-305.
- Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med.* 1990;323:776-782.
- Jung AC, Paauw DS. Management of adverse re-

- actions to trimethoprim-sulfamethoxazole in human immunodeficiency virus-infected patients. *Arch Intern Med.* 1994;154:2402-2406.
49. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related *Pneumocystis carinii* pneumonia. *J Infect Dis.* 1995;171:1295-1301.
 50. Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol.* 1991;127:740-741.
 51. Greenberg S, Reiser IW, Chou SY. Hyperkalemia with high-dose trimethoprim-sulfamethoxazole therapy. *Am J Kidney Dis.* 1993;22:603-606.
 52. Abouafia DM. Tremors associated with trimethoprim-sulfamethoxazole therapy in a patient with AIDS: case report and review. *Clin Infect Dis.* 1996;22:598-600.
 53. Jurado R, Carpenter SL, Rimland D. Case reports: trimethoprim-sulfamethoxazole-induced meningitis in patients with HIV infection. *Am J Med Sci.* 1996;312:27-29.
 54. Singer SJ, Racoosin JA, Viraraghavan R. Rhabdomyolysis in human immunodeficiency virus-positive patients taking trimethoprim-sulfamethoxazole. *Clin Infect Dis.* 1998;26:233-234.
 55. Shafer RW, Seitzman PA, Tapper ML. Successful prophylaxis of *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole in AIDS patients with previous allergic reactions. *J Acquir Immune Defic Syndr.* 1989;2:389-393.
 56. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis.* 1995;20:849-853.
 57. Gompels MM, Simpson N, Snow M, Spickett G, Ong E. Desensitization to co-trimoxazole (trimethoprim-sulphamethoxazole) in HIV-infected patients: is patch testing a useful predictor of reaction? *J Infect.* 1999;38:111-115.
 58. Bach MC, Finland M, Gold O, Wilcox C. Susceptibility of recently isolated pathogenic bacteria to trimethoprim and sulfamethoxazole separately and combined. *J Infect Dis.* 1973;128(suppl):S508-S533.
 59. Huovinen P. Resistance to trimethoprim-sulfamethoxazole. *Clin Infect Dis.* 2001;32:1608-1614.
 60. Huovinen P, Sundström L, Swedberg G, Sköld O. Trimethoprim and sulfonamide resistance. *Antimicrob Agents Chemother.* 1995;39:279-289.
 61. Stamm WE, Hooten TM. Management of urinary tract infections in adults. *N Engl J Med.* 1993;329:1328-1334.
 62. Goldstein FW, Papadopoulos B, Acar JF. The changing pattern of trimethoprim resistance in Paris, with a review of worldwide experience. *Rev Infect Dis.* 1986;8:725-737.
 63. Gruneberg RN. Changes in urinary pathogens and their antibiotic sensitivities, 1971-1992. *J Antimicrob Chemother.* 1994;33(suppl A):1-8.
 64. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA.* 1999;281:736-738.
 65. Martin JN, Rose DA, Hadley WK, Perdreau-Remington F, Lam PK, Gerberding JL. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis.* 1999;180:1809-1818.
 66. Lepelletier D, Caroff N, Reynaud A, Richet H. *Escherichia coli*: epidemiology and analysis of risk factors for infections caused by resistant strains. *Clin Infect Dis.* 1999;29:548-552.
 67. Steinke DT, Seaton RA, Phillips G, MacDonald TM, Davey PG. Factors associated with trimethoprim-resistant bacteria isolated from urine samples. *J Antimicrob Chemother.* 1999;43:841-843.
 68. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med.* 1999;14:606-609.
 69. Zhanel GG, Karlowsky JA, Harding GKM, et al, for the Canadian Urinary Isolate Study Group. A Canadian national surveillance study of urinary tract isolates from outpatients: comparison of the activities of trimethoprim-sulfamethoxazole, ampicillin, mecillinam, nitrofurantoin, and ciprofloxacin. *Antimicrob Agents Chemother.* 2000;44:1089-1092.
 70. Sahn DF, Thornsberry C, Mayfield DC, Jones ME, Karlowsky JA. Multidrug-resistant urinary tract isolates of *Escherichia coli*: prevalence and patient demographics in the United States in 2000. *Antimicrob Agents Chemother.* 2001;45:1402-1406.
 71. Huovinen P. Increases in rates of resistance to trimethoprim. *Clin Infect Dis.* 1997;24(suppl):S63-S66.
 72. Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, Riley LW. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *N Engl J Med.* 2001;345:1007-1013.
 73. Gupta K, Hooten TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med.* 2001;135:41-50.
 74. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE, for the Infectious Diseases Society of America. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis.* 1999;29:745-758.
 75. Lipsky BA. Prostatitis and urinary tract infection in men: what's new; what's true? *Am J Med.* 1999;106:327-334.
 76. Marchant C, Shurin PA. Antibacterial therapy for acute otitis media: a critical analysis. *Rev Infect Dis.* 1982;4:506-513.
 77. Blumer JL, Bertino JS Jr, Husak MP. Comparison of cefaclor and trimethoprim-sulfamethoxazole in the treatment of acute otitis media. *Pediatr Infect Dis.* 1984;3:25-29.
 78. Feldman W, Sutcliffe T, Dulberg C. Twice-daily antibiotics in the treatment of acute otitis media: trimethoprim-sulfamethoxazole versus amoxicillin-clavulanate. *CMAJ.* 1990;142:924-925.
 79. Schwartz RH, Rodriguez WJ, Khan WN, Mann R, Barsanti RG, Ross S. Trimethoprim-sulfamethoxazole in the treatment of otitis media caused by ampicillin-resistant strains of *Haemophilus influenzae*. *Rev Infect Dis.* 1982;4:514-516.
 80. Williams JW, Holleman DR, Samsa GP, Simel DL. Randomized controlled trial of 3 vs 10 days of trimethoprim-sulfamethoxazole for acute maxillary sinusitis. *JAMA.* 1995;273:1015-1021.
 81. Renmarker K. A comparative trial of co-trimoxazole and doxycycline in the treatment of acute exacerbations of chronic bronchitis. *Scand J Infect Dis.* 1976;8:75-78.
 82. Hughes DT. Single-blind comparative trial of trimethoprim-sulphamethoxazole and ampicillin in the treatment of exacerbations of chronic bronchitis. *BMJ.* 1969;4:470-473.
 83. Pines A, Greenfield JS, Raafat H, Rahman M, Siddiqui AM. Preliminary experience with trimethoprim and sulphamethoxazole in the treatment of purulent chronic bronchitis. *Postgrad Med J.* 1969;45(suppl):89-90.
 84. Anderson G, Williams L, Pardoe T, Peel ET. Co-trimoxazole versus cefaclor in acute on chronic bronchitis. *J Antimicrob Chemother.* 1981;8:487-489.
 85. Hughes DT. The use of combinations of trimethoprim and sulphonamides in the treatment of chest infections. *J Antimicrob Chemother.* 1983;12:423-434.
 86. Gaskins JD, Holt RJ, Kyong CU, Weart CW, Ward J. Chemoprophylaxis of recurrent otitis media using trimethoprim/sulfamethoxazole. *Drug Intell Clin Pharm.* 1982;16:387-390.
 87. Principi N, Marchisio P, Massironi E, Grasso RM, Filiberti G. Prophylaxis of recurrent acute otitis media and middle-ear effusion: comparison of amoxicillin with sulfamethoxazole and trimethoprim. *AJDC.* 1989;143:1414-1418 [published correction appears in *AJDC.* 1990;144:1180].
 88. Niederman MS, Bass JB Jr, Campbell GD, et al, for the American Thoracic Society and the Medical Section of the American Lung Association. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis.* 1993;148:1418-1426.
 89. Hoban DJ, Doern GV, Fluit AC, Rousseau-Delvallez M, Jones RN. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clin Infect Dis.* 2001;32(suppl):S81-S93.
 90. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2000;123(pt 2):S5-S31.
 91. Niederman MS, Mandell LA, Anzueto A, et al, for the American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med.* 2001;163:1730-1754.
 92. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2000;31:347-382.
 93. Ansdell VE, Ericsson CD. Prevention and empiric treatment of traveler's diarrhea. *Med Clin North Am.* 1999;83:945-973.
 94. Murray BE. Resistance of *Shigella*, *Salmonella*, and other selected enteric pathogens to antimicrobial agents. *Rev Infect Dis.* 1986;8(suppl):S172-S181.
 95. Ackers M-L, Pühr ND, Tauxe RV, Mintz ED. Laboratory-based surveillance of *Salmonella* serotype Typhi infections in the United States: antimicrobial resistance on the rise. *JAMA.* 2000;283:2668-2673.
 96. Bandres JC, Mathewson JJ, Ericsson CD, Dupont HL. Trimethoprim/sulfamethoxazole remains active against enterotoxigenic *Escherichia coli* and *Shigella* species in Guadalajara, Mexico. *Am J Med Sci.* 1992;303:289-291.
 97. Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Ech-

- everria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis*. 1998;26:341-345.
98. Gutman LT, Wilfert CM, Quan T. Susceptibility of *Yersinia enterocolitica* to trimethoprim-sulfamethoxazole. *J Infect Dis*. 1973;128(suppl):S538.
 99. Pastore G, Rizzo G, Fera G, Schiraldi O. Trimethoprim-sulphamethoxazole in the treatment of cholera: comparison with tetracycline and chloramphenicol. *Chemotherapy*. 1977;23:121-128.
 100. Kuijper EJ, Peeters MF, Schoenmakers BS, Zanen HC. Antimicrobial susceptibility of sixty human fecal isolates of *Aeromonas* species. *Eur J Clin Microbiol Infect Dis*. 1989;8:248-250.
 101. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. *N Engl J Med*. 1993;328:1821-1827.
 102. Diekema DJ, Pfaller MA, Schmitz FJ, et al, and the SENTRY Participants Group. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clin Infect Dis*. 2001;32(suppl):S114-S132.
 103. Hoskins TW, Bernstein LS. Trimethoprim/sulphadiazine compared with penicillin V in the treatment of streptococcal throat infections. *J Antimicrob Chemother*. 1981;8:495-496.
 104. Hughes WT, Feldman S, Chaudhary SC, Ossi MJ, Cox F, Sanyal SK. Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr*. 1978;92:285-291.
 105. Ruf B, Rohde I, Pohle HD. Efficacy of clindamycin/primaquine versus trimethoprim/sulfamethoxazole in primary treatment of *Pneumocystis carinii* pneumonia. *Eur J Clin Microbiol Infect Dis*. 1991;10:207-210.
 106. Safrin S, Finkelstein DM, Feinberg J, et al, for the ACTG 108 Study Group. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS: a double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. *Ann Intern Med*. 1996;124:792-802.
 107. Toma E, Thorne A, Singer J, et al, for the CTN-PCP Study Group. Clindamycin with primaquine vs trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). *Clin Infect Dis*. 1998;27:524-530.
 108. Kazanjian P, Locke AB, Hossler PA, et al. *Pneumocystis carinii* mutations associated with sulfa and sulfone prophylaxis failures in AIDS patients. *AIDS*. 1998;12:873-878.
 109. Keystone JS, Kozarsky P. *Isospora belli*, *Sarcocystis* species, *Blastocystis hominis*, and *Cyclospora*. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia, Pa: Churchill Livingstone Inc; 2000:2915-2920.
 110. Bartlett JG. *Medical Management of HIV Infection*. Baltimore, Md: Johns Hopkins University; 1999.
 111. Canessa A, Del Bono V, De Leo P, Piersantelli N, Terragna A. Cotrimoxazole therapy of *Toxoplasma gondii* encephalitis in AIDS patients. *Eur J Clin Microbiol Infect Dis*. 1992;11:125-130.
 112. Torre D, Speranza F, Martegani R, Zeroli C, Banfi M, Airoldi M. A retrospective study of treatment of cerebral toxoplasmosis in AIDS patients with trimethoprim-sulphamethoxazole. *J Infect*. 1998;37:15-18.
 113. US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Recomm Rep*. 1999;48(RR-10):1-59, 61-66.
 114. Stein DS, Stevens RC, Terry D, et al. Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 1991;35:1705-1709.
 115. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome: AIDS Clinical Trials Group protocol 021. *N Engl J Med*. 1992;327:1842-1848.
 116. Ioannidis JPA, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. *Arch Intern Med*. 1996;156:177-188.
 117. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117:106-111.
 118. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1 infected adults in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*. 1999;353:1463-1468.
 119. Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet*. 1999;353:1469-1475.
 120. Buskin SE, Newcomer LM, Koutsky LA, Hooton TM, Spach DH, Hopkins SG. Effect of trimethoprim-sulfamethoxazole as *Pneumocystis carinii* pneumonia prophylaxis on bacterial illness, *Pneumocystis carinii* pneumonia, and death in persons with AIDS. *J Acquir Immune Defic Syndr*. 1999;20:201-206.
 121. Fishman JA. Prevention of infection caused by *Pneumocystis carinii* in transplant patients. *Clin Infect Dis*. 2001;33:1397-1405.
 122. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep*. 2000;49(RR-10):1-125.
 123. Kerr KG. The prophylaxis of bacterial infections in neutropenic patients. *J Antimicrob Chemother*. 1999;44:587-591.
 124. Hughes WT, Armstrong D, Bodey GP, et al, for the Infectious Diseases Society of America. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*. 2002;34:730-751.
 125. Fass RJ, Barnishan J, Solomon MC, Ayers LW. In vitro activities of quinolones, β -lactams, tobramycin, and trimethoprim-sulfamethoxazole against nonfermentative gram-negative bacilli. *Antimicrob Agents Chemother*. 1996;40:1412-1418.
 126. Gales AC, Jones RN, Forward KR, Liñares J, Sader HS, Verhoef J. Emerging importance of multi-drug resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). *Clin Infect Dis*. 2001;32(suppl):S104-S113.
 127. Winslow DL, Pankey GA. In vitro activities of trimethoprim and sulfamethoxazole against *Listeria monocytogenes*. *Antimicrob Agents Chemother*. 1982;22:51-54.
 128. Spitzer PG, Hammer SM, Karchmer AW. Treatment of *Listeria monocytogenes* infection with trimethoprim-sulfamethoxazole: case report and review of the literature. *Rev Infect Dis*. 1986;8:427-430.
 129. Meyer RD, Liu S. Determination of the effect of antimicrobials in combination against *Listeria monocytogenes*. *Diagn Microbiol Infect Dis*. 1987;6:199-206.
 130. Lerner PI. Nocardiosis. *Clin Infect Dis*. 1996;22:891-903.
 131. Feurle GE, Marth T. An evaluation of antimicrobial treatment for Whipple's disease: tetracycline versus trimethoprim-sulfamethoxazole. *Dig Dis Sci*. 1994;39:1642-1648.
 132. Durand DV, Lecomte C, Cathébras P, Rousset H, Godeau P, and the SNFMI Research Group on Whipple Disease. Whipple disease: clinical review of 52 cases. *Medicine (Baltimore)*. 1997;76:170-184.
 133. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CGM. Trimethoprim-sulfamethoxazole (cotrimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med*. 1996;335:16-20.
 134. *Red Book Updates*. Montvale, NJ: Medical Economics Books; 2001.