Resistance to Trimethoprim-Sulfamethoxazole

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Sulfonamides have a glorious history. In 1935, they were the first class of true antimicrobial agents with life-saving potency. Today, 66 years later, increased bacterial resistance to sulfonamides and to trimethoprim (TMP), a synthetic antimicrobial agent that is 30 years younger than sulfonamides, has limited their use to only a few indications. In the treatment and prophylaxis of patients with urinary tract infections, trimethoprim-sulfamethoxazole (TMP-SMZ) or TMP alone is still considered the first-line drug of choice, although increased bacterial resistance to these agents has been linked with treatment failure. TMP-SMZ has a possible role as a second- or third-line treatment for patients who have respiratory tract infections. In the developing world, where this inexpensive drug is widely used as first-line treatment, bacterial resistance has caused problems, especially with regard to the treatment of patients with severe respiratory tract infections. Use of TMP-SMZ as prophylaxis for *Pneumocystis carinii* infection has rapidly increased the multidrug resistance of bacterial pathogens found in human immunodeficiency virus–infected patients. Today, detailed and reliable knowledge on the resistance of bacterial pathogens to both TMP-SMZ and TMP is an essential requirement for the safe and effective use of these drugs in all clinical settings.

Sulfonamides, the first class of antimicrobial agents, were discovered in 1932 and put into clinical use in 1935 [1]. Since then, they have been used extensively in many different clinical indications. The medium long-acting sulfonamides, sulfamethoxazole (SMZ) and sulfadiazine, remain the most useful members of this class of antimicrobial agents. However, sulfonamides can cause serious side effects, including significant hypersensitivity or toxic reactions. In addition, sulfonamides are the most important drugs to be considered causes of blood dyscrasias. With the introduction of new, safer antibacterial agents, these side effects have reduced the attractiveness of sulfonamides.

Trimethoprim (TMP) was first used for the treatment of infections in humans in 1962 [2], and it was registered for clinical use, in combination with sulfonamides, in 1968. TMP, administered alone, was introduced as prophylaxis for urinary tract infections in Finland in 1972, and it was introduced for the treatment of patients with acute urinary tract infections in 1979. TMP has fewer side effects than do sulfonamides. Rashes and other hypersensitivity reactions have been reported, especially among patients with AIDS. TMP is one of the most important causative agents of, among other, more-rare side effects, drug-induced aseptic meningitis [3]. Of interest, both allergic reactions to these antimicrobial agents and TMP-induced nonallergic systemic reactions (e.g., CNS irritation) are more prevalent among patients with Sjögren’s syndrome than they are among patients with osteoarthrosis [4]; patients with other rheumatic disorders and HIV-infected patients may also have more of these reactions.

Use of TMP and sulfonamides in combination is thought to have a synergistic effect [5]. Both drugs affect bacterial folic acid synthesis. Sulfonamides inhibit dihydropteroate synthetase (DHPS), which catalyses the formation of dihydrofolate from para-aminobenzoic acid. In the subsequent step of the pathway, TMP inhibits dihydrofolate reductase (DHFR), which catalyses the formation of tetrahydrofolate from dihydrofolate. Although these steps follow one another and cause a sequential blockade, this does not necessarily explain the aforementioned synergy. When a particular pathway is completely inhibited at any one point, an inhibitor that is present at another point may not be able to increase the degree of inhibition. A combination of 2 drugs that have slightly different bacterial spectrums and different resistance profiles among pathogenic bacteria improves the usefulness of the drug combination, regardless of whether it produces a synergistic effect.

Sulfonamides and TMP both cover a wide antibacterial spec-
MECHANISMS OF BACTERIAL RESISTANCE

Different mechanisms mediate bacterial resistance to TMP and sulfonamides. Because resistance to both drugs can be transferable, these resistance traits are often linked to one another, as is the case in the well-known transposons of the Tn21 family [2]. Bacterial resistance to TMP and to sulfonamides is mediated by the following 5 main mechanisms: (1) the permeability barrier or efflux pumps, (2) naturally insensitive target enzymes, (3) regulational changes in the target enzymes, (4) mutational or recombinational changes in the target enzymes, and (5) acquired resistance by drug-resistant target enzymes.

Resistance that is mediated by the permeability barrier has been said to act against both sulfonamides and TMP. Moreover, this can also be the case with regard to efflux pumps. It may be difficult to separate the influences of these 2 mechanisms on resistance levels. *P. aeruginosa* is a type of bacteria that has these types of resistance mechanisms. Before efflux pumps were known, permeability barrier was considered to be the main mechanism of resistance to sulfonamides and TMP. Efflux pumps, however, have recently been shown to mediate resistance to both SMZ and TMP, even simultaneously [6, 7]. The real role of the permeability barrier with regard to resistance to sulfonamides and TMP remains to be seen. Impaired permeability can also be acquired, as is the case with the resistance to TMP that is found among isolates of *Klebsiella pneumoniae* and *Serratia marcescens* [8]; whether efflux pumps are also behind this resistance should be studied.

RESISTANCE TO TMP

Naturally insensitive DHFR enzymes are found among, for instance, *Bacteroides* species, *Clostridium* species, *Neisseria* species, and *M. catarrhalis* [8]. Overproduction of chromosomal DHFR caused by promoter mutation has reportedly occurred in *E. coli*. A single amino acid substitution in the *dhfr* gene and altered chromosomally encoded DHFR have been considered responsible for resistance to TMP among *S. aureus* [9] and *S. pneumoniae* [10]. In strains of TMP-resistant *H. influenzae*, changes in both promoter and coding regions of the *dhfr* genes have been found [11].

In 1972, 4 years after the TMP-SMZ combination was launched in the United Kingdom, transferable resistance to TMP was reported. Since 1972, ~20 different TMP-resistant transferable *dhfr* genes have been characterized [2, 12]. The most prevalent of these genes, *dhfrI* and variants of *dhfrII*, mediate high-level resistance to TMP with MICs that are greater than normal MIC values by >1000-fold, and they are most frequently found in gram-negative enteric bacteria; however, high-level transferable resistance to TMP has also been found in staphylococci, from which the resistance genes may have been transferred to *Listeria monocytogenes* [13].

RESISTANCE TO SULFONAMIDES

Single amino acid mutations in the chromosomal *dhps* gene of *E. coli* can be isolated easily in the laboratory [1]. Accordingly, mutations are also prevalent in nature among many clinically important bacteria; in addition to *E. coli*, these bacteria include *S. aureus*, *Staphylococcus haemolyticus*, *Campylobacter jejuni*, and *Helicobacter pylori*. In isolates of sulfonamide-resistant *S. pneumoniae*, resistance is based on 2 amino acid duplications in the *folP* gene (*dhps* gene) that alter the tertiary structure of the enzyme [14]. Strains of sulfonamide-resistant *S. pyogenes* emerged rapidly after the introduction of sulfonamides; it is more likely that the changes in the *dhps* gene were introduced by means of transformational recombinations than by a series of mutations [15].

One much studied sulfonamide-resistant bacteria is *Neisseria meningitidis* [1]. Analysis of resistance mechanisms has revealed 2 main types of resistance. The first is most likely to be born by means of recombination, because the *folP* gene of resistant strains shows a 10% difference from the corresponding gene in susceptible isolates. This may have been the result of horizontal gene transfer from other *Neisseria* species. The other ubiquitous sulfonamide-resistant *folP* gene has been subjected to mutational changes in the *dhps* gene. It is most likely that this gene also evolved from other species of bacteria that transferred into *N. meningitidis* by means of transformation and recombination. Although sulfonamides are no longer used to treat patients with meningitis, sulfonamide-resistant strains of *N. meningitidis* are still common. The resistance to sulfonamides still seen today in *N. meningitidis* has been referred to as a “scar” left from the earlier intensive use of this drug group for the prophylaxis and treatment of patients with meningococcal diseases.
The occurrence of transferable resistance to sulfonamides between *E. coli* and *Shigella* species was demonstrated as early as the late 1950s in Japan [16]. Transferable resistance to sulfonamides is mediated by 2 drug-resistant DHPS enzymes, which are encoded by *sulII* or *sulIII* genes [1]. These genes are only 57% identical with regard to amino acid level, and their origin is unknown. The *sulII* gene is normally linked to other transferable resistance genes, often in the transposons that belong to the Tn21 family. Both *sulI* and *sulII* are found among sulfonamide-resistant gram-negative enteric bacteria with roughly the same frequency. For sulfonamides, the number of different transferable resistance genes is only 2, but for TMP, it is ~20; why these numbers differ is unknown. However, despite the difference in the number of resistance genes for these agents, transferable resistance to both sulfonamides and TMP is widely spread.

**SPREAD OF RESISTANCE**

A few decades ago, it was generally believed that the use of TMP and sulfonamides in combination would inhibit the development of bacterial resistance to both agents. Clinical experience worldwide, however, does not support this hypothesis. Resistance to both agents has developed rapidly among all major species of bacteria.

To get an impression of how widely TMP- and sulfonamide-resistant strains have spread, it is necessary to refer to publications based on nationwide data. It is noteworthy that data on resistance may vary greatly in different surroundings, according to the nature of the strains of bacteria that were studied; even results from a single geographic location may be very different, depending on the origin of the bacteria that were studied. In addition, the techniques used to measure resistance to TMP-SMZ have the potential to be misinterpreted. Therefore, susceptibility testing for TMP-SMZ should be carried out and interpreted carefully according to the guidelines.

Susceptibility testing is usually performed for the TMP-SMZ combination; results of tests performed on either drug alone are lacking. However, despite the increase in the levels of resistance to TMP during the most recent decades, resistance to sulfonamides is usually more common than is resistance to TMP. In addition, resistance to TMP-SMZ is somewhat less prevalent than is resistance to either sulfonamides alone or TMP alone.

Resistance to TMP-SMZ among isolates of *E. coli* varies greatly, from 10% to 70% in different parts of the world. However, a clear trend is seen: strains isolated in the developing world are more often resistant than are strains isolated in developed countries [2]. In addition, *E. coli* isolated from elderly patients tends to be more resistant to TMP-SMZ than is *E. coli* isolated from younger patients. This may be a result of the wider use of antimicrobial agents for the treatment of elderly patients with urinary tract infections. The widespread use of antimicrobial agents is, however, not the only factor that explains why resistant strains have also become widespread. In developing countries, children who have not received any antimicrobial therapy have harbored *E. coli* isolates that are resistant to these agents [17]. A tropical or subtropical climate, combined with poor hygienic conditions, also offers excellent conditions for resistant gram-negative enteric bacteria to spread in the community. Bacteria also spread easily in tertiary-care hospitals, where they have been documented to have high levels of resistance to TMP-SMZ [8].

Patients with shigellosis have previously been successfully treated with TMP-SMZ. Today, however, practically all isolates of *Shigella* species are resistant to both TMP and SMZ [2, 18, 19]. In Thailand, the level of resistance reported among non-typhoidal *Salmonella* species and enterotoxigenic *E. coli* strains has reached 40% [18]. In *Salmonella* serotype Typhi, multidrug resistance, including resistance to TMP-SMZ, is also common. In a recent study from the United States, 17% of the *S. Typhi* isolates that were recovered from 293 persons were resistant to ampicillin, chloramphenicol, and TMP-SMZ [20]. Most strains of the *Campylobacter* species vary with regard to resistance to TMP-SMZ [21].

Resistance to TMP and sulfonamides among respiratory tract pathogens varies greatly in different parts of the world. Resistance to TMP-SMZ is one of the most prevalent properties of *S. pneumoniae* in many parts of the world, including both developed and developing countries [22–27]. Levels of resistance vary from ~9% to >50%. In Iceland, the use of TMP-SMZ was significantly associated with the carriage of resistant pneumococci [28], which may reflect the common multidrug-resistant property of pneumococci more than it reflects the particular importance of TMP-SMZ selection. Many penicillin- or macrolide-resistant pneumococci are also resistant to TMP-SMZ. In a recent Finnish study, however, a statistically significant correlation was found between sulfonamide-TMP use and the resistance of pneumococci in different geographic areas to TMP-SMZ [29].

The prevalence of resistance to TMP-SMZ has also increased in 2 other important respiratory tract pathogens, *H. influenzae* and *M. catarrhalis*. Resistance to TMP-SMZ occurs in 14% of *H. influenzae* isolates in Canada and in 33% of isolates in the United States [27, 30]; for *M. catarrhalis*, the rate of occurrence ranges from 2% to 50% of isolates. (Data from the United States also include information on intermediately resistant strains, which shows that there are apparent differences in the reporting of susceptibility.)

Different data exist regarding the susceptibility of *S. pyogenes* to TMP-SMZ [1, 31]. There is, however, a lack of good controlled studies concerning the efficacy of TMP-SMZ in the management of group A streptococcal infections. Because of
this uncertainty, and because more-effective antimicrobial agents exist, TMP-SMZ is not considered the drug of choice for the treatment of patients with pharyngitis or skin infections caused by S. pyogenes.

How important is the resistance property of bacteria? In a report on the treatment of patients with urinary tract infections, resistance to TMP-SMZ among bacterial pathogens was linked to treatment failure [32]. The importance of bacterial resistance to TMP-SMZ among patients with respiratory tract infections is difficult to establish because of the prevalent spontaneous cure rate that is associated with these infections. With regard to the treatment of patients with severe pneumonia, however, TMP-SMZ has been suggested by some to be inferior to amoxicillin because of bacterial resistance to TMP-SMZ [25]. It is likely that high-level resistance to TMP-SMZ (>1000-fold increase in MICs, compared with MICs of susceptible strains) more frequently causes therapeutic failure than does low-level resistance; however, more clinical studies are needed to establish the role of both types of resistance to TMP-SMZ in clinical settings.

USE OF TMP AND SULFONAMIDES

Only fractional data exist regarding the use of antimicrobial agents in different parts of the world. There is no doubt, however, that sulfonamides and TMP are still considered among the most frequently used antimicrobial agents. In Northern European countries, TMP-SMZ or TMP account for ~10%–15% of the total number of antimicrobial agents used. In Finland, TMP is used almost exclusively for the management and prophylaxis of urinary tract infections, and >70% of TMP-SMZ therapy involves the treatment of patients with otitis media and sinusitis [33].

Interesting variations have been observed with regard to the use of these drugs. In Denmark, >50% of patients with urinary tract infections are treated with sulfonamides alone, whereas sulfonamides alone are no longer on the market in Sweden and Finland. In Sweden and Finland, TMP alone is used to treat approximately one-third of patients with urinary tract infection, and TMP-SMZ is used to treat fewer than one-tenth of all patients with urinary tract infection. In the light of these examples, which involve countries with very similar health care systems and profiles of bacterial resistance, one can expect that indications for TMP-SMZ, TMP, and sulfonamides vary greatly around the world.

SPECIAL OBSERVATIONS

TMP-SMZ has been widely used for the prevention of Pneumocystis carinii, an opportunistic pathogen that causes pneumonia in patients with HIV. Selection pressure caused by yearlong, often lifelong, use of TMP-SMZ has resulted in an increase in the levels of resistance to TMP-SMZ among all clinically important bacterial species in the HIV units of the San Francisco General Hospital [34]. The wider use of TMP-SMZ for P. carinii prophylaxis began in 1988. In 1988, 24% of isolates of E. coli were resistant to TMP-SMZ, but by 1995, after several years of prophylactic use, the percentage of such isolates had reached 74%. The resistance levels are so high that TMP-SMZ is no longer a reasonable choice for the empirical antibacterial treatment of HIV-infected patients. Moreover, because resistance to TMP-SMZ among many bacterial pathogens was associated with the property of multidrug resistance, prophylactic use of TMP-SMZ can, in fact, select multidrug-resistant bacteria, which can also further complicate therapy with other antibacterial agents.

Another interesting finding concerning the increased levels of resistance to TMP-SMZ among clinically important bacteria comes from Africa. Use of sulfadoxine-pyrimethamine was expanded to include treatment of patients with chloroquine-resistant malaria; this has been linked to a significant increase in the prevalence of S. pneumoniae that is resistant to TMP-SMZ [35]. These 2 recent observations lead one to conclude that the use of sulfonamides for the treatment of patients with nonbacterial infections simultaneously increases the level of bacterial resistance to sulfonamides. There are not many other therapeutic options for the treatment of patients with P. carinii and malarial infections. Therefore, members of the infectious diseases community should carefully discuss whether we have any options other than simply to accept this increased prevalence of resistance to TMP-SMZ (and even multidrug-resistance) among clinically important bacteria.

TMP-SMZ has also been used for the treatment of patients with infections due to Stenotrophomonas maltophilia [36]; TMP-SMZ is often administered with a β-lactam/β-lactamase inhibitor combination, in which the β-lactamase inhibitor plays the significant role. However, there are no good controlled studies of the efficacy of TMP-SMZ, administered either alone or in combination, in the treatment of infections caused by this pathogen. Whether the in vitro susceptibility of S. maltophilia to TMP-SMZ also reflects susceptibility in vivo has not been confirmed. Although TMP-SMZ is often the only effective drug in vitro, resistance may develop during the course of therapy. Recently introduced fluoroquinolones may provide new therapeutic options for the treatment of patients with S. maltophilia infections [37].

There has also been discussion regarding whether TMP-SMZ is an effective treatment for patients with urinary tract infections caused by enterococci [2]. TMP-SMZ is not bactericidal against enterococci in vitro [38], and it has not been successful in the treatment of patients with enterococcal endocarditis [39]. In addition, development of bacteremia has been described in 2 patients who received treatment with TMP-SMZ for uncom-
Table 1. Suggested roles of trimethoprim-sulfamethoxazole (TMP-SMZ) in different clinical indications.

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Suggested role of TMP-SMZ</th>
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<tbody>
<tr>
<td>Respiratory tract infection</td>
<td></td>
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<tr>
<td>Otitis media, sinusitis</td>
<td>Second- or third-line drug</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>Not indicated; <em>Streptococcus pyogenes</em> often resistant</td>
</tr>
<tr>
<td>Exacerbations of chronic bronchitis</td>
<td>Second- or third-line drug</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Empirical therapy (e.g., in developing countries)</td>
<td>Not for severe infections</td>
</tr>
<tr>
<td>Skin infection with supposed causative pathogen</td>
<td></td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Second-line drug; several more-effective drugs are available</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>One of the first-line drugs; TMP can also be used alone; resistance impairs treatment results</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>One of the first-line drugs; TMP alone preferred</td>
</tr>
<tr>
<td>Bacterial gastroenteritis with supposed causative agent</td>
<td></td>
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<tr>
<td>Empirical treatment</td>
<td>Not indicated</td>
</tr>
<tr>
<td><em>Salmonella</em> species</td>
<td>Not indicated</td>
</tr>
<tr>
<td><em>Shigella</em> species</td>
<td>Not indicated; resistance levels very high worldwide</td>
</tr>
<tr>
<td><em>Campylobacter</em> species</td>
<td>Not indicated; resistance to TMP-SMZ variable</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em></td>
<td>Not indicated; resistance levels are high</td>
</tr>
<tr>
<td><em>Cholera</em></td>
<td>Second- or third-line drug; resistance levels vary</td>
</tr>
<tr>
<td>Sexually transmitted diseases</td>
<td></td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Not indicated; resistance levels are high</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Not indicated; efficacy not shown in good clinical trials</td>
</tr>
<tr>
<td>Chancroid (<em>Haemophilus ducreyi</em>)</td>
<td>Not indicated; resistance levels are high</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Not effective</td>
</tr>
<tr>
<td>Infection prophylaxis of HIV-infected patients</td>
<td>Use with caution; increase of bacterial resistance during long-term use is likely.</td>
</tr>
</tbody>
</table>

Complicated urinary tract infections caused by in vitro enterococcus that was susceptible to TMP-SMZ [40]. Although there is lack of controlled clinical studies, it is reasonable to assume that TMP-SMZ is not indicated for the treatment of patients with enterococcal urinary tract infection.

**CONCLUSIONS**

The clinical importance of TMP-SMZ and TMP has gradually declined during the most recent decades (table 1), primarily as a result of the development and rapid spread of resistance to these agents among all major bacterial pathogens. Also, serious side effects limit the use of sulfonamides and the TMP-SMZ combination. Finally, new, more-effective, safer antimicrobial agents have replaced TMP-SMZ and TMP in most of their clinical indications.

In the developed world, TMP-SMZ can be replaced relatively easily with other, usually more-expensive antibacterial drugs. Long-term prophylaxis of *P. carinii* pneumonia with TMP-SMZ causes an increase in the prevalence of multidrug-resistant strains of many bacterial species. This increased prevalence is a real threat to the successful treatment of HIV-infected patients with bacterial infections.

Because TMP-SMZ is a relatively inexpensive drug, it has been widely used in the developing world for various infections. Sulfonamides and TMP, both alone and in combination, are considered major drugs on the World Health Organization’s list of essential drugs. Increased resistance to these drugs is particularly a problem in developing countries, and TMP-SMZ may no longer be effective in the treatment of patients with infections due to resistant bacteria. This should be taken into account during the development of new treatment recommendations for developing countries.

When TMP-SMZ or TMP are used, it is essential to know the resistance profile of the causative bacterial pathogen or to be very well aware of the local resistance situation of the major
bacterial pathogens. This fact stresses the importance of performing qualified susceptibility testing and providing regular, timely bacterial susceptibility reports to clinicians in both hospital and community settings. The usefulness of TMP-SMZ and TMP alone can only be justified after careful local consideration of resistance situations.

References


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