Tuberculosis and Trimethoprim-Sulfamethoxazole

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The sulfonamides were the first drugs with antituberculous effects. Their use was abandoned and basically forgotten with the advent of streptomycin and isoniazid combination treatment. There is a widespread belief, apparently based on testing a single isolate on questionable media, that Mycobacterium tuberculosis is resistant to trimethoprim-sulfamethoxazole (TMP-SMX). We saw a complex immunocompromised patient with tuberculosis who was initially treated with TMP-SMX without antituberculous drugs and defervesced on this treatment. An isolate of M. tuberculosis from this patient was found to be sensitive to TMP-SMX. We examined how frequently M. tuberculosis is sensitive to TMP-SMX. Isolates were tested for susceptibility to TMP-SMX on the Department of Research, Lahey Clinic, Burlington, MA 01805. Phone: (781) 744-3017. Fax: (781) 744-5486. E-mail: pltcf@verizon.net.

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Between the late 1930s and the early 1950s, sulfonamides (10, 14, 24, 32, 33, 40) and sulfones (31) were used, usually as monotherapy, for the treatment of tuberculosis; the early preparations of sulfonamides other than sulfanilamide were in general found to have some efficacy. Because of the toxicity of the sulfones and the early sulfonamides (36), and because isoniazid (INH) and streptomycin were stronger antituberculous drugs (31), both groups of drugs were abandoned for the treatment of tuberculosis in the early 1950s, and their use was basically forgotten.

We saw a complex immunocompromised patient with fever and pulmonary infiltrates who was initially thought to have possible nocardiosis. He was treated with trimethoprim-sulfamethoxazole (TMP-SMX) for 2 1/2 weeks and defervesced on this treatment. He was found to have tuberculosis without nocardiosis or any other significant infection. Because of his clinical response (defervescence), testing of the susceptibility of his isolate of M. tuberculosis to TMP-SMX was performed, and it was found to be susceptible. It is widely thought that M. tuberculosis is resistant to TMP-SMX (2, 29, 37, 40). After looking at the basis for this belief, we decided to proceed with testing a large number of M. tuberculosis isolates for susceptibility to TMP-SMX.

CASE REPORT

An 81-year-old man was admitted to the Lahey Clinic Medical Center because of fever, chills, cough, and dyspnea for 1 day; he had noted fatigue without sweating or weight loss for 2 to 3 weeks. He had undergone a porcine aortic valve replacement 3 years previously. He was receiving prednisone for temporal arteritis, with gradual tapering of the dosage in the month prior to admission from 60 to 20 mg daily. He had lived in Italy until the age of 39, and his mother had tuberculosis when he was a child. His tuberculin skin test was positive.

Upon physical examination, there was temporal pallor of the left optic disk, a grade 1–2/6 long systolic murmur best heard at the apex, rales at the right base, and a diffuse grade 2–3/4 hypertrophy of the prostate gland. The remainder of the physical examination was unremarkable.

His hemoglobin was 9.0 gm/dl, and the sedimentation rate was 31. His white blood cell count varied between 4,500 and 6,900 cells/mm³, with 86 to 95% neutrophils and band forms and 4 to 7% lymphocytes. A baseline white blood cell count 3 months previously, while the patient was taking 20 mg of prednisone daily, was 7,900 cells/mm³, with 79% neutrophils and 17% lymphocytes. His creatinine was initially 1.9 mg/100 ml and then decreased to normal.

Blood cultures for bacteria, drawn prior to the administration of any antibiotic and obtained at least 1 h apart, were negative after 3 weeks of incubation, as were blood cultures for fungi. A transthoracic echocardiogram showed no significant valvular regurgitation; the patient refused to go through with a transesophageal echocardiogram. Chest X rays showed scarring in the apices and the right lower lobe, hilar calcification, a new, somewhat nodular infiltrate in the right upper lobe, and possibly an infiltrate in the right lower lobe. He was treated with intravenous cephalosporins and then with oral cephalosporins for a total of 4 days after admission without response. A computed tomography (CT) scan of the lungs revealed hilar calcification, bilateral pleural thickening and small effusions, patchy interstitial infiltrates or fibrosis, and a somewhat nodular infiltrate in the right upper lobe. A repeat CT scan 2 weeks...
later showed progression of the right upper lobe/superior segment of the right lower lobe (RLL) nodular infiltrate, additional nodular infiltrates in the left lower lobe, an RLL infiltrate versus atelectasis, and a subcarinal node with a low-density center.

No acid-fast bacilli (AFB) were seen on bronchoalveolar lavage specimens from two bronchosopies; only organisms consistent with normal oral flora were seen on Gram stains and grew on bacterial cultures. The second procedure was accompanied by a biopsy; the histological findings were nonspecific, with histological stains negative for AFB. No secretions or purulence was seen at bronchoscopy.

The prednisone was maintained at ≤20 mg/day except for an increase of up to 60 mg on the day of admission and for a 3-day period. A fever, usually 102 to 104°F, continued daily through 3 weeks of hospitalization and investigation, except during the 3-day period of increased doses of prednisone. There was little in the way of a cough during this time period.

Six days after the second bronchoscopy, an open-lung biopsy was performed with wedge resection of two small palpable nodules from the lingula and the left lower lobe. The histology was originally thought to represent acute bronchitis, with rare foci of early bronchopneumonia, negative acid-fast and Gomori’s methenamine silver stains, and rare bacterial clusters in the bronchi but not in the lung on Gram stains of tissue. A Gram stain of the portion of the specimen sent to the microbiology laboratory revealed gram-positive cocci and gram-positive bacilli that formed short filaments with limited branching, thought to possibly (but not definitely) represent Nocardia spp. The results of a modified acid-fast stain were not recorded but, to our recollection, were negative.

Because of the possibility of nocardiosis and stains negative for AFB for all specimens taken at bronchoscopy and open-lung biopsy, the patient was treated with TMP-SMX intravenously for 2 1/2 weeks without antimicrobial drugs. TMP-SMX therapy was started on the day of the open-lung biopsy and was given three times daily at daily doses of 1,080 mg of TMP (i.e., 15 mg/kg) and 5,400 mg of SMX.

The patient was afebrile during these 2 1/2 weeks except for a period of 5 days when he developed a severe Clostridium difficile infection. The prednisone dose, after the open-lung biopsy, was 15 to 20 mg daily (with the exception of the first postoperative day, the 3 days of symptoms of C. difficile infection, and two subsequent days).

The open-lung biopsy and one of the specimens taken at bronchoscopy grew M. tuberculosis, which was subsequently found to be sensitive to all first-line antituberculous drugs. Cultures for Nocardia spp. were negative for all specimens. The patient was started on antituberculous drugs (INH, rifampin [RIF], and ethambutol) 2 1/2 weeks after the open-lung biopsy, and TMP-SMX was discontinued. Cultures of the open-lung biopsy for fungi and viruses were negative. Also negative were cultures of urine and bone marrow for tuberculosis and fungi and of bronchoalveolar lavage for fungi, Legionella spp., Mycoplasma pneumoniae, and Chlamydia spp. Tissue from the open-lung biopsy grew mixed aerobic and anaerobic flora.

A CT scan of the lungs, performed toward the end of the TMP-SMX course, showed improvement of the subcarinal lymphadenopathy and the left-sided nodular infiltrates (not only in areas of resection) but worsening of the initial right upper lobe/superior segment of the right lower lung infiltrate. The sedimentation rate decreased from 31 to 6. Two specimens of sputum taken 6 and 12 days after the TMP-SMX course were negative for tuberculosis by stain and culture. The M. tuberculosis isolate was subsequently found to be sensitive to a MIC of ≤0.5/9.5 µg/ml of TMP-SMX.

The main finding of a pathologist’s subsequent review of the open-lung biopsy, without any clinical information, was an interstitial infiltrate of mononuclear cells and eosinophils, with intra-alveolar collections of histiocytes. There were also foci of acute bronchitis. The histology was suggestive of an early mycobacterial or fungal infection; it was not thought to be consistent with a significant bacterial pneumonia, aspiration, or abscess.

The patient’s subsequent hospital course was difficult, with development within a month after starting standard antituberculous drugs of a myocardial infarction with a left ventricular-ejection fraction decrease to 35 to 45% and multiple other complications. He expired in a chronic care hospital 5 months after the open-lung biopsy.

**MATERIALS AND METHODS**

Forty-four isolates of M. tuberculosis were tested for susceptibility to TMP-SMX. Thirty-eight of these isolates were clinical isolates, each from a different patient, and six separate isolates were submitted to us for proficiency testing. Four of these 44 isolates were resistant to both INH and RIF (all four were clinical isolates).

Susceptibility testing was performed, using culture plates divided into quadrants containing various amounts of TMP-SMX in Middlebrook 7H10 medium with OADC (oleic acid, albumin, dextrose, and catalase) supplement (Hardy Diagnostics, Santa Maria, CA). The quadrants contained the following amounts of TMP-SMX (µg/ml): plate 1, 0/0, 0.125/2.4, 0.25/4.8; and 0.5/9.6; and plate 2, 0/0, 1/19, 2/38, and 4/76.

An inoculum of M. tuberculosis equivalent to a 1:100 dilution of McFarland standard no. 1 was prepared from pure growth on Middlebrook 7H10 medium. Using a transfer pipette, 0.1 ml of the 1:100 dilution was inoculated onto each quadrant of the plate. The plate was slowly rotated to spread the inoculum over the surface. A blood agar plate and a Middlebrook 7H10 plate were also inoculated as purity controls. A Mycobacterium abscessus isolate known to be resistant to TMP-SMX served as a control, as did seven replicates of M. tuberculosis strain H37Rv. Plates were incubated at 35 to 37°C with 5% CO2. The TMP-SMX plates were read weekly for 21 days by comparing the number of colonies on the control quadrant and the number of colonies on each quadrant containing the drug. The TMP-SMX MIC was defined as the lowest concentration of TMP-SMX that provided at least 80% inhibition of growth, which is the criterion recommended by the CLSI for rapidly growing mycobacteria, Mycobacterium kansasii, and Mycobacterium marinum (25). The plates were also read at 99% inhibition.

Six isolates were sent to another laboratory (National Jewish Medical and Research Center, Denver, CO) for determination of the MIC of TMP/SMX using the Bactec 460 system radiometric method.

**RESULTS**

For 43 of 44 isolates of M. tuberculosis, including 4 of 4 multidrug-resistant (MDR) isolates, there was at least an 80% inhibition of growth at a MIC of ≤1/19 µg/ml of TMP-SMX (Table 1). For 36 of 44 isolates (82%), there was at least a 99% inhibition by ≤2/38 µg/ml of TMP-SMX. Six isolates of M. tuberculosis tested by another method (the radiometric Bactec 460 system) were found to be susceptible to TMP-SMX, with a MIC of ≤0.5/9.5 µg/ml.
TABLE 1. Results of susceptibility testing of M. tuberculosis to TMP-SMX

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>Number of isolates at indicated % inhibition of growth:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥80</td>
</tr>
<tr>
<td>0.125/2.4</td>
<td>1</td>
</tr>
<tr>
<td>0.25/4.8</td>
<td>10</td>
</tr>
<tr>
<td>0.5/9.6</td>
<td>14</td>
</tr>
<tr>
<td>1/19</td>
<td>18</td>
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<tr>
<td>2/38</td>
<td>1</td>
</tr>
<tr>
<td>4/76</td>
<td>5</td>
</tr>
<tr>
<td>&gt;4/76</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
</tr>
</tbody>
</table>

* Results for the controls were as follows: for M. abscessus, the MIC was >4/76 µg/ml at both ≥80% and ≥99% inhibition of growth; for M. tuberculosis strain H37Rv, replicated on seven occasions, the MIC was 1/19 µg/ml on each occasion at ≥80% inhibition of growth, 1/19 µg/ml on five occasions at ≥99% inhibition of growth, and 2/38 on two occasions at ≥99% inhibition of growth.

DISCUSSION

The clinical response of our patient (defervescence) to TMP-SMX and the susceptibility of the M. tuberculosis isolate from the patient to TMP-SMX were surprising, as there is a widespread belief that M. tuberculosis is resistant to TMP-SMX (2, 29, 37, 40).

The initial response to antituberculous treatment (at approximately 1 to 2 weeks) is usually determined by a decrease in fever, decreased coughing, and a smaller number of acid-fast organisms on sputum smears (in smear-positive patients). As our patient had little in the way of a cough in the hospital prior to lung biopsy and had two smears on bronchoalveolar lavage that were negative for AFB, these criteria could not be used to ascertain improvement. Only defervescence remained as a major objective criterion of his early response to treatment.

There were also “soft” secondary criteria for measuring improvement with the course of TMP-SMX: a moderate improvement in sedimentation rate, two sputum smears and cultures negative for mycobacteria several days after the completion of TMP-SMX therapy, and possible improvement observed on the CT scan of the lung done toward the end of TMP-SMX treatment. There was a decrease in the necrotic subcarinal adenopathy and in the more-recent nodular infiltrates (not secondary to resection at biopsy) but progression of the initial and largest abnormality; this dichotomy represents a possible response to treatment, with a not-uncommon paradoxical early progression of some lesions.

Although our patient’s condition was complex, another etiology for his 3 weeks of almost daily high fevers is unlikely, and his defervescence during 2 1/2 weeks of TMP-SMX therapy was unlikely to be due to factors other than a response of his tuberculosis infection to therapy. His defervescence was not due to changes in prednisone dosage, as the patient remained on the same the same low dosage of 15 to 20 mg daily except for brief periods before his open-lung biopsy and during treatment with TMP-SMX. He did not receive masking nonsteroidal anti-inflammatory drugs or other antipyretic treatment. He did not receive antibacterial drugs with an antitubercular spectrum, such as quinolones or aminoglycosides.

Approximately 1 to 2 days of nonspecific defervescence can occur after surgery, possibly related to the production of stress hormones, but this reaction would not explain a long afebrile period. The resection of two small pulmonary lesions should have produced defervescence, as multiple larger lesions, including the initial main lesion, were not resected.

The patient was extensively tested for other etiologies of his fever prior to his open-lung biopsy. Endocarditis was looked for (though the echocardiogram was only transthoracic). Although his initial symptoms of temporal arteritis included fever, a flare-up is not consistent with his test results and antibacterial response.

Upon open-lung biopsy, there was evidence of a bacterial process. The patient had acute bronchitis with pyogenic inflammation, and histological evaluation revealed that bacteria were present in the bronchi but not in the lung tissue. Mixed aerobic and anaerobic flora grew on the open-lung biopsy specimen. It is quite unlikely that aspiration pneumonia or other bacterial pneumonia responsible for the patient’s fever was missed. Although one could postulate that an open-lung biopsy might miss a focal lesion elsewhere in the lungs, the nodular nature of the infiltrates on CT scans does not support such a diagnosis, nor, clinically, does the absence of increased coughing. Additionally, there was no purulence encountered at the time of the two bronchoscopies, the second of which was performed only a few days prior to the open-lung biopsy; only some “normal oral flora” were seen and grown from the bronchoalveolar lavages taken from multiple lobes. There was no response to antibacterial treatment during the early days of hospitalization. Thus, in all likelihood, there was not an occult bacterial process in the lungs more significant than the bacterial bronchitis seen upon histological examination.

There is controversy about the clinical significance of bacterial bronchitis or tracheobronchitis. However, in a patient with tuberculosis, a finding of bacterial bronchitis or tracheobronchitis may represent a bacterial superinfection. Such a superinfection would most likely have started shortly before the open-lung biopsy for the same reasons as noted above and would not explain the prolonged prebiopsy fever in our patient.

In planning our study, we were faced with the absence of recommendations by the CLSI for the interpretation of susceptibility testing of M. tuberculosis to TMP-SMX. Therefore, we based the interpretation of the susceptibility testing of our isolates on principles governing TMP-SMX susceptibility testing and on existing recommendations for related organisms. Bauer and Sherris suggested using at least an 80% reduction in growth for determining the MIC of sulfonamides for aerobic bacteria (4). This recommendation is still followed for sulfonamides and TMP-SMX, whereas 100% inhibition is used for other antibiotics (20) because of the frequent trace presence in culture media or inoculum of substances antagonizing the activity of TMP-SMX (4, 20). Similarly, the CLSI recommends at least an 80% inhibition of growth for determining the susceptibility to TMP-SMX of rapidly growing mycobacteria and of certain other nontuberculous mycobacteria, such as M. marinum and M. kansyasis (25). Wallace and colleagues have used at least an 80% inhibition of growth to determine the susceptibility of any mycobacterium, including M. tuberculosis, to sulfonamides or TMP-SMX for the same reason as Bauer and Sherris (35). Although at least 99% inhibition is used in testing the susceptibility of M. tuberculosis to other antibiotics, the
most appropriate proportion for determining the susceptibility of this organism to TMP-SMX seemed to us to be at ≥80% inhibition of growth. By this criterion, we found that 43 of 44 (98%) of our M. tuberculosis isolates were sensitive to ≤1/19 μg/ml of TMP-SMX.

In the absence of correlation of extensive tuberculosis treatment results with various MICs of TMP-SMX, we cannot define a specific susceptibility cutoff. However, the CLSI recommends that slowly growing nontuberculous mycobacteria such as M. kansasii (25) should be considered sensitive to TMP-SMX at a MIC of ≤1/19 μg/ml, as should Nocardia spp. and rapidly growing mycobacteria at a MIC of ≤2/38 μg/ml.

At least a 99% inhibition of growth has been used for determining the susceptibility of M. tuberculosis to other antibiotics but has never been recommended for testing of mycobacterial susceptibility to TMP-SMX. Nevertheless, we determined MICs at both the ≥80% and ≥99% inhibition levels. At ≥99% of inhibition of growth, 23 of 44 (52%) of our isolates were inhibited by ≤1/19 μg/ml of TMP-SMX and 36 of 44 (82%) by ≤2/38 μg/ml of the drug.

In all four MDR isolates, at least 80% of growth was inhibited at an MIC of ≤1/19 μg/ml of TMP-SMX. For three of the four isolates, the MIC was ≤2/38 μg/ml at ≥99% inhibition of growth. For two of these four MDR isolates, the MICs of TMP-SMX were quite low by both criteria, i.e., ≤0.5/9.0 μg/ml.

There is some evidence that one of the antituberculous mechanisms of action of INH is the inhibition of dihydrofolate reductase (3). Sixteen of our 44 M. tuberculosis isolates were resistant to INH; the distribution of the MICs of TMP-SMX for these isolates did not differ from that of the total group.

We examined the basis for the general belief that M. tuberculosis is resistant to TMP-SMX. In the “old” literature from between 1930 and 1953, the sulfonamides were the first drugs used against M. tuberculosis that had some efficacy (10, 14, 24, 32, 33, 40). Susceptibility testing of M. tuberculosis was not standardized as to inoculum, media, or length of incubation. However, simultaneous testing of the susceptibility of M. tuberculosis to various sulfonamides revealed the following MICs (in μg/ml): for sulfathiazole, 10; for sulfadiazine, slightly over 50; for sulfapyridine, 50 to 500; and for sulfanilamide (the first sulfonamide), approximately 1,000 (15, 39).

Similarity, treatment of tuberculosis in experimental animals (mice, guinea pigs, and rabbits) gave various results depending primarily on the sulfonamide used and whether the drug was administered prior to or simultaneously with infection or after infection had occurred (9, 12, 13, 18, 19, 30). Sulfadiazine improved animal survival significantly more than did other old sulfonamides (13, 19, 30). There was often significant gastrointestinal toxicity with the early sulfonamides, especially with long courses of treatment (12, 30).

Sulfadiazine and sulfathiazole gave, in general, better in vitro susceptibility results than sulfones; however, experimental studies with tuberculosis-infected animals, thought to be more relevant than susceptibility testing (11), showed that sulfones had better efficacy than most sulfonamides. It is possible that some of these animal studies underestimated the activity of sulfonamides because of the higher concentrations of thymidine in certain animal species (e.g., rodents) (26).

Although sulfanilamide treatment of patients with tuberculosis had little (39) or no (14, 24) therapeutic effect, uncontrolled monotherapy studies with other sulfonamides in general showed clinical improvement (17, 21, 32, 33).

P. Ellman (10) performed a randomized study of sulfapyridine treatment of 89 patients with pulmonary tuberculosis, assigning alternate unselected patients to sulfapyridine or to no medication. There was little or no therapeutic effect for patients with “severe” disease, i.e., those expected to die within 6 months; however, in those with “mild” or “moderate” disease, 36% treated with sulfis became culture negative for M. tuberculosis (versus 0% with no treatment), and there was more frequent improvement seen in chest X rays and decreased fever than for those not receiving treatment. Drug toxicity was a significant problem.

A small study by Spies et al. used combination therapy with streptomycin and para-aminosalicylic acid or sulfones and showed sulfones to be equivalent or superior to para-aminosalicylic acid (31). In the early 1950s, the use of sulfonamides and sulfones for the treatment of tuberculosis was abandoned.

Prior to the introduction of oral treatment with TMP-SMX in the United States, S. R. Bushby of Wellcome Laboratories performed susceptibility testing of one isolate of M. tuberculosis on an egg yolk medium; the MIC of TMP was 250 μg/ml, and that of SMX was >1,000 μg/ml (8) (results for the combination were not mentioned). However, egg-containing media are not recommended for sulfanamide or TMP-SMX testing because of substances which interfere with the antimicrobial activity of these drugs and “produce false resistance” (15, 28).

In subsequent publications on treatment with TMP-SMX, Bushby reported identical MIC results for tests with a single M. tuberculosis isolate or an unspecified number of isolates on the same media or on unspecified media (4–7). An identical result was reported in an investigational drug brochure by Roche Pharmaceuticals prior to the introduction of the intravenous form of TMP-SMX (28). Bushby concluded that “Mycobacterium tuberculosis [is] relatively insensitive to both drugs” (7).

Subsequently, multiple reviews of the spectrum of TMP-SMX mention that M. tuberculosis is resistant to this drug (2, 29, 37, 38); reviews referenced to original articles with susceptibility results (2, 37) cite these articles by Bushby.

Like sulfadiazine, TMP-SMX did not achieve 2 to 3 weeks of survival for mice following intravenous injection of lethal quantities of M. tuberculosis (16).

In the modern era, few studies have looked at the susceptibility of M. tuberculosis to TMP-SMX. In a study reported in the Argentine literature, 75% of 175 clinical isolates of M. tuberculosis were inhibited by ≤2/40 μg/ml of TMP-SMX, with a 99% reduction in colonies used to determine the MIC (22).

During the evaluation of a new testing system (7H9 broth microdilution), Wallace et al. found that ≥90% of 10 isolates of M. tuberculosis were sensitive to 8 μg/ml of SMX, though a comparison to standard methodology was not performed for this drug (34). The interactions of a combination of RIF and TMP-SMX were evaluated in vitro by observing a large inoculum of M. tuberculosis for 7 weeks. All isolates incubated with RIF alone grew RIF-resistant colonies; two of five isolates incubated with RIF and TMP-SMX had no growth, and the three others remained RIF sensitive (23). Multiple studies of the effect of prophylactic TMP-SMX on mortality in human immunodeficiency virus-infected individuals with or without tuberculosis in Africa have found decreased mortality in indi-
individuals on prophylaxis (27). In at least one randomized, controlled study (1), a non-statistically significant reduction of approximately 25% in the occurrence of definite and severe tuberculosis was observed during a short study period (mean length, 9.5 months).

Thus, the current belief that M. tuberculosis is resistant to TMP-SMX seems to be based on the testing of a single isolate, most likely in the presence of inhibitors of TMP-SMX. We found that 43 of 44 isolates of M. tuberculosis were sensitive to \( \leq 1/19 \mu g/mL \) of TMP-SMX. Nontuberculous mycobacterial infections for which the MIC is similar often respond to regimens that include TMP-SMX. Although only four of our study isolates were MDR, they were susceptible to \( \leq 1/19 \mu g/mL \) of TMP-SMX.

In vitro susceptibility does not necessarily predict the clinical response. Our patient represents only a single case of tuberculosis that responded to a high dose of intravenous TMP-SMX. In the above randomized, noncontrolled 1941 study by Ellman, sulfapyridine monotherapy was frequently microbiologically and clinically efficacious in tuberculous patients, though with significant toxicity.

At a time when MDR and extended drug resistance are significant problems with tuberculosis, especially in certain countries, and when new drugs are sought for the treatment of drug-resistant tuberculosis, TMP-SMX may represent a “new,” inexpensive, and rarely toxic antituberculous drug for patients with MDR or extended drug resistant tuberculosis. As there is extensive data on the use of the older, more-toxic sulfonamides and sulfoxones for the treatment of tuberculosis in experimental animals, a clinical trial of tuberculosis treatment for humans with regimens that include TMP-SMX should be considered.

ACKNOWLEDGMENTS

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