Brain Abscess Caused by *Streptomyces* Infection following Penetration Trauma: Case Report and Results of Susceptibility Analysis of 92 Isolates of *Streptomyces* Species Submitted to the CDC from 2000 to 2004\(^7\)

Charles E. Rose III,\(^1\)* June M. Brown,\(^2\) and John F. Fisher\(^1\)

Department of Medicine, Medical College of Georgia, Augusta, Georgia,\(^1\) and Bacterial Zoonoses Branch, Division of Foodborne, Bacterial and Mycotic Diseases, National Center for Zoonotic, Vector-borne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333\(^2\)

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The case of a patient who presented with a brain abscess caused by *Streptomyces* infection following penetrating cerebral trauma with a soil-contaminated object generated an interest in optimizing antimicrobial therapy. Collaboration with the Centers for Disease Control and Prevention led to the analysis of susceptibility data for *Streptomyces* isolates that suggested that amikacin (100% susceptibility for 92 isolates tested) and linezolid, an oxazolidinone (100% susceptibility for 41 isolates tested), offer reliable activity against all isolates.

CASE REPORT

A 19-year-old previously healthy man sustained a parietal skull fracture after a penetrating injury caused by a rake in a freak accident involving a groundskeeping maintenance vehicle. Immediately after the injury occurred, the patient was transferred to the Trauma Center of the Medical College of Georgia Hospital. On arrival, he was disoriented and nauseous. Computed tomography (CT) imaging of the head revealed a right parietal skull fracture and a posterior parietal lobe hematoma with pneumocephalus. The patient was given vancomycin and cefazidime preoperatively and underwent a right parietal craniotomy with debridement, duraplasty, and reduction of the depressed skull fracture. Gram staining of the debrided material showed a few neutrophils in most microscopic fields, but no organisms were noted by medical technologists in the microbiology laboratory. The patient improved and was discharged. He was given phenytoin to prevent seizures and cephalaxin to treat any residual infection. Within 48 h he returned with headache of increasing intensity, chills, nausea, vomiting, and somnolence. Findings from a head CT scan were consistent with a brain abscess and extensive edema in the postsurgical area. The patient was given vancomycin intravenously and ceftriaxone empirically and monitored in the intensive care unit. Magnetic resonance imaging (MRI) suggested the presence of a serosanguinous collection deep to the craniotomy flap, and the patient underwent a second craniotomy. The operating surgeons noted the odor of moist soil upon removing the bone flap and evacuating the abscess. Aerobic and anaerobic cultures were repeated. Again, microscopy of the abscess cultures was unhelpful. At the recommendation of infectious disease consultants, treatment with vancomycin, cefepime, and intravenous metronidazole was begun. The patient made steady improvement. On postoperative day 9, the microbiology laboratory reported isolating a filamentous gram-positive bacillus growing aerobically from the original culture, which was tentatively identified as *Streptomyces* species. With this finding in mind, we reviewed the initial examination and were able to appreciate rare gram-positive bacilli on the smear from the intraoperative specimen. Subsequently, the antibiotic regimen was modified to ceftriaxone, intravenous metronidazole, and oral doxycycline. The last antibiotic was added on the basis of in vitro susceptibility data that had been reported previously (12). The administration of intravenous antibiotics at home was arranged for the patient, and he was discharged but was readmitted several hours later because he had developed a diffuse morbilliform rash. The rash was attributed to phenytoin and resolved after valproic acid was substituted for phenytoin. The same antibiotic regimen was continued. Identification of the isolate was confirmed by the reference Associated Regional and University Pathologists Laboratories (ARUP, Salt Lake City, UT) as *Streptomyces* species. Based on the CLSI microdilution and breakpoint guidelines for nocardiae and other aerobic actinomycetes (6), the susceptibility results performed at ARUP showed that the isolate was susceptible to amikacin (MIC, <1.0 μg/ml), clarithromycin (MIC, 1.0 μg/ml), linezolid (MIC, 2.0 μg/ml), and tobramycin (MIC, <0.5 μg/ml). However, resistance to ceftriaxone and minocycline and susceptibility to macrolides led to a further modification of the patient’s therapeutic regimen to include oral clarithromycin in lieu of doxycycline. Ceftriaxone and intravenous metronidazole were continued empirically. The patient completed 1 month of intravenous therapy before his percutaneously inserted central catheter inadvertently came out. By the time of his follow-up appointment at 3 weeks after discharge, the patient had made a full recovery. He returned to college for the following semester.

In an attempt to determine the species of the organism, growth from the isolate was sent to the CDC, and 16S rRNA gene sequencing showed the closest similarity to *Streptomyces*...
cælestis (99.24%; GenBank accession number X80824). Ironically, based on the same CLSI guidelines that were used by ARUP, results of the assays repeated with the antimicrobial susceptibilities of the original Streptomyces isolate now indicated resistance to clarithromycin (MIC, >8 μg/ml) and susceptibility to minocycline (MIC, <0.5 μg/ml) but were otherwise identical to the initial test results. Because of the clinical improvements made to clarithromycin, the patient continued taking this antibiotic for 3 months, and an MRI showed a complete resolution of the abscess. The patient received a titanium plate 6 months after the initial injury.

Organisms belonging to the genus Streptomyces are classified among the aerobic actinomycetes, but unlike other members of the group, such as Nocardia spp. and Rhodococcus spp., they are not weakly acid fast. Investigation of Streptomyces spp. has yielded many classes of antimicrobial substances and has led to the discovery and development of aminoglycosides, tetracyclines, and glycopeptides, among other antibiotics (5, 13).

While Streptomyces spp. remain uncommon causes of deeply invasive human infections, it is well known that they cause superficial disease following traumatic inoculation. Indeed, these organisms are among those that frequently cause mycetomas in the feet of farmers in east Africa and have been known to cause perianal soft tissue infection in people who use vegetative matter in lieu of toilet tissue in Central America (4, 7). In contrast to the more frequent occurrence of this organism in superficial infections, we could find only 12 reported cases of visceral disease due to Streptomyces infection, the majority of which occurred in patients who were immunocompromised by human immunodeficiency virus infection, by malignancy, or by treatment with immunosuppressive agents, including corticosteroids and cancer chemotherapy (8). Previously reported cases of infection have included patients with brain abscess, pneumonia, infective arthritis, periarteritis, endocarditis, peritonitis, lymphadenitis, and vertebral infections (1, 5, 8, 9, 14). More recently, Carey and colleagues described a catheter-related bloodstream infection involving the intravenous infusion of holistic compounds (3). A patient with a Streptomyces brain abscess provided an incentive to review the optimal therapy for life-threatening infections, to review previously published susceptibilities for these organisms, and to consult with colleagues at the CDC.

A total of 86 isolates of Streptomyces species from the Actinomycete Reference Laboratory at the CDC were submitted from state laboratories (more than half were from South Carolina, Tennessee, Florida, New York, and Ohio), and 6 were from Canada and India. The 92 stored isolates of Streptomyces species were from wounds, sputum, bronchial lavage fluid, lung tissue, blood, bone marrow, eyes, nails, cerebral spinal fluid, knee fluid, and otherwise undetermined body fluid. Traditional biochemicals and whole-cell-wall analyses were performed with all isolates to identify these strains to the genus level, as described previously (2). No 16S rRNA gene sequence analysis was used at this time. MICs were determined according to CLSI (formerly NCCLS) guidelines using PML panels (PML Microbiological Inc., Wilsonville, OR) with cation-supplemented Mueller-Hinton broth (6). The drugs tested were amikacin, amoxicillin-clavulanate, ampicillin, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, minocycline, sulfamethoxazole, and trimethoprim-sulfamethoxazole (TMP-SMX). The interpretive criteria for breakpoints used for all drugs were those recommended by the CLSI for Nocardia species and other actinomycetes (6).

Applying the broth microdilution breakpoints for Nocardia and other aerobic actinomycetes (6, 12), the percentages of susceptibilities were ascertained by assigning each isolate to a susceptible, intermediate, or resistant category according to MIC and then by dividing the number of isolates susceptible to each antibiotic by the number of all organisms tested. Applying the assigned breakpoints, all isolates (100%) tested were susceptible to amikacin (92 of 92 isolates) and linezolid (41 of 41 isolates); susceptibilities to amoxicillin-clavulanate, clarithromycin, minocycline, and imipenem were 51, 51, 77, and 67%, respectively. Fewer than 50% of the Streptomyces isolates were susceptible to beta-lactams, ciprofloxacin, and sulfonamides, with or without trimethoprim (Table 1).

After consulting the literature available for cases of deep-seated Streptomyces infection, we treated our patient’s brain abscess with ceftriaxone and doxycycline because both offered good central nervous system (CNS) penetration as well as availability (10, 12, 16). To our surprise, the initial testing indicated resistance to ceftriaxone and minocycline, which led to our substitution of clarithromycin with doxycycline. Despite the apparent resistance of our patient’s isolate to clarithromycin, as found upon repeat testing, the macrolide was continued because of the patient’s marked clinical improvement.

Of the 12 published cases of invasive disease, 9 were described in a review article (8), and 1 patient was the subject of a recent case report (3). Of the available descriptions of antibiotic therapy, various compounds have been used, including

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>No. of isolates tested</th>
<th>MIC breakpoint for susceptibility (μg/ml)</th>
<th>% of susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>92</td>
<td>≥8</td>
<td>100</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>92</td>
<td>≥8/8</td>
<td>51</td>
</tr>
<tr>
<td>Cefotaxime&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51</td>
<td>≥8/8</td>
<td>35</td>
</tr>
<tr>
<td>Ceftriaxone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92</td>
<td>≥8</td>
<td>21</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>92</td>
<td>≤1</td>
<td>46</td>
</tr>
<tr>
<td>Clarithromycin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>41</td>
<td>≤2</td>
<td>51</td>
</tr>
<tr>
<td>Erythromycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>51</td>
<td>≥0.5</td>
<td>25</td>
</tr>
<tr>
<td>Imipenem</td>
<td>92</td>
<td>≤8</td>
<td>67</td>
</tr>
<tr>
<td>Linezolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41</td>
<td>≥8</td>
<td>100</td>
</tr>
<tr>
<td>Minocycline</td>
<td>92</td>
<td>≤1</td>
<td>77</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>92</td>
<td>≥32</td>
<td>25</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>92</td>
<td>≥2/32</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> The MIC breakpoints for susceptibility used are those reported by the CLSI (6), except for the breakpoint for susceptibility of erythromycin, which is from the NCCLS (15).

<sup>b</sup> Ceftriaxone and erythromycin were removed from the panel on 25 January 2002.

<sup>c</sup> Ceftriaxone remained on the panel as a cephalosporin class representative; clarithromycin replaced erythromycin on the panel on 25 January 2002 as a macrolide class representative; and linezolid was added to the panel on 25 January 2002 as recommended by CLSI (6).
TMP-SMX, ceftriaxone, clarithromycin, penicillin, sulfadiazine, streptomycin, chlorotetracycline, cefuroxime, amikacin, amoxicillin-clavulanate, piperacillin-tazobactam, imipenem, and oxytetracycline.

Only two isolates (S. griseus and S. somaliensis) underwent complete species identification. Successful therapy using macrolides, tetracyclines, ceftriaxone, and imipenem and amikacin was reported (3, 8). Previously reported in vitro susceptibilities exist only for infection by S. griseus, which showed susceptibility to ceftriaxone, doxycycline, erythromycin, imipenem, minocycline, and TMP-SMX in 80, 81, 86, 81, 90, and 71% of 28 isolates, respectively (12).

In the previous study (12), susceptibility testing for Streptomyces organisms was not standardized. In our study of 92 isolates, guidelines were available for methodology, but in this study as with the previous study, the testing of most actinomycetes was hampered by an inability to standardize the inoculum. Our focus on 92 stored isolates from the CDC offered a unique opportunity to predict the susceptibilities of members of the entire genus. Our results suggest that the traditional therapies such as TMP-SMX favored for the treatment of Nocardia infection might not be optimal for treating Streptomyces infection.

Additionally, the recent testing of linezolid and amikacin suggests consistent activity against all Streptomyces isolates. Thus, for deep-seated infections, our data indicate that these compounds should be considered for initial treatment. In retrospect, linezolid would have provided both excellent coverage for Streptomyces infection as well as great CNS penetration into our patient’s brain abscess. It should be noted that prolonged therapy with linezolid should be given with due caution in light of reported cases of lactic acidosis, bone marrow suppression, and neuropathy (including optic neuropathy). Other agents with reasonable antibiotic activity that have good CNS penetration include carbapenems, tetracyclines, and macrolides (10, 11, 16).

Aminoglycosides should have less of a role in CNS infection because of poor penetration, but in other sites of infection, aminoglycosides have consistent activity against infection by Streptomyces isolates (10).

While Streptomyces species are not commonly recovered, this organism can cause invasive infections, especially in immunocompromised hosts. Despite a growing number of newly reported isolates, the susceptibility data from 2000 to 2004 indicate reliable activity of amikacin and linezolid against infection by most if not all isolates. Various combinations of carbapenems, tetracyclines, and macrolides may also have utility. While sulfa drugs are traditionally used for treating Nocardia species infection, only 35% of Streptomyces isolates recovered were susceptible to TMP-SMX.

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REFERENCES