Identification of *Streptomyces* spp. in a Clinical Sample: Always Contamination? Results of a French Retrospective Study

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**Background.** *Streptomyces* are environmental gram-positive bacilli that can cause ubiquitous mycetoma and, more rarely, invasive infections. We describe the clinical relevance of *Streptomyces* spp. identified in human samples and characteristics of patients with invasive *Streptomyces* infections.

**Methods.** We conducted a retrospective (2006–2017) study of *Streptomyces* isolates identified in clinical samples in French microbiology laboratories. *Streptomyces* genus was confirmed by a specific 16S RNA polymerase chain reaction, and antibiotic susceptibility testing was performed by disk diffusion and trimethoprim-sulfamethoxazole minimum inhibitory concentration (E-test) if resistance was suspected. Patient characteristics, treatments, and outcomes were collected. Invasive infection was defined as a positive culture from a sterile site with signs of infection but without cutaneous inoculation.

**Results.** Of 137 *Streptomyces* isolates, all were susceptible to amikacin (113/113) and linezolid (112/112), and 92.9% to imipenem (105/113). Using disk diffusion, 50.9% (57/112) of isolates were susceptible to trimethoprim-sulfamethoxazole, but most of the apparently resistant isolates (25/36, 69.4%) tested by E-test were ultimately classified as susceptible. Clinical data were obtained for 63/137 (45.9%) isolates: 30 (47.6%) invasive infections, 8 (12.7%) primary cutaneous infections, 22 (34.9%) contaminations, 3 (4.7%) respiratory colonization. Patients with invasive infection were more frequently receiving corticosteroids than patients without invasive infection (11/30, 36.7%, vs 2/25, 8.0%; \( P = 0.03 \)), and at 6-month follow-up, 14 of them were cured, 3 had relapsed, 4 were dead, and 9 were lost to follow-up.

**Conclusions.** Half of the clinical samples that grew *Streptomyces* were from patients with invasive infection. In that case, antimicrobial therapy should include 1 or 2 antibiotics among linezolid, amikacin, or imipenem.

**Keywords.** Actinobacteria; contamination; environment; invasive infection.

*Streptomyces* are filamentous gram-positive aerobic bacilli belonging to the *Actinobacteria* phylum that can be found in natural environments [1]. More than 650 species within the *Streptomyces* genus have currently been identified [2]. *Streptomyces* can cause actinomycetoma, a chronic subcutaneous infection resulting from repeated bacterial inoculation. Actinomycetoma has been described worldwide but has a higher prevalence in the “mycetoma belt” on both sides of the Tropic of Cancer, with >3 cases per 100 000 inhabitants in Mauritania [3]. *Streptomyces somaliensis* is the main species responsible for *Streptomyces* actinomycetoma and was identified in >10% of cases of mycetoma in a recent meta-analysis [3]. Actinomycetoma presents as a painless tumor often localized on the extremities [4, 5], but local extension may lead to severe complications when vital organs are invaded [6, 7].
In addition to these primarily cutaneous infections, *Streptomyces* can, rarely, be responsible for invasive infection, independent of any cutaneous trauma. Since 1951, 40 cases of invasive infection have been published, including a limited case series [8] (Supplementary Table 1). Most of these patients had underlying conditions, such as drug-induced immunosuppression, cancer, or hematological malignancies. The lungs were the most frequently involved organs, and chest imaging revealed nodules, lung consolidation, and interstitial changes [8–10]. The presence of foreign materials, a central venous catheter [11], and a prosthetic cardiac valve [12, 13] have also been reported. Identification of *Streptomyces* spp. in a clinical sample may also be related to environmental contamination during or after sample collection or to *Streptomyces* colonization of the patient’s airways.

The main objective of this study was to describe the microbiological diversity of *Streptomyces* isolates identified in human samples and their antibiotic susceptibilities. Secondary objectives were to describe the clinical characteristics, therapeutic strategies, and outcomes of a large cohort of patients with invasive *Streptomyces* infection and compare these factors with those in patients with *Streptomyces* colonization or contamination.

**METHODS**

**Study Design**

We conducted a retrospective study in France, including data related to all *Streptomyces* isolates identified in a human clinical sample that had been sent during the study period (2006–2017) to the Observatoire Français des Nocardioses (OFN), a French laboratory studying Actinobacteria through species identification and antibiotic susceptibility testing (AST) [14]; to ensure completeness, we also reached out to a French national network of microbiologists working in >200 general hospitals (Collège de Bactériologie, Virologie et Hygiène) and contacted every French infectious disease specialist through the Infecto-Flash mailing list. No additional cases were identified with these 2 latter strategies, suggesting that the vast majority of *Streptomyces* isolates are sent to the OFN. Nonhuman samples were excluded (n = 12).

For each *Streptomyces* isolate, we asked the microbiologist or infectious disease specialist at the hospital that had sent the sample to complete a standardized clinical record form.

**Microbiology**

After receipt of the microbiological sample at the OFN, genus identification was performed by a *Streptomyces*-specific polymerase chain reaction (PCR) based on amplification and detection of the gene encoding the 16S rRNA. *Streptomyces* DNA was extracted from bacterial colonies by the boiling method using achromopeptidase (10 U/mL, Sigma-Aldrich) [15]. AM42 (5= CAA GGG CAT CCA CCG T -3=) and AM44 (5= CTT CGG GGT GAT GGG ACT CAC -3=) primers were used to amplify a *Streptomyces* genus-specific 700-bp fragment of 16S rRNA [16]. Amplification was carried out using packaged PCR tubes (Ready-to-Go PCR beads, Amersham Biosciences, Orsay, France). Two hundred nanograms of DNA and primers, at a final concentration of 0.4 µM for each primer, was added, for a final volume of 25 µL of PCR mixture. Initial denaturation was then performed at 98°C for 5 minutes. After 30 cycles of denaturation at 95°C for 60 seconds, primer annealing at 45°C for 40 seconds, and extension at 72°C for 120 seconds, followed by postamplification extension at 72°C for 10 minutes, PCR products were purified using the E.Z.N.A. gel extraction kit (Omega Bio-Tek, Vaulx-en-Velin, France).

No guidelines are available for *Streptomyces* AST, but these bacteria share common features with *Nocardia*, including culture techniques. AST was therefore performed using the disk diffusion on cation-adjusted Mueller Hinton (CA-MH) agar plates, as previously described for *Nocardia* [14], upon request from the laboratory sending the sample. Inocula were prepared according to the Clinical Laboratory Standards Institute (CLSI) M24-A2 standard, and results were read after 72 hours of culture [14]. For each antibiotic disk, the diameter of the inhibition zone was recorded and compared with thresholds (Supplementary Table 2). *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Nocardia asteroides* ATCC 19247 T were used as quality control organisms. Resistant or intermediate isolates were considered “nonsusceptible” to the antibiotic in question. For trimethoprim-sulfamethoxazole, plates were read at 80% of growth inhibition following the same criterion as that used for *Nocardia* genus [17]. If resistance to trimethoprim-sulfamethoxazole was suspected (inhibition zone <10 mm) using the disk diffusion method, susceptibility was also assessed using an E-test strip placed on Muller-Hinton blood agar plates and read at 72 hours (Figure 1). An isolate was considered susceptible using this method if the trimethoprim-sulfamethoxazole minimum inhibitory concentration (MIC) obtained was ≤2/38 mg/L and resistant if the MIC was ≥4/76 mg/L.

**Clinical Data and Definitions**

For each *Streptomyces* isolate, we tried to complete a standardized clinical record (Supplementary Methods) including the following:

- Patient characteristics included age, sex, underlying diseases (eg, chronic pulmonary diseases, malignancies, or organ transplant before the date of sampling), and calculated Charlson Comorbidity Index score [18]. Patients with lung cancer were included in the chronic pulmonary disease category as this condition is frequently associated with local immunosuppression.
- Clinical presentation at the time of sampling included general symptoms (fever, chills), organ-specific symptoms, and
delay between symptom onset and diagnosis. Recorded blood markers included serum creatinine, leukocyte count, and C-reactive protein (CRP). Sample source and presence of other pathogens in the same sample were recorded. *Streptomyces* was considered a contaminant when present in a single sample with no clinical, radiological, or biological signs suggestive of infection. Colonization was defined when the *Streptomyces* isolate was isolated at least twice in a clinical sample from a patient with no sign of infection. Primary cutaneous *Streptomyces* infection was confirmed when cutaneous or subcutaneous infection followed direct inoculation from a wound, bite, or post-traumatic skin lesion. Invasive *Streptomyces* infection was diagnosed when there were signs of infection in an otherwise sterile site associated with a positive culture and no history of cutaneous inoculation. Disseminated infection was diagnosed when 2 noncontiguous organs were involved. Classifications were made by the physician completing the clinical record and 1 senior author (E.G.).

Therapeutic data included antibiotic regimen (duration and appropriateness [defined as at least 1 antibiotic with in vitro activity against the *Streptomyces* isolate]) and need for surgery. Relapse was defined as symptom recurrence after the end of treatment.

For *Streptomyces* isolates with no standardized clinical form completed, we extracted the patient’s sex and age at the time of sampling, type of clinical sample, and AST of the *Streptomyces* isolate from the clinical microbiology laboratory database.

**Statistical Analysis**

Median (extreme variables) or mean (SD) values are used for continuous variables. Categorical variables are expressed as numbers and percentages. We compared 2 groups of isolates: “invasive infection” and “no infection.” Because primary cutaneous *Streptomyces* infection following soil-contaminated wounds has already been comprehensively described in the literature and likely does not bear the same mechanism of
infection as invasive infection, we deliberately removed these cases from the analysis. Univariate analysis was conducted using the Fisher or chi-square test for categorical variables and the Student t test for continuous variables or the Wilcoxon-Mann-Whitney U test when a nonparametric test was required.

Ethics
The study was approved by the local ethics committee (Comité d’Éthique Necker-Enfants Malades reference 2018-DL10) and a national expert committee (Comité d’Expertise pour les Recherches, les Études et les Évaluations dans le Domaine de la Santé, reference TPS 95334) and was declared to the CNIL (Comité National de l’Informatique et des Libertés, reference MMS/OTB/AR1813447). Patients were informed of the present study by mail and could refuse to allow their data to be included in the study at any time. Patient confidentiality was ensured by anonymization of their clinical record.

RESULTS
Microbiological Diversity of Streptomyces Isolates In France
Between 2006 and 2017, Streptomyces was isolated from 137 samples at the OFN, which were included in the microbiological analysis (Table 1; Supplementary Table 3). The majority of the patients were men (91/131, 69.5%), and the median patient age (range) was 62 (47–75) years (Table 1). The lungs were the most frequent source of a positive culture (n=70, 51.9%); Streptomyces were isolated from blood cultures or an indwelling device in 24 (17.8%) and 6 cases (4.4%), respectively (Table 1).

On AST, all tested isolates were susceptible to linezolid (112/112) and amikacin (113/113) (Figure 2A). Most isolates were susceptible to imipenem (92.9%, 105/113); 52.1% (37/71) were susceptible to meropenem. Trimethoprim-sulfamethoxazole susceptibility results depended on the method chosen: 50.8% (57/112) of the isolates were susceptible using the disk diffusion method on CA-MH agar plates, but 69.4% (25/36) were susceptible to trimethoprim-sulfamethoxazole when isolates previously classified as resistant were tested again using an E-test strip on CA-MH-blood agar plates (Figure 2B). Twenty-one of the isolates identified as resistant using disk diffusion did not resume growth, so they could not be tested using the E-test. A majority of Streptomyces isolates were susceptible to tetracyclines, although most data were available for minocycline (94.7% susceptibility, n=113) (Figure 2A). Isolates were susceptible to moxifloxacin and ciprofloxacin in 96.0% (72/75) and 76.1% (86/113) of cases, respectively.

Description of the Population, Characteristics, and Outcomes of Patients With Invasive Infection
For the 137 Streptomyces isolates, we obtained complete clinical data for 63 patients (39 men [61.9%]; median age [range], 62.5 [1–92] years) from 25 hospitals (Table 2). The mean (SD) Charlson Comorbidity Index score was 3.8 (2.8). Twenty-four of the patients (38.1%) had chronic lung disease, and 4 patients (6.3%) had received a lung transplant. Nineteen patients had drug-induced immunosuppression (30.6%), 10 of whom (52.6%) were receiving >1 immunosuppressive drug. Corticosteroids were the main immunosuppressive drugs used (n=13, 20.9%); 9 patients (14.3%) had received a daily dose of >10 mg for >3 months (Table 2).

Invasive Streptomyces infection was diagnosed in 30 (47.6%) cases with no disseminated infection reported. Primary cutaneous infection, contamination, and respiratory colonization were diagnosed in 8, 22, and 3 patients, respectively.

| Characteristics | 137 Streptomyces Isolates |
|-----------------|---------------------------|
| Patients’ demographic data | |
| Age (n = 130), median [range], y | 62 [47–75] |
| Male (n = 131), No. (%) | 91 (69.5) |
| Country of origin, No. (%) | |
| France | 132 (97.9) |
| Other | 3 (2.1) |
| Site and method of sampling (n = 135), No. (%) | |
| Lung | 70 (51.9) |
| Sputum | 16 |
| Bronchial aspirate | 28 |
| Protected pulmonary sampleb | 20 |
| Lung biopsy | 4 |
| Pleural fluid | 2 |
| Blood cultures | 24 (17.8) |
| Skin and soft tissues | |
| Skin biopsy | 3 |
| Post-traumatic skin lesions | 6 |
| Cutaneous abscess | 4 |
| Bone and joint | 8 (5.9) |
| Bone biopsy | 4 |
| Open fracture | 2 |
| Otherc | 2 |
| Ears, eyes, nose, and throat | 6 (4.4) |
| External auditory canal | 2 |
| Nasal swab | 2 |
| Otherd | 2 |
| Cerebrospinal fluid | 2 (1.5) |
| Digestive tract | 3 (2.2) |
| Gastric tube | 2 |
| Gall bladder stone | 1 |
| Lymph node biopsy | 1 (0.7) |
| Heart and vesselsa | 2 (1.5) |
| Indwelling devicef | 6 (4.4) |

Abbreviation: PICC, peripherally inserted central catheter.

aOther countries: Belgium, Senegal, Netherlands.
bProtected pulmonary sample: broncho-alveolar lavage, protected bronchial brush.
cBone and joint other: joint fluid and hygroma aspirate.
dEars, eyes, nose, and throat other: maxillary sinus and corneal abscess.
eHeart and vessels: aortic biopsy, cardiac valve.
fIndwelling device: 1 of each: PICC-line catheter, spinal cord neurostimulator cable, peridural catheter, humeral fixation, aortic prosthetic, peritoneal dialysis fluid.

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Most of the cases of invasive Streptomyces infection were in men (n = 20, 66.7%), with a mean age (SD) of 60 (17) years, and a mean Charlson Comorbidity Index score (SD) of 3.6 (2.4) (Table 2). The main comorbidities were chronic lung disease (n = 14, 46.7%), solid tumor (n = 9, 30.0%), and solid organ transplantation (n = 4, 13.3%). Thirteen patients (n = 13, 43.3%) had drug-induced immunosuppression, including 11 patients who were receiving corticosteroid therapy (36.7%). For 17 (56.7%) patients, symptoms had started 7 days before diagnosis (mean [SD], 112 [187] days). The lungs were involved in 21 cases (66.6%), and 2 cases were related to an indwelling device (1 bioprosthetic cardiac valve and 1 aortic prosthesis). Dyspnea, cough, and sputum production were present in 12 (42.9%), 9 (30.0%), and 8 (26.7%) patients, respectively. Fatigue and fever were present in 9 (30.0%) and 6 (20.0%) patients, respectively. Among the 21 patients with pulmonary infection, the most frequent images on chest computed tomography (CT) scan were crazy paving (n = 7, 33.3%) and micronodules (n = 7, 33.3%). Eight patients (26.7%) were coinfected with other pathogens.

Twenty-eight patients received treatment (antibiotic only [n = 24], surgery only [n = 1], or antibiotic and surgery [n = 3]) for invasive Streptomyces infection (Supplementary Table 4). Antibiotic regimens included a beta-lactam (21/27, 77.7%), trimethoprim-sulfamethoxazole (12/27, 44.4%), amikacin (8/27, 29.6%), and fluoroquinolones (9/27, 33.3%). The antibiotic regimen was appropriate in 24/27 patients (88.8%). Twenty-one out of 27 patients (77.7%) received a multidrug regimen. The median antibiotic treatment duration (range) was 30.5 (7-365) days. At 6-month follow-up, 14 patients were cured, 3 had relapsed, 4 had died, and 9 were lost to follow-up. One patient relapsed at 8 months. The median follow-up period (range) was 12 (0–156) months.

Comparison of Patients With Invasive Streptomyces Infection and No Infection

There was no statistically significant difference in the proportion of patients with drug-induced immunosuppression among the patients with invasive infection and those with no infection (13/30 [43.3%] vs 6/25 [24.0%]; P = .224) (Table 2); patients with invasive infection were more frequently receiving corticosteroids (11/30 [36.7%] vs 2/25 [8.0%]; P = .03). There were no differences between groups in other causes of immunosuppression (solid organ transplant, solid cancer, hemopathy) or in chronic lung pathologies.
### Table 2. Characteristics of the 63 Patients With Clinical Data and Comparison of Patients With *Streptomyces* Invasive Infections and Those Without Infection (Isolates Considered Contamination \(n = 22\) or Colonization \(n = 3\))

| Characteristics                        | Total Population | Invasive Infection* | No Infection | \(P^*\) |
|----------------------------------------|------------------|---------------------|--------------|---------|
|                                        | \(n = 63\)       | \(n = 30\)          | \(n = 25\)   |         |
| **Demography**                         |                  |                     |              |         |
| Age                                    | 59 (20)          | 60 (17)             | 60 (24)      | .840    |
| Male                                   | 39 (61.9)        | 20 (66.7)           | 13 (52.0)    | .407    |
| **Comorbidities \(n = 62\)**          |                  |                     |              |         |
| Chronic lung disease\(^a\)             | 24 (38.7)        | 14 (46.7)           | 10 (40.0)    | .823    |
| Cardiovascular disease\(^d\)           | 17 (27.4)        | 9 (30.0)            | 6 (24.0)     | .847    |
| Solid tumor\(^a\)                      | 16 (25.8)        | 9 (30.0)            | 7 (28.0)     | .000    |
| Diabetes \(n = 61\)                    | 10 (16.4)        | 3 (10.3)            | 5 (20.8)     | .499    |
| Hematological malignancy\(^f\)         | 9 (15.5)         | 6 (20.0)            | 3 (12.0)     | .665    |
| Solid organ transplant                  | 5 (8.0)          | 4 (13.3)            | 1 (4.0)      | .467    |
| Moderate to severe kidney failure       | 2 (3.2)          | 1 (3.3)             | 1 (4.0)      | .000    |
| Charlson score                          | 3.7 (2.8)        | 3.6 (2.4)           | 4.3 (3.3)    | .407    |
| **Drug-induced immunosuppression \(n = 62\)** | 19 (30.6)        | 13 (43.3)           | 6 (24.0)     | .224    |
| Corticosteroids\(^g\)                  | 13 (20.9)        | 11 (36.7)           | 2 (8.0)      | .030    |
| Antimetabolites                         | 8 (12.9)         | 6 (20.0)            | 2 (8.0)      | .383    |
| Antineoplastic chemotherapy             | 8 (12.9)         | 4 (13.3)            | 4 (16.0)     | .000    |
| Anticalcineurin/mTOR inhibitor          | 8 (12.9)         | 7 (23.3)            | 1 (4.0)      | .101    |
| **Biological data**                     |                  |                     |              |         |
| CRP, mg/L                               | 79 [86]          | 87.8 [92.6]         | 86.1 [86.3]  | .952    |
| Leukocyte count, Giga/L                 | 8.9 [4.9]        | 7.9 [4.4]           | 9.8 [5.5]    | .202    |
| PMN, Giga/L                             | 6.8 [4.2]        | 5.8 [3.5]           | 7.8 [4.6]    | .136    |
| Lymphocytes, Giga/L                     | 1.5 [0.7]        | 1.3 [0.7]           | 1.6 [0.8]    | .284    |
| Creatinine, µmol/L                      | 92 [62]          | 88 [44]             | 98 [87]      | .731    |
| **Pulmonary samples**                   |                  |                     |              |         |
| Sputum culture                          | 5 (7.9)          | 2 (6.7)             | 3 (12.0)     | .830    |
| Bronchial aspirate                      | 15 (23.8)        | 8 (26.7)            | 7 (28.0)     | .000    |
| Bronchoalveolar lavage                  | 9 (14.3)         | 8 (26.7)            | 1 (4.0)      | .058    |
| Direct examination of the pulmonary sample | 18 (28.6)       | 7 (23.3)            | 7 (28.0)     | .932    |
| Coinfection                             | 26 (41.3)        | 8 (26.7)            | 12 (48.0)    | .225    |
| **Radiological findings**               |                  |                     |              |         |
| Chest TDM                               | \(n = 32\)       | \(n = 21\)          | \(n = 10\)   |         |
| Micronodules                            | 11 (34.3)        | 7 (33.3)            | 4 (40.0)     | .735    |
| Nodules                                 | 5 (15.6)         | 4 (19.1)            | 1 (10.0)     | .467    |
| Cavities                                | 4 (12.5)         | 4 (19.1)            | 0 (0.0)      | .844    |
| Alveolar pattern                        | 6 (18.75)        | 4 (19.1)            | 2 (20.0)     | .844    |
| Ground glass pattern                    | 10 (31.2)        | 7 (33.3)            | 3 (15.0)     | .463    |
| Pleural effusion                        | 2 (6.2)          | 1 (4.7)             | 1 (10.0)     | .000    |
| Normal                                  | 6 (18.75)        | 3 (14.3)            | 2 (20.0)     | .000    |
| Head imaging                            | \(n = 6\)        | \(n = 4\)           | \(n = 2\)    |         |
| Normal                                  | 4                | 2 (50.0)            | 1 (50.0)     | .000    |
| Other\(^h\)                             | 2                | 2 (50.0)            | 1 (50.0)     | .000    |

Data are presented as No. (%) or mean (SD).

*The 8 patients with primary cutaneous infection were not included in the statistical analysis.

Comparison of invasive *Streptomyces* infections with no infection in univariate analysis using the Fisher or chi-square tests for categorical variables and the Student \(t\) test for continuous variables or the Wilcoxon-Mann-Whitney \(U\) test when a nonparametric test was required.

\(^a\)Chronic lung diseases = 23 patients: chronic obstructive pulmonary disease = 9, bronchiectasis = 2, lung cancer = 4, asthma = 3, obstructive sleep apnea = 1, pulmonary hypertension = 1, cystic fibrosis = 1, Sweet syndrome = 1, mechanical ventilation for diphtheritic hemia = 1, lung surgery for prior lung cancer = 1, exuviscent lung = 1; 4 patients had >1 chronic pulmonary disease.

\(^b\)Cardiovascular diseases: myocardial infarction, congestive heart failure, obliterating arteriopathy, stroke.

\(^d\)Solid tumor: metastatic status = 4.

\(^f\)Hematological malignancies: lymphoma = 3, leukemia = 6.

\(^g\)Corticosteroids: >10 mg/d for 3 months = 9.

\(^h\)Other: findings not related to *Streptomyces* invasive infection.
For pulmonary samples, bronchoalveolar lavage cultures were positive in 8/30 (26.7%) patients with invasive infection compared with 1/25 (4.0%) in the no infection group ($P = .058$). There was no statistically significant difference between the groups in the percentage of direct examinations that were positive (7/30 [23.3%] vs 7/25 [28.0%]; $P = .932$) (Table 2).

**DISCUSSION**

In this retrospective analysis of 137 *Streptomyces* isolates, most frequently involved organ (20/30 cases, 66.6%), as previously reported (15/30, 50.0%) [8–10, 26]. *Streptomyces* pneumonia was diagnosed mainly from bronchoalveolar lavage samples in our cases and in previous reports [9, 10, 23, 24]. Because *Streptomyces* is an environmental pathogen, when invasive *Streptomyces* pulmonary infection is considered, deep specimen should be preferred over other lung samples to reduce the risk of contamination. The main lung CT scan features of invasive infection were crazy paving and micronodules, which is consistent with the previous literature [8, 10, 23, 24]. In addition to the pulmonary infections, we also had 2 cases of prosthetic endovascular infection, as also reported in the literature [12, 13]. Conversely, we had no cases of catheter-related bloodstream infection, although this forms part of the clinical spectrum of invasive *Streptomyces* infection [8, 11, 27, 28]. However, we were unable to obtain a clinical report form for 12/24 (50.0%) of the patients with *Streptomyces* BSI, and it is possible that some of them had catheter-related infection.

We had no cases of disseminated infection. However, compared with routine practice for *Nocardia* infection, imaging workup [29] is not systematic, so we are unable to draw definitive conclusions regarding the presence of disseminated infection.

A majority of the cases of invasive infection reported in the literature involved immunosuppressed patients. Most of these patients had systemic immunosuppression such as cancer [8, 11, 28], hemopathy [8], or drug-induced immunosuppression [27]. Other patients with lung involvement had local immunosuppression, either as a result of COPD or inhaled corticosteroids [9, 25]. By contrast with other reports, in our series, only half of the patients with invasive infection had ongoing, systemic, or local immunosuppression. Only corticosteroids were associated with invasive infection. Nonetheless, we cannot exclude that, given the small number of patients receiving systemic immunosuppressive drugs other than corticosteroids, our analysis was underpowered to detect a significantly higher rate of immunosuppression in the invasive infection group. Of note, no patient in the invasive infection group had undergone bone marrow transplant, and, interestingly, diabetes was not associated with invasive infection.

When identifying ramified gram-positive bacilli in a clinical sample from a patient with suspected ongoing infection, a multidrug regimen active against *Nocardia*, *Streptomyces*, and other gram-positive bacilli may be considered. In our series, linezolid, imipenem, and amikacin covered almost 100% of the *Streptomyces* isolates and would be active against most *Nocardia* isolates as well [14].

Treatment duration relies on the clinical resolution of symptoms, the organ involved, and associated complications. Overall, our data suggest that shorter antimicrobial duration may be necessary compared with treatment of *Nocardia* infections, with few relapses in our patients (13.6%) despite an average treatment duration of just 30 days. In the literature, a treatment duration of about 6 months was reported for most patients [9, 10, 30], although 4 patients had a 6-week course of treatment [12, 13, 24, 28]. All patients with known follow-up were cured, except for 3 [8, 11, 27].

We compared patients with invasive infection with those with no infection to identify factors that could help the physician to distinguish these 2 scenarios. In contrast to the previous literature, in our study a positive direct microscopic examination did not differ in these 2 subgroups. A previous report from Kapadia and coworkers suggested that clinical specimen with a positive direct Gram staining were more frequently *Streptomyces* infection (rather than contamination or colonization) [8]. However, direct examination may be difficult, as illustrated by a case report in which a negative initial direct
examination was later corrected after culture positivity for _Streptomyces_ [19]. In this comparison, we decided to exclude primary cutaneous _Streptomyces_ infections as we assumed that their mechanism of infection is different than invasive infection. Furthermore, the clinical diagnosis of primary cutaneous infections is less challenging considering the available literature in this field, although microbiological diagnosis of actinomycetoma remains difficult.

Our study has several limitations. As with any retrospective study, memory biases were present. To limit classification biases, cases were discussed between the physician completing the clinical record and the principal investigator when needed. Given the rareness of the infection, a prospective study to counteract the mentioned biases cannot be reasonably considered.

In conclusion, we report the largest series to date of 30 invasive _Streptomyces_ infections, along with antibiotic susceptibilities of 113 _Streptomyces_ isolates. When such an infection is considered, first-line antimicrobial therapy should include linezolid, imipenem, or amikacin, to which the isolates were most likely to be susceptible. Optimal treatment duration could be shorter than for _Nocardia_ infection, but further data are needed to determine the appropriate management of invasive _Streptomyces_ infection in terms of antibiotic choice(s) and duration. In addition, when the disk diffusion method is used for AST and trimethoprim-sulfamethoxazole resistance is suspected, a second attempt should be made using the E-test method with a lecture criterion set at 80% of inhibition to confirm this observation.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Acknowledgments**

The authors would like to thank Fatima Zohra DIJEUAT for their help with data collection. The authors would like to thank Karen Pickett for her editorial assistance.

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**Financial support.** David Lebeaux was supported by the following grant: Bourse Junior 2015—Société de Pathologie Infectieuse de Langue Française (SPIFLF).

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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