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## ***Exserohilum*: an emerging human pathogen**

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**Abstract** *Exserohilum* is a dematiaceous fungus that may cause a spectrum of diseases in humans, including skin and corneal infection, invasive disease, and allergic fungal sinusitis. The aim of this work is to describe two new cases of *Exserohilum* infection and to review the literature. The review yielded 33 cases of *Exserohilum* infection, of which 23 were reported since 1993. Most occurred in regions with hot climates, such as India, Israel, and the southern USA. Impaired immunity was present in the majority of patients with invasive and skin infections, whereas local trauma and atopy were the predisposing factors in those with corneal infections and allergic fungal sinusitis, respectively. Surgical debridement was the principal mode of therapy for allergic fungal sinusitis. Amphotericin B was the initial

single antifungal agent used in all cases of invasive disease; the response rate was low but improved with the addition of triazole agents. Outcome appeared to be better than for other mold infections and depended mainly on the underlying diseases.

### **Introduction**

Phaeohyphomycosis is a group of systemic dematiaceous fungal infections characterized by the presence of dark septate mycelial elements in tissue [1]. More than 100 species and 60 genera of fungi have been reported to cause phaeohyphomycosis [2]. These include three species of the genus *Exserohilum*, *Exserohilum rostratum*, *Exserohilum longirostratum*, and *Exserohilum mcginnisii*. *Exserohilum* may infect both immunocompromised and immunocompetent hosts with variable clinical manifestations, ranging from cutaneous infections to fulminant disseminated disease.

During the last decades, there has been an increase in the number of reported cases of *Exserohilum* infection [3]. In this article, we present two new cases, including the first report of successful treatment of invasive infection with voriconazole, and review the expanding literature.

### **Patients and methods**

#### Case 1

An 8-year-old girl with acute lymphoblastic leukemia (ALL) presented with persistent epistaxis from the right nares without fever. The diagnosis of leukemia had been made 40 days previously, and induction chemotherapy with prednisone, vincristine, daunorubicin, L-asparaginase, and intrathecal methotrexate was initiated, along with prophylactic antimicrobial therapy with trimethoprim-sulphamethoxazole. Severe neutropenia (absolute neutrophil count <500 cells/μl) had been present until 5 days prior to presentation. The patient had had three episodes of

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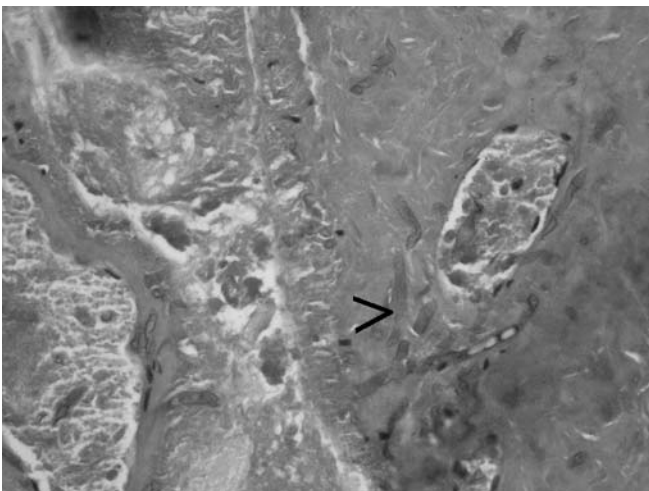
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neutropenic fever of undetermined cause that were treated with piperacillin-tazobactam and amikacin.

Fiberoptic endoscopic sinus surgery for evaluation of the nasal bleeding revealed a necrotic lesion with blood clots on the right nasal septum. Computerized tomography (CT) of the paranasal sinuses showed mucosal thickening without bone destruction. On microscopic examination of the biopsy specimen, hyphae were noted within the mucosal stroma and blood vessels, which were stained positive for periodic acid-Schiff (Fig. 1) and silver methenamine. Fungal culture of the paranasal sinuses on Sabouraud dextrose agar yielded dark colonies with a velvet-like surface. Microscopic examination revealed sympodial conidiophore and ellipsoidal, darkly-pigmented conidia with a protruding, truncate hilum, characteristic of *Exserohilum* species. Treatment with intravenous amphotericin B (AmB) was started. Chest CT scan identified two nodular lesions measuring 1 cm in diameter in the right upper lobe. As the nasal bleeding persisted after 9 days of AmB treatment, intravenous voriconazole 100 mg two times per day was added, and AmB was discontinued 4 days later. Six days after initiation of voriconazole, repeated fiberoptic endoscopic sinus surgery revealed a small hole in the left nasal septum and exposed bone in the right nasal floor. Repeated chest CT showed enlargement of the previous pulmonary lesions and several new ones. Two weeks after voriconazole was started, the nasal lesions began to improve and the bleeding ceased. The nasal mucosa healed completely after 6 weeks of treatment, and the pulmonary lesions decreased. The patient was treated with oral voriconazole for an additional 3 months (for a total period of 19 weeks), with reinstatement of therapy during periods of neutropenia. She has now been in remission for over a year, under maintenance treatment with 6-mercaptopurine and methotrexate.



**Fig. 1** Septate hyphae of *Exserohilum* species (arrowhead) invading a blood vessel wall of the paranasal sinus mucosa (periodic acid-Schiff stain,  $\times 400$ )

## Case 2

A 3-year-old girl with ALL presented with swelling of the left lower eyelid. The diagnosis of leukemia had been made 26 days previously, and induction chemotherapy along with prophylactic antimicrobial therapy with trimethoprim-sulphamethoxazole was initiated. Severe neutropenia had been present during the treatment period, and the patient received piperacillin-tazobactam and amikacin for a total of 13 days because of neutropenic fever with left lower lobe pneumonia.

Eight days later, a swelling appeared in the left eyelid, and 3 days later, two black lesions in the soft palate were noted. CT scan of the paranasal sinuses showed erosion in the medial wall of the left maxillary sinus and soft tissue thickening without intracranial or orbital involvement. Findings on chest radiograph and abdominal sonogram were normal. Treatment with piperacillin-tazobactam, amikacin, and AmB was started. One day later, fiberoptic endoscopic sinus surgery was performed, with debridement of the necrotic tissues from the left nasal floor, middle concha, and ethmoidal sinus. After microscopic examination of the biopsy specimens showed hyphae within the blood vessels and the necrotic tissue, antibacterial therapy was withheld. At that time, the severe neutropenia resolved. Ten days later, necrotic lesions were still present in the nasal floor, an ulcer appeared in the soft palate, and CT scan showed worsening of the previous lesions. Antifungal treatment was switched from AmB to liposomal AmB at a dose of 6 mg/kg, and itraconazole was added. Repeated surgical debridement of the soft palate and the nasal floor was performed, resulting in a hole between the oral and nasal spaces. After 2 weeks, fungal culture identified the mold as *Exserohilum* (as described in case 1). Repeated examinations and biopsy of the nasal and oral mucosa showed granulation tissue with no signs of active infection. At 2 months from onset of the infection, the patient continued to receive oral itraconazole. The ALL was found to be associated with an 11q23 rearrangement, and allogeneic cord-blood stem-cell transplantation was successfully performed 9 months after diagnosis. The hole in the soft palate was closed surgically. The patient has now been in remission for over 3 years.

## Literature review

We performed a PubMed search of the English-language literature from 1950 to the present for all cases of human *Exserohilum* infections. The key words used in the search were *Exserohilum* and *Drechslera*. The following data were collected: year of report; *Exserohilum* species and antifungal susceptibility pattern (when recorded); patient age, sex, and country of origin; predisposing conditions or precipitating events; infection type; treatment; and outcome. Cure was defined as resolution of all infection-related symptoms and findings, without relapse during the outlined follow up.

*Exserohilum* infections were divided into two groups: invasive and noninvasive infections. Noninvasive infections were subdivided according to the main site of infection: solitary skin infections, corneal infections, and chronic sinusitis (cases of sinusitis were categorized as acute-invasive or chronic [4]).

Isolates originally reported to be *Drechslera* species were included in the present study, since these reports probably represent a misidentification or obsolete classification of *Exserohilum* infections [3].

## Results

Thirty-three cases of *Exserohilum* infection were found: 20 *E. rostratum*, 2 *E. longirostratum*, and 1 *E. mcginnisii*; in 10 cases, the species was not defined (Tables 1, 2, 3). The

first case was reported in 1975, and 23 cases were reported after 1993. Thirteen (39%) patients were less than 18 years old. Most of the invasive infections (7 of 10, Table 1) occurred in children. Although the cases originated worldwide, the majority were reported from India (five cases), Israel (six cases), and the USA (16 cases), almost all from southern or southwestern states.

### Invasive infections

There were ten cases of invasive infection (Table 1), located most commonly in the paranasal sinuses (seven cases) or lungs (five cases, four of them combined with paranasal sinus infection). Thus, the major mode of transmission was probably by inhalation. Other sites were bone and soft tissues (three cases), brain (one case), and

**Table 1** Characteristics of patients with invasive *Exserohilum* infection

Patient number [ref.]	Age (y)/ sex	<i>Exserohilum</i> species	Country/ year of report	Underlying disease and predisposing factors	Sites of infection	Therapy (antifungal susceptibility; duration)	Outcome
1 [5]	12/ M	<i>rostratum</i> <sup>a</sup>	Western USA/1980	None	Bone	Surgery, local and systemic AmB <sup>c</sup>	Cure
2 [6]	20/F	<i>longirostratum</i> <sup>b</sup>	France/1983	Surgical correction of congenital VSD and AI	Endocarditis, vertebral osteomyelitis	AmB, keto (72 h MFC=1 µg/ml for both; 10 months), surgery	Cure
3 [7]	63/ M	<i>rostratum</i>	Israel/1987	AML; antimicrobial and chemotherapy; neutropenia	Skin (cutaneous), nasal mucosa	AmB (2 months)	Cure
4 [8]	5/F	<i>rostratum</i>	Texas, USA/1990	Aplastic anemia; cytotoxic therapy	Paranasal sinuses, soft tissue	AmB (48 h MIC<0.14 µg/ml), itra (48 h MIC<0.02 µg/ml)	Progression, death due to bacterial sepsis
5 [9]	16/ M	NR	South Africa/1993	None	Skin (subcutaneous), lung, brain	AmB (total dose 2.5 g), 5-flu	Cure
6 [10]	7/F	<i>rostratum</i>	Texas, USA/1994	Aplastic anemia	Paranasal sinuses, lungs	AmB	Death
7 [11]	41/F	NR	Israel/2004	AML	Paranasal sinuses, lungs	AmB, itra	Failed, death due to bacterial sepsis
8 [12]	8/M	NR	Israel/2003	ALL, antimicrobial and chemotherapy; neutropenia	Skin (cutaneous), Paranasal sinuses, lungs	AmB, itra (5 months)	Cure; death due to malignancy and <i>Fusarium</i> infectioir
9 [PR]	8/F	NR	Israel/2005	ALL; antimicrobial and chemotherapy; neutropenia	Paranasal sinuses, lungs	AmB, voriconazole (9 months), surgery	Cure
10 [PR]	3/F	NR	Israel/2005	ALL; antimicrobial and chemotherapy; neutropenia	Paranasal sinuses, soft palate	AmB, itra (13 months), surgery	Cure

PR present report, VSD ventricular septal defect, AI aortic insufficiency, AmB amphotericin B, keto ketoconazole, MFC minimum fungicidal concentration, 5-flu 5-flucytosine, AML acute myelogenous leukemia, MIC minimum inhibitory concentration, itra itraconazole, ALL acute lymphoblastic leukemia, voriconazole, NR not reported

<sup>a</sup>Isolate originally reported as *Drechslera rostrata*

<sup>b</sup>Isolate originally reported as *Drechslera longirostrata*

<sup>c</sup>Therapy was required intermittently for frequent recurrences of the infection up to 8 years after presentation

**Table 2** Characteristics of patients with *Exserohilum* skin and corneal infections

Patient number [ref.]	Age (y)/sex	<i>Exserohilum</i> species	Country/year of report	Underlying diseases and predisposing factors	Sites of infection	Therapy (antifungal susceptibility; duration)	Outcome
11 [3]	34/F	<i>rostratum</i>	Calif., USA/1986	Cardiac transplantation; immunosuppression	Skin (subcutaneous)	AmB, keto, surgery	Cure
12 [13]	55/F	<i>rostratum</i>	S. Carolina, USA/1987	Fish sting	Skin (subcutaneous)	Surgery, keto (6 weeks)	Cure
13 [14]	3/M	<i>rostratum</i>	Tenn., USA/1991	ALL; antimicrobial and chemotherapy; neutropenia; local cloth tape	Skin (cutaneous)	AmB (24 h MIC=0.39 µg/ml; 1 mon.), 5-flu (24 h MIC >20 µg/ml; 2 weeks)	Cure
14 [15]	74/M	<i>rostratum</i>	Texas, USA/1991	COPD; steroid therapy	Skin (cutaneous)	Keto+topical clotrimazole (6 weeks)	Cure
15 [16]	63/M	<i>rostratum</i>	Taiwan/1993	Diabetes; local trauma	Skin (subcutaneous)	Keto (3 weeks)	No improvement, death due to bacterail sepsis
16 [16]	31/M	<i>rostratum</i>	Taiwan/1993	Topical steroids for psoriasis	Skin (cutaneous)	Topical bifonazole (2 weeks)	Cure
17 [17]	22/M	<i>rostratum</i>	Va., USA/1993	Superficial lacerations; cocaine use, MOF	Skin (cutaneous)	AmB	Death due to MOF
18 [18]	40/F	<i>rostratum</i>	India/1995	None	Skin (cutaneous)	None	Unknown
19 [19]	NR/NR	<i>rostratum</i> <sup>a</sup>	Fla., USA/1975	None	Cornea	Topical gentamicin	Cure
20 [20]	40/F	<i>rostratum</i>	India/1991	Rt. eye injury from a paddy leaf	Cornea	Topical keto	No improvement
21 [21]	47/M	<i>longirostratum</i>	Honduras/1994	Left eye struck by unknown foreign body during train riding	Cornea and uvea	Surgery, keto	Cure following enucleation
22 [22]	55/M	<i>rostratum</i>	India/1996	Lash injury to rt. eye by cow's tail	Cornea	Topical nata+mico (6 weeks)	Cure (vision 6/18)
23 [23]	42/M	<i>rostratum</i>	India/1999	None	Cornea	Surgery, topical keto+nata	Cure (vision 6/18)
24 [24]	18/F	<i>rostratum</i>	India/2004	None	Cornea	Topical itra	Cure

AmB, amphotericin B, *keto* ketoconazole, *MIC* minimum inhibitory concentration, *ALL* acute lymphoblastic leukemia, *5-flu* 5-flucytosine, *COPD* chronic obstructive pulmonary disease, *MOF* multiorgan failure, *mico* miconazole, *NR* not reported

<sup>a</sup>Isolate originally reported as *Drechslera halodes*

heart valves (one case). In none of the cases were the fungi isolated in blood cultures. Seven patients were immunocompromised due to hematologic malignancy or aplastic anemia combined with cytotoxic therapy. One patient developed endocarditis following cardiac surgery, and in two patients, no risk factor was identified.

#### Noninvasive infections

There were eight cases of solitary skin infection (five cutaneous, three subcutaneous) (Table 2) and three cases of skin infection combined with invasive infection (Table 1). Skin lesions were diverse, and included papules and

plaques (usually with black discoloration), vesicles, nodules, and ecthyma gangrenosum. Three patients acquired the infection following local trauma, and six patients were immunocompromised or had significant systemic diseases (e.g., diabetes). In one case, no risk factor was identified.

There were six cases of corneal infection, three of them following local trauma (Table 2). None of the patients with corneal infection had immunodeficiency or severe systemic disease.

There were nine cases of chronic sinusitis, of which five were defined as allergic fungal sinusitis (AFS). Two of the five patients with AFS had predisposing factors. Of the other four patients in this group, three had nasal polyps or previous allergic disorders. The infection extended beyond

**Table 3** Characteristics of patients with chronic sinusitis due to *Exserohilum*

Patient number [ref.]	Age (y)/sex	<i>Exserohilum</i> species	Country/year of report	Underlying diseases	Therapy (antifungal susceptibility; duration)	Outcome
25 [25]	10/M	<i>rostratum</i>	Ariz., USA/1986	Allergic rhinitis	Surgery, AmB (48 h MIC=0.58 µg/ml; 6 weeks)	Cure
26 [25]	25/M	NR	Ariz., USA/1986	Nasal polyps	Surgery	Improvement
27 [26]	27/M	<i>mcginnisii</i>	Ariz., USA/1986	Allergies, nasal polyps	Surgery	Cure
28 [27]	19/M	<i>rostratum</i>	Caribbean area/1990	None	Surgery, keto (1 month)	Cure
29 [28] <sup>a</sup>	11/M	NR	Texas, USA/1991	Asthma	Surgery	Cure
30 [29] <sup>a</sup>	31/M	NR	Texas, USA/1991	NR	Surgery	Cure
31 [30] <sup>a</sup>	34/F	NR	Texas, USA/1996	None	Surgery	Cure
32 [30] <sup>a</sup>	11/M	NR	Texas, USA/1996	Asthma	Surgery	Cure
33 [31] <sup>a</sup>	15/M	<i>rostratum</i>	Israel/2002	None	Surgery, AmB (12 days)	Cure

AmB amphotericin B, MIC minimum inhibitory concentration, NR not reported, keto ketoconazole

<sup>a</sup>Cases originally reported as allergic fungal sinusitis

the paranasal sinuses in two cases (to the orbit, case 33, and intracranially as mucocoeles, case 28). Tissue eosinophilic infiltrates were reported in all except one patient (case 28). Only one patient (case 27) had histological evidence of tissue invasion. This case was included because it resembled AFS in all other aspects: patient's history of atopy, chronic course (several months) of the infection, presence of eosinophilic infiltrates, and lack of extra-sinus extension.

#### Treatment and outcome

The modes of therapy differed according to the type of infection. Invasive infections (ten cases) were always treated with systemic antifungal agents; four (40%) of these infections required surgical procedures. AmB was the initial agent in all cases but was successful in only three of them. In four cases, the infection resolved only after azole compounds (itraconazole in two cases, ketoconazole in one case, and voriconazole in one case) were added. In three of these cases, the infection persisted despite the addition of itraconazole in two of them, including one case in which the MIC of the isolate for both drugs was low (case 4). *Exserohilum* infection was the probable direct cause of death in one patient (case 6); another three patients died of other infections. The duration of systemic antifungal therapy was prolonged, from 2 to 13 months.

Skin infections were managed with systemic drugs, with or without topical antifungal agents, in all patients except one who was lost to follow-up (case 18) and one who was treated successfully with topical bifonazole (case 16). Surgery was required in two patients with subcutaneous infections.

Corneal infections were managed with topical antifungal agents in all patients except one, who was successfully treated with systemic ketoconazole. Two patients required surgical intervention. All patients with skin and corneal infections recovered except two who died of unrelated causes (cases 15 and 17) and two who refused treatment and were lost to follow-up (cases 18 and 20). In case 21, enucleation was performed, owing to an erroneous initial diagnosis of zygomycete infection.

All nine cases of chronic sinusitis were managed surgically, usually with fiberoptic endoscopic sinus surgery or Caldwell–Luc procedure. Only three patients, one reported to have AFS, were treated with systemic antifungal agents for 12 days to 6 weeks. None of the patients with chronic sinusitis received systemic steroids. Outcome was good in all cases.

#### Discussion

We presented two new cases of invasive *Exserohilum* infection in immunocompromised children and reviewed the relevant literature. *Exserohilum* is a filamentous fungus that belongs to the *Pleosporaceae* family. Related genera are *Alternaria*, *Bipolaris*, and *Drechslera* [32]. The diagnosis of *Exserohilum* infections is based primarily upon the morphologic findings [1]. *Exserohilum*, like its related genera, is characterized by a sympodial conidiophore. It has an ellipsoidal to fusoid conidium and, more specifically, a protruding, truncate, pigmented hilum [3]. The dark pigmentation is caused by deposition of dihydroxynaphthalene melanin [12].

*Exserohilum* is mainly a terrestrial plant pathogen, but it can also be found in marine environments [33]. Although

commonly considered a cosmopolitan pathogen [12], the results of our review show that human *Exserohilum* infections occur mainly in warm, tropical, and subtropical areas such as the southern USA, India, and Israel. Interestingly, southern Israel was also the source of two recently discovered species of *Exserohilum*, *Exserohilum israeli* [34] and *Exserohilum sodomii* [35]. In their review of disseminated phaeohyphomycosis, Revankar et al. [2] failed to find a similar pattern of geographic distribution, although Ferguson et al. [36] noted an increased incidence of AFS in the southern states and the Mississippi basin compared to other parts of the USA. As the analysis in the latter study did not show a correlation between the regional mold counts and the incidence of infection, the geographic difference in prevalence could be related to a climate-induced alteration in the physiology of the mold, which renders it more pathogenic to humans.

Almost all of the cases identified in our review were reported within the last 2 decades. Although this increased trend of *Exserohilum* infection is usually attributed to the increase in the number of immunocompromised patients [1–3, 37], we found that many of the patients had normal immune function. Therefore, we believe the increase may also be related to a heightened awareness of this infection in humans and improved diagnostic techniques.

Our study showed that the different types of *Exserohilum* infections are associated with distinct clinical presentations and modes of therapy. Invasive infections, most commonly of the respiratory tract, affected mainly immunocompromised patients. Apparently, the mode of transmission in these cases was inhalation, sometimes with hematogenous spread to other sites (brain, bone, skin). Blood cultures were negative for *Exserohilum* in all cases, unlike findings for other agents of phaeohyphomycosis [2] but similar to those for *Aspergillus* [38]. The management of patients with invasive disease included prolonged courses of systemic antifungal agents and, if feasible, surgery. Outcome appeared to be better (attributed mortality of 30% in invasive infections) than for other mold infections [2, 38, 39] and depended mainly on the underlying diseases.

About half the skin and corneal infections followed local trauma. The majority of patients with skin infection were immunocompromised, whereas the patients with corneal infection had no systemic diseases. Skin infections were usually treated with systemic antifungal agents, whereas corneal infections were treated with topical agents. The prognosis was good in most cases. The clinical features and disease course resembled those of other dematiaceous and *Aspergillus* infections of the skin [38, 40] and cornea [38, 41].

All five cases of chronic sinusitis reported after 1991 were defined as AFS, in contrast to the four cases reported from 1986 to 1990. Nevertheless, there were many similarities in these two subgroups in patient characteristics (history of allergies or nasal polyps and lack of immunodeficiency), clinical features (one case of extension beyond the sinuses in each subgroup), histological findings (tissue eosinophil infiltrates and lack of invasion, except in one

case), therapy (surgery; systemic antifungal agents were administered to a few patients in each subgroup), and outcome (full recovery). Chronic fungal sinusitis can be divided into three forms: AFS, chronic invasive disease, and fungal ball. The first two forms share many clinical, microbiologic (dematiaceous fungi are the most common cause of both), and histological features, so the distinction depends on the presence of tissue invasion [4]. Today, most cases of chronic sinusitis reported from the USA are defined as AFS, whereas the chronic invasive disease is endemic to Sudan and northern India [4]. Therefore, we believe that all nine cases in our review were probably AFS. All of them also resembled AFS caused by other fungi [28, 30]. Since surgical debridement is the principal treatment for both forms, the distinction is important only for decisions regarding the need for systemic antifungal agents [4]. Judging from the cases presented, it appears that surgical therapy is sufficient in *Exserohilum* AFS, but it is prudent to add systemic antifungal agents in cases of tissue invasion or disease extension beyond the sinuses. Systemic steroids were not used in any of the patients reported, and therefore are probably not necessary.

In addition to paranasal sinus infections, surgery was required in other invasive infections (bone and cardiac valve) as well as in subcutaneous infections and in two of the corneal infections, similar to other mold infections [2, 38]. Regarding medical therapy, AmB was considered the drug of choice for *Exserohilum* infection [10, 25] and was initially administered to all patients with invasive disease. However, as reported also for disseminated phaeohyphomycosis [2] or invasive aspergillosis [38], the response rate was low, despite apparent sensitivity in one case (case 4). Drawing from our own experience (cases 8–10), the triazoles (itraconazole and voriconazole) seem to have better activity against *Exserohilum*, although itraconazole combined with AmB failed in two of the reported cases (cases 4 and 7). Unfortunately, antifungal susceptibility testing was performed in only four of the cases that were treated with systemic antifungal medications (cases 2, 4, 13, and 25). Therefore, it is impossible at this point to deduce in vitro–in vivo correlations, and hence the data are insufficient to support recommendation of any single agent as initial therapy. We hope that as standardized techniques for susceptibility testing become more readily available, in vitro findings may aid the clinician in making therapeutic decisions, and in vivo correlations will then be possible.

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