Clinical Characteristics, Diagnosis, Management, and Outcomes of Disseminated Emmonsiosis: A Retrospective Case Series

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Background. We describe the geographic distribution, clinical characteristics, and management of patients with disease caused by Emmonsia sp., a novel dimorphic fungal pathogen recently described in South Africa.

Methods. We performed a multicenter, retrospective chart review of laboratory-confirmed cases of emmonsiosis diagnosed across South Africa from January 2008 through February 2015.

Results. Fifty-four patients were diagnosed in 5/9 provinces. Fifty-one patients (94%) were human immunodeficiency virus coinfected (median CD4 count 16 cells/µL [interquartile range, 6–40]). In 12 (24%) of these, antiretroviral therapy had been initiated in the preceding 2 months. All patients had disseminated disease, most commonly involving skin (n = 50/52, 96%) and lung (n = 42/48, 88%). Yeasts were visualized on histopathologic examination of skin (n = 34/37), respiratory tissue (n = 2/4), brain (n = 1/1), liver (n = 1/2), and bone marrow (n = 1/15). Emmonsia sp. was cultured from skin biopsy (n = 20/28), mycobacterial/fungal and aerobic blood culture (n = 15/25 and n = 9/37, respectively), bone marrow (n = 12/14), lung (n = 1/1), lymph node (n = 1/1), and brain (n = 1/1). Twenty-four of 34 patients (71%) treated with amphotericin B deoxycholate, 4/12 (33%) treated with a triazole alone, and none of 8 (0%) who received no antifungals survived. Twenty-six patients (48%) died, half undiagnosed.

Conclusions. Disseminated emmonsiosis is more widespread in South Africa and carries a higher case fatality rate than previously appreciated. Cutaneous involvement is near universal, and skin biopsy can be used to diagnose the majority of patients.

Keywords. Emmonsia sp.; emmonsiosis; AIDS-related mycosis; endemic mycosis; dimorphic fungi.

Emmonsia sp., a novel, pathogenic, dimorphic fungus, was recently described as the cause of disseminated disease in 13 patients with advanced human immunodeficiency virus (HIV)–related immunosuppression in South Africa, 12 of whom were from Cape Town, Western Cape Province [1]. Five more cases have since been reported, including 2 HIV-uninfected patients from Cape Town [2] and 3 HIV-associated cases from Johannesburg [3].

Very little is known about Emmonsia sp. or the disease caused by this fungus. The objective of the current study was to describe the geographical distribution, clinical presentation, diagnostic findings, and management of the first 54 patients with disseminated emmonsiosis in South Africa.

METHODS

We conducted a multicenter, retrospective chart review of patients diagnosed with emmonsiosis in South Africa...
between July 2008 and February 2015. A case of emmonsiosis was defined as a patient with a clinically compatible illness and laboratory confirmation of infection with *Emmonsia* sp., identified either by culture or nucleic acid detection from a clinical specimen. We defined dissemination as multifocal disease that involved extrapulmonary sites.

Cases were passively identified by the National Institute of Communicable Diseases, which provides a national reference mycology service, and Ampath National Laboratory Services, a private laboratory group with national coverage. Cultured isolates were confirmed as *Emmonsia* sp. with a broad-range fungal polymerase chain reaction (PCR) and sequencing of the internal transcribed spacer region or based on phenotypic characteristics of colonies based on macroscopic and microscopic examination by an experienced mycologist [1].

The suppliers for the microbiological tests used were BACTEC Myco/F Lytic (Becton Dickinson, Franklin Lakes, New Jersey) for mycobacterial/fungal blood cultures, IMMY kit (Immuno-Mycologics, Norman, Oklahoma) for urine Histoplasma antigen test, and Fungitell (Associates of Cape Cod Inc., East Falmouth, Massachusetts) for 1,3-β-D-glucan.

Charts were reviewed for clinical details. Data collected included demographics, history of previous medical conditions including HIV and coinfections, details of clinical presentation, diagnostic investigations, management, and outcomes. Initial clinical diagnoses were noted from consultation notes and laboratory requisitions, where applicable.

Fisher exact test was used for comparisons of categorical variables, and the Mann–Whitney U test was used for comparisons of nonparametric variables with a level of significance of .05. No corrections were made for multiple testing. All analyses were conducted with SPSS version 22.0 (IBM Corp., Armonk, New York).

Patients consented to publication of facial photographs. The human research ethics committees of the Universities of Cape Town and the Witwatersrand approved this study.

**RESULTS**

Fifty-four patients with emmonsiosis were identified, among whom 18 were previously reported [1–3]. All had disseminated disease. In 52 patients, *Emmonsia* sp. was cultured from a clinical specimen; identification was by nucleic acid sequencing in 49 of these, and based on phenotype alone in 3 others. In 2 patients, the diagnosis was made by detecting *Emmonsia* sp. nucleic acid directly from skin tissue.

Full details of each case are provided in Supplementary Table 1. Select demographic and historical details of patients are summarized in Table 1. The distribution of patients by geography and healthcare sector where diagnosed is illustrated in Figure 1. Results of routine laboratory and radiographic investigations are summarized in Table 2; histopathology and microbiology results are summarized in Table 3.

Fifty-one patients (94%) were HIV infected. Of 3 HIV-uninfected patients, 1 was receiving immunosuppressants following renal transplantation, and 2 had no apparent cause for immunodeficiency (clinical features of the 2 immunocompetent patients are shown in Figure 2). Of HIV-infected patients, the median CD4+ T-cell lymphocyte count was 16 cells/µL (interquartile range [IQR], 6–40). Eleven patients were newly diagnosed with HIV infection at the time of presentation.

HIV-1 viral load measurements were available for 28 of 51 HIV-infected patients, including 18 of 27 patients on antiretroviral therapy (ART) and 10 of 24 not on ART at presentation. Viral suppression (<50 copies/µL) was achieved in just 1 patient. Among the remaining HIV-infected patients, the median viral load was 5.9 log10 copies/µL (IQR, 4.3–6.2). There was no difference in the viral loads of patients according to ART status (P = .07).

In 12 patients, ART had been either initiated or changed from a failing regimen within the preceding 2 months. All had cutaneous lesions, and these appeared after ART initiation in 11 patients. In 1 patient in whom cutaneous lesions preceded ART initiation, the lesions became more numerous and larger on ART. Cutaneous lesions were also present in 22 of 24 HIV-infected patients not on ART (and unknown for 1).

In total, cutaneous lesions were present in 50 of 52 patients (96%) where this was ascertained. The distribution of lesions was generalized in 43 (86%) and limited in 7 (14%). Documented cutaneous lesions could morphologically be grouped as follows: papules (n = 28), plaques (n = 12, including infiltrated [n = 7]), purulent crusted hyperkeratotic [n = 2], scaly [n = 2], and verrucous plaques [n = 1]), nodules (n = 3), ulcers (n = 1), and hyperpigmented patches (n = 1) (see Figure 3 for mucocutaneous lesions in HIV-associated emmonsiosis; additional clinical photographs are shown in Supplementary Figure 1). In 5 patients, the lesions were not adequately described for classification. The median estimated duration of cutaneous lesions at diagnosis was 4 weeks (IQR, 2–8).

**Table 1. Select Demographic and Health Characteristics at the Time of Diagnosis for 54 Patients With Disseminated Emmonsiosis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (interquartile range)</td>
<td>36 (30–42)</td>
</tr>
<tr>
<td>Male</td>
<td>32/64 (59)</td>
</tr>
<tr>
<td>Human immunodeficiency virus infected</td>
<td>51/54 (94)</td>
</tr>
<tr>
<td>Not on ART</td>
<td>24/51 (47)</td>
</tr>
<tr>
<td>ART, controlled viral load</td>
<td>1/51 (2)</td>
</tr>
<tr>
<td>ART, uncontrolled viral load</td>
<td>17/51 (33)</td>
</tr>
<tr>
<td>ART initiated ≤ 2 mo prior to presentation</td>
<td>12 (24)</td>
</tr>
</tbody>
</table>

Data are number/total number (%) unless indicated otherwise.

Abbreviation: ART, antiretroviral therapy.
Cutaneous lesions were frequently misdiagnosed. Primary care clinicians and internists misdiagnosed lesions as varicella (n = 5), drug reactions (n = 4), Kaposi sarcoma (n = 4), cutaneous disseminated tuberculosis (n = 2), papular pruritic eruption of HIV (n = 2), syphilis (n = 2), post-inflammatory pigmentation (n = 1), acne (n = 1), herpes zoster (n = 1), disseminated bacterial infection (n = 1), and scrofuloderma (n = 1). Dermatologists examined 25 patients; deep fungal infections were considered in 18 (72%). Dermatologists misdiagnosed lesions as secondary syphilis, varicella, drug reactions, Kaposi sarcoma, seborrheic dermatitis, guttate psoriasis, and pyoderma gangrenosum (n = 1 patient each). Skin biopsies were performed in 37 patients; yeasts (2–7 µm in diameter) were seen with fungal stains in 34 (92%). Histopathologic findings were not sufficient to distinguish *Emmonsia* sp. from other dimorphic fungi. The median turnaround time for histopathology results was 4 days (IQR, 2–7). *Emmonsia* sp. was cultured from skin biopsy in 21/28 patients (74%) after a median of 14 days (IQR, 12–22).

Clinical features suggestive of upper respiratory involvement occurred in 12 patients, including 5 each with epistaxis and nasal congestion, another with nonspecific nasal complaints, and 1 with an oroantral fistula (see Figure 3G). Lower respiratory involvement was suggested in 42/48 patients (88%) by chest radiograph abnormalities that included diffuse and focal infiltrates, lobar atelectasis, and hilar adenopathy. Diagnostic bronchoscopy was performed in 5 patients, resulting in biopsy of an intrathoracic mass on 4 occasions (2 endobronchial and 2 endobronchial lesions [see Figure 2C for an example of an endobronchial lesion]). Two of 4 biopsies demonstrated yeasts in tissue, and 1/1 biopsy sent for fungal culture grew *Emmonsia* sp. On the other hand, *Emmonsia* sp. was not recovered from culture of sputum or bronchoalveolar lavage in any patient, although samples were rarely sent for prolonged fungal culture.

Thirteen patients (24%) had ≥1 neurologic clinical feature on presenting to care. These included mental status alteration (n = 7); headache (n = 2); seizure (n = 1); headache and ataxia (n = 1); loss of visual acuity (n = 1); and headache, mental status alteration, and personality changes (n = 1). Six other patients developed altered mental status during hospitalization. Ten patients had brain imaging; a space-occupying lesion was seen in 1 (Figure 2F). Cerebrospinal fluid examination was performed in 17 patients; abnormal findings were identified in 2: low glucose in 1 and elevated protein (but with a blood-contaminated tap) in another. Fungi were not visualized in or cultured from cerebrospinal fluid in any patients. A patient with headache, ataxia, and a cerebellar mass (who was not HIV infected) underwent a brain biopsy; histopathology examination demonstrated yeasts and culture grew *Emmonsia* sp.

Laboratory-confirmed opportunistic coinfections occurred in 13 patients (24%). Five had proven concomitant tuberculosis; these were in addition to 3 patients with tuberculosis in the preceding 12 months and 3 others in the 12 months before that. Nontuberculous mycobacteria were isolated from blood in 3 patients (not speciated in any case). One patient had both...
disseminated tuberculosis and nontuberculous mycobacterial infection in addition to emmonsiosis. One patient had herpes zoster ophthalmicus, complicated by varicella-zoster viral encephalitis; 5 months later, emmonsiosis-related cutaneous lesions occurred in the distribution of the zoster. Other coinfections included Kaposi sarcoma (n = 2), syphilis (n = 1), nontyphoid salmonella bacteremia (n = 1), and hepatitis B infection (n = 1).

Details of management and outcomes are presented in Table 4. Forty-six patients (85%) received antifungals; 8 patients (15%) died without receiving antifungals. Thirty-four patients (63%) received amphotericin B deoxycholate, of whom 10 (29%) died. Of amphotericin B–treated patients, 4 died early while receiving this drug; 29 of the remaining 30 patients subsequently received maintenance triazole therapy, during which another 6 patients died (after a median of 24 days [IQR, 6–73]). Twelve patients (22%) received a triazole alone; 3/5 patients (60%) who received itraconazole and 5/7 (71%) who received fluconazole died. In 6/7 patients who received fluconazole, therapy had been incidentally prescribed for presumed esophageal candidiasis, dosed as 200 mg daily for up to 14 days; 4 died.

Seven patients treated with a triazole received tuberculosis treatment that included rifampin concomitantly or in the antecedent 2 weeks (with neither dose adjustment nor drug-level monitoring); 5 died compared with 3/5 patients with no concomitant rifampin ($P = 1.0$). In only 4 patients was triazole therapy neither incidental (ie, dosed for esophageal candidiasis) nor concomitant to rifampin; 2 died. In total, 8 patients (67%) treated with a triazole alone died after a median of 14 days (IQR, 5–19). On univariate analysis, improved survival was noted among patients treated with amphotericin B (24/34 [71%]) compared with those treated with a triazole alone (4/12 [33%]; $P = .04$).

Management of ART was known for 48/51 HIV-infected patients (94%). ART was continued (with adherence counseling) in 22 (46%), switched from a failing regimen in 4 (8%), and newly initiated in 15 (31%). Five patients (11%) died prior to initiation of ART. In 2 patients, ART was stopped and both died prior to ART being restarted. Of patients newly initiated on ART, the median timing of ART was 14 days after initiation of antifungals (IQR, 2–22). Timing of ART initiation was not
significantly different among patients who survived and those who died \((P = .94)\). No definite cases of paradoxical immune reconstitution inflammatory syndrome (IRIS) were recorded. Twenty-six patients (48%) died. In 13 patients (24%), the diagnosis of deep fungal infection was only made after death, when blood or bone marrow cultures became positive (median time to positivity, 10 days [IQR, 5–22]). Among these patients, 12 had skin lesions, but only 1 had a skin biopsy. No patients had postmortem examinations.

**DISCUSSION**

This study expands our understanding of the geographical distribution of disseminated emmonsiosis in South Africa and builds on the diagnostic and clinical knowledge gained from earlier reports [1–3]. Clinicians should take note of the protean nature of skin and lung disease and the potential for disease in other organ systems. *Emmonsia* sp., the etiological agent of emmonsiosis in South Africa, is most closely related to *E. pasteuriana*, a rare cause of disseminated disease in immunocompromised hosts. Only 2 human cases of *E. pasteuriana* have been reported, including an Italian woman with AIDS [4] and a transplant recipient with HIV from Spain [5, 6]. The other members of the genus are *E. parva* and *E. crescens*, the agents of adiaspiromycosis, a granulomatous lung disease of rodents and occasionally humans following inhalation of conidia that, once in the lungs, transform into large (50–500 µm diameter) adiaspores [7].
Unlike *E. parva* and *E. crescens*, which are incapable of replicating in tissue, *E. pasteuriana* and *Emmonsia* sp. are thermally dimorphic, and conidia are capable of converting to a yeast phase in mammalian tissue, with subsequent dissemination beyond the lungs [1, 8, 9].

The geographic distribution of cases of disseminated emmonsiosis was wider than previously reported, and patients were diagnosed in 5 of 9 South African provinces. However, we hypothesize that the true burden of disease is underestimated. Public hospitals, which provide care to roughly 85% of the population [10], contributed only 24% of emmonsiosis cases described in this series from outside Western Cape Province. In contrast, 92% of cases diagnosed in the Western Cape were from public hospitals. Hence, it is very likely that emmonsiosis
Disseminated emmonsiosis is being underdiagnosed in public hospitals outside of the Western Cape. Furthermore, underdiagnosis is also likely to occur in the private healthcare sector. To our knowledge, Ampath National Laboratory Services, which provides laboratory services to approximately 40% of the private healthcare sector [11], is the only private laboratory in South Africa currently using broad-range fungal PCR for molecular confirmation of dimorphic fungi. Whether emmonsiosis occurs in other sub-Saharan African countries is even more uncertain. Resource challenges in terms of basic diagnostic mycology services [12], molecular diagnostics, and a lack of *Emmonsia* sp.–specific serology mean that the true geographic range and burden of disease in sub-Saharan Africa remains unknown.

Disseminated emmonsiosis is predominately an opportunistic infection of immunocompromised patients, with just 2 immunocompetent patients in this series. Preliminary results indicate that significant genotypic and phenotypic differences may exist between the recently described *Emmonsia* sp. infecting immunocompromised and immunocompetent South African patients (authors’ unpublished results). All cases of emmonsiosis in South Africa have involved disseminated disease, and it remains to be demonstrated whether subclinical infections and/or self-limited disease such as isolated pulmonary disease occur, particularly in immunocompetent persons.

Disseminated emmonsiosis presented a diagnostic challenge, even to experienced clinicians, and a quarter of patients died prior to the diagnosis of a deep fungal infection. This series included only cases with a confirmed microbiological diagnosis, and thus it is likely that the true proportion of patients who remain undiagnosed (or misdiagnosed) is even higher. The most common diagnostic dilemma encountered by clinicians was differentiating emmonsiosis from tuberculosis, inferred by the fact that three-quarters of patients were treated for the latter. Tuberculosis coinfection was proven in 5 patients, although given the high prevalence of tuberculosis in South Africa [13] and the incomplete sensitivity of currently available tuberculosis diagnostics in advanced HIV infection [14], coinfection may have been underestimated.

Cutaneous manifestations of emmonsiosis were also commonly misdiagnosed, most often as varicella, Kaposi sarcoma, and drug reactions. The protein nature of cutaneous involvement is highlighted by the fact that deep fungal infections were considered unlikely, or not considered at all, in the documented differential diagnoses of dermatologists in more than one-quarter of the cases examined. Skin biopsy was a valuable diagnostic test, with yeasts seen on histology in 92% of the 37 patients biopsied. Skin biopsy for histological examination is also inexpensive, noninvasive, and has the potential for earlier turnaround of results than culture-based diagnostics [15]. Urine *Histoplasma* antigen may prove a useful diagnostic tool, given the apparent cross-reactivity with *Emmonsia* sp. infection (2 of 3 patients with disseminated emmonsiosis had positive tests).

In one-fifth of patients, cutaneous lesions were noted soon after initiation of ART, suggesting a possible unmasking IRIS. This observation is consistent with a previous report of increased inflammation of emmonsiosis-related cutaneous lesions in patients on ART [1].

Disseminated emmonsiosis was uniformly fatal if untreated, and patients treated with an antifungal regimen that included amphotericin B were more likely to survive than those treated with a triazole alone. Both itraconazole and fluconazole were associated with poor outcomes. However, in most patients treated with fluconazole, this drug was prescribed incidentally for esophageal candidiasis in doses and for durations considered inadequate for the treatment of severe disseminated disease caused by other endemic mycoses [16]. Surprisingly, 2 of 4 survivors treated with a triazole alone were in this group. Drug–drug interactions may also have affected treatment efficacy of triazoles, particularly in patients concomitantly receiving rifampin [17]. Excluding patients who received incidental (lower dose) fluconazole or concomitant rifampin, only 4 patients were treated with a triazole alone; 2 died. The degree to which differences in antifungal susceptibility patterns may

### Table 4. Treatment and Outcomes of 54 Patients With Disseminated Emmonsiosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survived (n = 28)</th>
<th>Died (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>.0001</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Triazole</td>
<td>4</td>
<td>8</td>
<td>.20</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2</td>
<td>3</td>
<td>.66</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2</td>
<td>5</td>
<td>.24</td>
</tr>
</tbody>
</table>
| Incidentally prescribed<sup>c</sup>                        | 2                 | 4             | 1.0<sup>d</sup>
| Triazole with concomitant rifampin<sup>e</sup>             | 2                 | 5             | 1.0<sup>f</sup>
| No antifungals                                             | 0                 | 8             | .002    |
| Tuberculosis therapy<sup>g</sup>                           | 17                | 21            | .14     |
| ART newly initiated after diagnosis<sup>h</sup>             | 10 (38)           | 5 (20)        | .22     |
| Timing of ART initiation, median, days after antifungal initiation (interquartile range) | 14 (3–21)         | 13 (2–24)     | 1.0     |

Data are number (%) unless indicated otherwise.

Abbreviation: ART, antiretroviral therapy.

<sup>a</sup> Except for 1 patient (who survived), all patients who completed amphotericin B subsequently received maintenance triazole therapy.

<sup>b</sup> One patient treated with caspofungin and subsequently amphotericin B is enumerated in both treatment groups.

<sup>c</sup> Fluconazole incidentally prescribed for presumed esophageal candidiasis, dosed as 200 mg by mouth per day for 3 (n = 1), 4 (n = 1), or 14 days (n = 4).

<sup>d</sup> Comparing with other patients receiving a triazole.

<sup>e</sup> Includes rifampin administered in the antecedent 2 weeks.

<sup>f</sup> Comparing triazole with and without rifampin.

<sup>g</sup> Tuberculosis coinfection was proven in 5 patients.

### Cutaneous Manifestations

Cutaneous manifestations of emmonsiosis were also commonly misdiagnosed, most often as varicella, Kaposi sarcoma, and drug reactions. The protein nature of cutaneous involvement is highlighted by the fact that deep fungal infections were considered unlikely, or not considered at all, in the documented differential diagnoses of dermatologists in more than one-quarter of the cases examined. Skin biopsy was a valuable diagnostic test, with yeasts seen on histology in 92% of the 37 patients biopsied. Skin biopsy for histological examination is also inexpensive, noninvasive, and has the potential for earlier turnaround of results than culture-based diagnostics [15]. Urine *Histoplasma* antigen may prove a useful diagnostic tool, given the apparent cross-reactivity with *Emmonsia* sp. infection (2 of 3 patients with disseminated emmonsiosis had positive tests).

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have contributed to outcome is unknown. Although clinical breakpoints do not exist, minimum inhibitory concentration data for 6 Emmonsia sp. isolates suggest that triazoles are active against this organism in vitro, despite some heterogeneity in antifungal susceptibility profiles [1].

In the absence of randomized controlled trials and based on the data presented here, we suggest that the management of HIV-associated disseminated emmonsiosis should follow the Infectious Diseases Society of America guidelines for the management of endemic mycoses in immunocompromised persons [18–20]. Amphotericin B (deoxycholate dosed 0.7–1 mg/kg daily or, preferably, a liposomal formulation dosed 3 mg/kg daily) for 7–14 days should be followed by itraconazole for at least 1 year. A longer duration may be necessary in the absence of immune reconstitution. The optimal timing of ART initiation has not been established. Close attention should be paid to potential interactions between antifungals and ART [21] and, where applicable, tuberculosis therapy [17,22].

This study has several important limitations. Case ascertainment is presumed incomplete due to passive laboratory-based surveillance. Consequently, we could not determine the prevalence of emmonsiosis in South Africa. This method of case ascertainment precludes an estimation of the sensitivity of currently available diagnostic methods. Similarly, since microbiological diagnoses may be less likely in less severe forms of disease, our conclusions may not be generalizable to other forms of emmonsiosis (including adiaspiromycosis and, if it exists, nondisseminated disease caused by Emmonsia sp.). Furthermore, there are a number of ways that the retrospective nature of this study limits the conclusions on epidemiology of disease, optimal therapeutic management, and attribution of morbidity and mortality of emmonsiosis. First, migration histories were generally unavailable; consequently, it is unclear whether cases were autochthonous or imported. Second, the choice of antifungal therapy was not randomized, and thus factors influencing both therapeutic decisions and prognosis may have confounded the relationship between management and outcome. Additionally, we cannot rule out the possibility that other therapies were prescribed at centers not included in chart reviews. Third, survival may have been overestimated due to censoring and the fact that outcome was not determined by active surveillance. Finally, clinical details regarding deterioration and death were often limited, and no patients had postmortem examinations.

Much remains to be learned about Emmonsia sp. Knowledge gaps include the environmental reservoir of the novel species (including possible existence of an animal reservoir), virulence factors, and pathogenesis of infection and disease. Clinical research priorities should include the validation of existing and new diagnostic tools to better understand the epidemiology of infection, aid in diagnosis of disease, and possibly identification of patients who may benefit from preemptive therapy.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**
