Fungal Infections in Immunocompromised Travelers

Olivier Lortholary,1,2,3 Caroline Charlier,1 David Lebeaux,1 Marc Lecuit,4,5 and Paul Henri Consigny6

1Université Paris Descartes, Sorbonne Paris Cité, Hôpital Necker-Enfants Malades, Centre d’Infectiologie Necker-Pasteur, and Institut Imagine, 2Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, 3CNRS URA3012, 4Institut Pasteur, Groupe Microorganismes et barrières de l’hôte, 5Inserm Avenir U604, and 6Institut Pasteur, Centre Médical, Centre d’Infectiologie Necker-Pasteur, Paris, France

Immunocompromised patients represent an increasing group of travelers, for business, tourism, and visiting friends and relatives. Those with severe cellular immunodeficiency (advanced human immunodeficiency virus infection and transplant recipients) display the highest risk of fungal infections. International travel is less risky in most other types of immunodeficiency (except those with neutropenia). A systematic visit in a travel clinic for immunocompromised patients traveling to the tropics ensures that the specific risks of acquiring fungal infections (and others) are understood. When immunocompromised hosts return to their area of residence, a nonbacteriologically documented, potentially severe, febrile pneumonia, with or without dissemination signs (skin lesions, cytopenia) should alert for travel-acquired fungal infection, even years after return. Localized subcutaneous nodule may be also ascribed to fungal infection. Finally, infectious diseases physicians should be aware of major clinical patterns of travel-acquired fungal infection, as well as the fungi involved, and risk factors according to the geographical area visited.

Keywords. traveller; solid organ transplant; HIV; steroids; biologic immunomodulators; pregnancy; fungi; endemic areas.

According to the World Tourism Organization, international tourist arrivals worldwide rose from 675 million to 940 million between 2000 and 2010 and will reach 1.6 billion by 2020 [1]. In parallel, the number of immunocompromised individuals is increasing (human immunodeficiency virus [HIV] pandemic and the improvement of life expectancy of patients treated for malignancies, chronic inflammatory diseases, diabetes, and solid organ transplant [SOT]), combined with an increased ability to travel [2–4]. Some of them are immigrants who may be less likely to seek pretravel advice and more prone to be exposed to infectious risks including fungal infection (FI). Indeed, data from a cohort of Canadian travelers undergoing SOT showed that 48% traveled to the tropics, and that individuals born outside Canada were more likely to return in their native place than Canadian natives [2]. In the GeoSentinel cohort involving 21 292 travelers, 32 cases of invasive FI, mostly histoplasmosis, were observed [5].

Some immunocompromised travelers have high risk of developing FI after travel, namely, those with defects of the interleukin 12/interferon gamma (IFN-γ) axis and/or tumor necrosis factor alpha (TNF-α). Indeed, cellular immunity is crucial to control some FIs, as for histoplasmosis [6] and coccidioidomycosis [7] (Figure 1A and 1B). This includes severely immunocompromised HIV-infected patients with a CD4 count of <100 cells/μL, patients undergoing solid organ transplant, recipients of long-term steroids or biologic immunomodulators, and those with primary cellular immune deficiencies [8–11]. Diabetes mellitus impairs neutrophil functions and the IFN-γ and TNF-α secretion of T cells [12, 13]. Patients with chronic obstructive pulmonary disease and particularly those receiving steroids may develop travel-acquired pneumonia [14–17]. Finally, neutropenic patients rarely
travel, whereas isolated B-cell–deficient patients do not exhibit higher susceptibility to FI [18].

The aim of the present article is to review the epidemiology and the preventive and diagnostic strategies of FI in immunocompromised travelers and to enhance the awareness of the infectious disease community on this topic of increasing importance.

**METHODS**

We searched PubMed for reports published between January 1966 and July 2012, using the terms HIV, transplantation, neoplasia, haematological malignancy, corticosteroids, chemotherapy, TNF-α antagonists, sarcoidosis, pregnancy, diabetes, chronic obstructive pulmonary disease, cirrhosis, renal insufficiency, elderly, older age, asplenic, mycetoma, rhinosporidiosis, Entomophthoromycosis, cryptococcosis, coccidioidomycosis, histoplasmosis, penicilliosis, phaeohyphomycosis, chromoblastomycosis, tinea capitis, and other specific terms when needed. Language restrictions were: English, French, German, and Spanish. We completed the search with a manual search of references from selected reports.

**Fungal Infections Potentially Acquired During Travel**

Most travel-acquired FIs described in immunocompromised patients are only found in tropical or subtropical areas (Figure 1). Inhalation of aerosolized fungi is responsible for a potentially severe pneumonia. Skin inoculation is responsible for circumscribed cutaneous and/or subcutaneous infections. In both cases, localized infection eventually lead to dissemination in the context of immunosuppression. It should be noted that travel-acquired FI may present as an acute infection or as a reactivation occurring up to years thereafter [6]. Infection through the inhalation route can occur as isolated or clusters (cryptococcosis, coccidiodomycosis, histoplasmosis). No interhuman transmission has been demonstrated excepted in the setting of SOT through infected grafts.

Travel-acquired FIs include those caused by dimorphic fungi, existing as filamentous form in the soil and as budding yeasts form in the host. In addition, Cryptococcus gattii has also emerged as a major opportunistic pathogen, with 38%–55% of the patients reported immunocompromised in a current outbreak [19, 20]. Finally, other mycoses can be rarely found in immunocompromised patients, such as (1) skin or disseminated phaeohyphomycoses, which include those causing brain abscesses like Cladophialophora bantiana, Exophiala dermatitidis, Ochroconis gallopava, and Rhinocladiella mackenziei (in patients living or originating from the Middle East, India, Pakistan, and Afghanistan); (2) entomophthoromycoses, chromoblastomycosis, fungal mycetoma, rhinosporidiosis; and (3) infections induced by anthropophilic dermatophytes. Immunocompromised travelers may also experience FI due to ubiquitous fungi, which are not the scope of this review.

**Tropical Mucosal and Cutaneous Fungal Infections in Immunocompromised Hosts**

Traumatic inoculation of fungi in tropical areas can lead to diverse primary mucosal, cutaneous, and subcutaneous FIs. Lesion patterns vary according to the causal agent and include isolated nodules, soft tissue infiltration, and ulcerative pseudotumoral lesions (Figure 2). In immunosuppressed patients, lesions may be more extensive than in the healthy host and should be differentiated from skin dissemination of FI. Cystic subcutaneous phaeohyphomycoses have been observed in SOT recipients [21, 22] (Figure 2) and those with neoplastic disorders, with systemic dissemination in one-third of cases [23], or with HIV infection [24]. Fungal mycetoma has also been reported in patients with SOT, hematological malignancy, diabetes, or idiopathic CD4 + lymphocytopenia [25–27]. Classical lesions as well as atypical isolated local swelling [28] or primary osteomyelitis [26] have been reported. A locally aggressive rhinosporidiosis has been reported in an HIV-infected patient from India [29].

Entomophthoromycosis has seldom been reported in neutropenic or kidney transplanted patients (reviewed in [30–32]). Chromoblastomycosis has been reported after renal transplant, in patients undergoing steroid therapy or with concomitant malignancy (reviewed in [33]).

Finally, immunocompromised patients might have an increased risk for tinea capitis, as suggested after kidney transplant [34].

**Immunocompromised Travelers at Risk of Endemic Invasive Fungal Infection**

Several groups can be identified by decreasing order of evidence for fungal risk.

**HIV-Infected Patients**

Fungal infections are the most frequent opportunistic infections, and travel-acquired FIs can reveal HIV infection [6]. Cryptococcus neoformans may be acquired in the tropics [35]. Three major travel-acquired FIs are described: histoplasmosis, coccidioidomycosis, and penicilliosis [36–39]. Cryptococcus gattii (Figure 1C) [18] is arising along with C. neoformans and now accounts for 30% of cryptococcal isolates in Botswana [40]; HIV infection was a risk factor for C. gattii infection during the US outbreak in the Pacific Northwest [19]. Histoplasmosis due to Histoplasma capsulatum is a major endemic FI (Figure 1A) [41]. Among HIV-positive patients living in endemic areas, its incidence varies from 1% to 25% [38, 42]. Infections occurring outside endemic areas usually reflect reactivations in patients with CD4 counts <100 cells/μL, although acute infection may also be seen [39, 43, 44]. Histoplasmosis due to Histoplasma...
**duboisii** occurs rarely in these patients living in or having traveled to Central and West Africa and Madagascar [45]. *Coccidioides immitis* and *Coccidioides posadasii* are found in semiarid areas [41] (Figure 1B), with an annual rate of infection reaching 27% in AIDS [46, 47]. *Penicillium marneffei* is present in Asia (Figure 1D), with few cases reported in Hong Kong, India, and Indonesia. Contact with soil is the strongest known risk factor [37, 48]. Primary infection is usually silent and revealed years later [49]. Distant history of short travel to endemic areas provides evidence for reactivation of latent penicilliosis [50]. In contrast, paracoccidioidomycosis, blastomycosis, and sporotrichosis are rarely reported in AIDS, suggesting that these fungi are not true opportunists [51–54].

**Solid Organ Transplant Recipients**

SOT recipients may experience FI because of contamination during travel to any endemic area. In addition, the donor might have stayed in such places and had a latent tissue infection present at the time of organ harvest. In the latter context, FIs most often occur early after transplant and sometimes are discovered when 1 or more recipients from the same donor have developed the FI [55, 56]. Histoplasmosis occurs in 0.1%–0.5% of SOT in endemic areas and presents as an acute primary infection or as a reactivation occurring a median of 11 months posttransplant (range, 1.2–90 months) [57]. Graft-transmitted histoplasmosis is responsible for local [58] or disseminated infections [55, 59, 60] and accounts for 5% of SOT-associated histoplasmosis in the United States [61]. Coccidioidomycosis occurs in 1.5%–8.7% of SOT recipients living in endemic areas, mostly during the first year following transplant [55]. Acute symptomatic infection may occur immediately after travel or as a reactivation at least 6 months posttransplant. Its acquisition from donor allograft has also been reported [55], even outside endemic areas [62]. Travel-acquired FI may also occur through an organ contamination at the time of sampling/transportation during transplant tourism. In this context, several mold infections including phaeohyphomycoses such as *Rhinocladiella mackenziei* acquired in the Middle East have been reported (reviewed in [63]). Because of the increasing number of donors coming from endemic areas in Europe (reaching 19% in Spanish cities), transplant physicians should be aware of travel-acquired invasive FI in solid organ recipients, along with other infectious diseases. Any travel to endemic areas for tropical fungi should now be acknowledged in the medical records of both living and deceased donors and recipients, and be taken into account in any infectious disease diagnostic procedure regarding transplant recipients.

**Inflammatory Diseases Receiving Corticosteroids or Biologic Immunomodulators**

Disease-modifying antirheumatic and immunosuppressive drugs, including weekly methotrexate and steroids at a dose of...
at least 20 mg/day for at least 2 weeks, are responsible for an increased risk of infection [64–67]. Patients suffering from systemic lupus erythematosus (SLE) have an increased risk of infection even before the initiation of steroid therapy [68]. Prolonged steroid therapy is reported in 27%–50% of C. gattii infections [19, 20] and is associated with a higher death rate [20]. It is difficult to assess the respective role of disease activity and immunosuppressive drugs in the development of FI [69, 70]. In Arizona, coccidioidomycosis incidence during rheumatic disease was 1.9% and mostly occurred in full-time local residents [67], with fulminant cases in steroid-treated patients with SLE [71]. For patients living in high-risk area, serological screening has been suggested before initiation of immunosuppressive therapy [72]. A retrospective study on histoplasmosis reported a mean duration of rheumatoid arthritis of 10.5 (±7.5) years before FI, even in patients who do not receive TNF-α antagonists [68, 69]. In addition, histoplasmosis was lethal in up to 50% of SLE cases [73]. In 2002, the first cases of severe histoplasmosis in patients treated with TNF-α antagonists and living in highly endemic areas were reported [70], with symptoms starting 1 week to 6 months after treatment initiation [74]. A similar observation was made for coccidioidomycosis [75]. Furthermore, a study of 753 sarcoidosis cases from Cincinnati described a 0.9% fungal infection rate in patients undergoing steroid therapy, including histoplasmosis and blastomycosis [76]. Cases of cryptococcosis have been described in patients with sarcoidosis, even those not receiving immunosuppressive therapy [77]. Finally, there is no specific study which has clearly assessed the fungal risk following the use of non–TNF-α antagonist immunomodulators.

Malignancies and Antineoplastic Chemotherapy

Patients with solid tumor can be classified as at low risk for community-acquired invasive FI. Yet, albeit infrequently, patients with lymphoma or cancer chemotherapy may develop severe coccidioidomycosis [78], penicilliosis [79], or histoplasmosis [80]. In contrast, malignancy (solid organ tumor 16%, hematological malignancy 8%) is an underlying disease in up to 24% of C. gattii recent cases [19].

**Elderly Patients**

Elderly patients represent an expanding population with increased risk for FI, due to decreased T-cell functions, narrowing in T-cell receptor repertoire, contraction of natural killer cell subsets, and defects in dendritic cell function and regulation [81, 82]. These patients, who are retired for the most part, frequently travel and perform outdoor activities [83]. Among endemic mycoses, histoplasmosis, coccidioidomycosis, and blastomycosis require specific attention in elderly patients [84]. The association between age and potentially severe coccidioidomycosis is controversial [85–88], but the number of cases in people > 65 years has more than doubled since 2000 in Arizona [89]. Of note, 11% of patients did not report exposure to traditional endemic areas [84]. Advanced age and immunosuppression are risk factors for disseminated and/or fatal histoplasmosis [90]. Advanced age has also been associated with increased risk of death from pulmonary blastomycosis [91]. Finally, patients ≥ 50 years accounted for 54% of the C. gattii reported cases; 12% were > 70 years and had poorer outcome [20].

**Pregnancy**

The pregnant traveler may develop FI with 2 major issues: (1) more severe presentation of some endemic mycoses, likely related to pregnancy-associated immunosuppression, and (2) therapeutic restrictions. Pregnancy is a risk factor for disseminated coccidioidomycosis [86, 92], particularly during the last trimester and immediate postpartum period [93]. Disseminated histoplasmosis has also been reported during pregnancy, with or without additional immunosuppressive condition [94]. Blastomycosis has been seldom reported during pregnancy, but available data suggest a higher prevalence of disseminated disease [95]. Amphotericin B is the antifungal of choice for travel-acquired FIs that require antifungal therapy.
Other Immunosuppressions

Diabetic travelers are at increased risk of developing severe blastomycosis [91] and coccidioidomycosis [96, 97]. Diabetes was also evidenced in up to 20% of recently reported C. gattii cases [20].

Chronic obstructive pulmonary disease patients may experience chronic pulmonary histoplasmosis [15, 83], blastomycosis [16], or sporotrichosis, with frequent visceral or osteoarticular involvement [17].

Specific data regarding chronic renal insufficiency are scant, but suggest an overall increased incidence for some FIs. In a large study involving >300 000 dialyzed patients, cryptococcosis and coccidioidomycosis accounted for 6% and 4.1%, respectively, of all reported FIs [98]. In recent C. gattii data, renal insufficiency was present in 24% of cases [20].

Case reports of primary immune deficiencies have evidenced the occurrence of histoplasmosis in idiopathic CD4 lymphocytopenia [9], CD40 ligand deficiency [10], hyperimmunoglobulin E syndrome [8], and autosomal dominant form of IFN-γ receptor 1 deficiency [11]. Endemic FIs are rare in asplenic patients who have no increased risk of travel-acquired FIs [99, 100].

No increased risk of travel-acquired FIs had been evidenced so far in patients with liver cirrhosis [101], although liver disease is reported in 9% of patients with C. gattii infection [20].

How to Investigate Fungal Infections in Immunocompromised Travelers from the Tropics?

Immunocompromised travelers with unexplained fever associated or not associated with focal symptoms—mostly respiratory, neurologic, and/or dermatologic—may have travel-acquired FI (Figure 2). Tropical skin infections may not induce fever. If thinking of FI is easy in the context of recent travel, much delayed occurrence of reactivation symptoms after travel-acquired primary infection is obviously more difficult. FI presentation is similar between immunocompromised travelers and those living in endemic areas.

More-frequent travel-acquired infections such as malaria, dengue, and enteric fever should always be urgently excluded. Travel history should include precisely the visited areas and the occurrence of any particular exposure (eg, earthquake, windy conditions, construction works, spelunking hobbies in bat-infested caves, outdoor trauma with vegetal inoculation). Immunocompromised hosts might experience severe pneumonia and disseminated disease [102–105]. In case of pulmonary involvement, chest radiography might show normal results at initial stage of management [106], and distinguishing FI from other causes can only be done microbiologically [102, 103, 105]. In case of severe disease, invasive microbiological investigations are mandatory and rely on bronchoalveolar lavage (Figure 3). The microbiology laboratory must be warned of dimorphic
immunodepression or immunosuppression. Patients with severe pneumonia or disseminated disease in immunocompromised patients, antifungal treatment must be started as soon as diagnosis samples have been obtained. A broad-spectrum antifungal regimen is required and recent guidelines recommend as initial treatment one of the amphoterterin B formulations in case of severe pneumonia or disseminated disease [102, 104, 105]. As immunosuppressive drugs are frequently tapered during severe FI, physicians must be aware of the risk of development of immune reconstitution inflammatory syndrome, especially during cryptococcosis and histoplasmosis. In case of histoplasmosis following TNF-α antagonist treatment, immune reconstitution inflammatory syndrome has indeed been observed after treatment discontinuation among 42% of patients [109].

### Recommendations Before Travel

International travel is not contraindicated in immunocompromised patients, although some itineraries need to be avoided and specific advice given in the context of a dedicated visit in an outpatient travel clinic [110]. The CDC identifies 4 groups of immunocompromised travelers: severely immunocompromised HIV-uninfected patients, severely immunocompromised HIV-infected patients, asymptomatic HIV-infected patients, and patients with chronic disorders associated with mild immune deficit [111]. For the first group, it is recommended to postpone the travel to the tropics until the end of the first year posttransplant for SOT patients and after the end of the first 2 years after allogeneic bone marrow transplant, provided no immunosuppressive therapy is given, especially for graft-vs-host disease. In the same way, severely immunocompromised HIV-infected patients (ie, those with a CD4+ blood cell count <200 cells/μL or any AIDS-defining illness or any clinical symptoms ascribed to HIV) should defer their travel to the tropics until immunological and/or clinical improvement is achieved. For asymptomatic HIV-infected patients (with CD4+ blood cell count >200 cells/μL) and chronic disorders with mild immune deficiency, there is no restriction to travel ascribed to a potential FI [111].

In case of travel, prevention of exposure to sources of FI in endemic areas is difficult. Some high-risk activities should be avoided to limit the potential contact with contaminated aerosolized material (Table 1). Antifungal prophylaxis is not

### Table 1. Major Recommendations Regarding Prevention of Histoplasmosis and Other Inhaled Endemic Fungi in Immunocompromised Travelers

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Prevention Measures</th>
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<tr>
<td>Histoplasmosis [5, 116]:</td>
<td>• Avoid high-risk activities in endemic areas:</td>
</tr>
<tr>
<td></td>
<td>• spelunking (caves)</td>
</tr>
<tr>
<td></td>
<td>• building construction, renovation, demolition, cleaning, soil excavation</td>
</tr>
<tr>
<td></td>
<td>• contact with chicken coops or bird roosts</td>
</tr>
<tr>
<td></td>
<td>• wood handle (transport, cutting, burning)</td>
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<tr>
<td>Coccidioidomycosis [5, 111]:</td>
<td>• Limit exposure to outdoor dust:</td>
</tr>
<tr>
<td></td>
<td>• by limiting activities generating dust: building construction, demolition, renovation, landscaping, farming, excavations (including archeological dig), numerous recreational pursuits</td>
</tr>
<tr>
<td></td>
<td>• by limiting voluntary exposure to natural events such as earthquakes, windstorms</td>
</tr>
<tr>
<td>Penicilliosis [5, 117]:</td>
<td>• Avoid travels to endemic areas of Southeast Asia, particularly during the rainy season (May–October)</td>
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fungus suspicion, as culture samples must be managed in biosafety level 3 conditions (at least for most of them) and incubated for several weeks [102, 103, 105]. The FI might also be disseminated and may require mycological and histopathological analysis of skin/mucosal biopsy samples (Figure 3) or blood or bone marrow cultures, at least for histoplasmosis and penicilliosis. Because fungal cultures take weeks to grow, indirect diagnostic tools can be used, when available. A recent report describes a sensitivity of 75% (60/80 patients) for anti-Histoplasma antibodies in case of disseminated histoplasmosis and 90% (48/53) in case of lung infection in mostly immunocompromised patients (those with AIDS, SOT, or primary immunodeficiencies or those undergoing immunosuppressive therapy) [72]. In the same cohort, the last-generation Histoplasma urine antigen assay yielded a sensitivity of 91.5% (145/158) in patients with disseminated histoplasmosis, higher among immunocompromised patients and/or in case of severe disease [72]. The Platelia Aspergillus galactomannan assay might be positive in the serum of HIV-infected patients and solid organ transplant recipients with histoplasmosis [107] or in the bronchoalveolar lavage fluid of patients with blastomycosis [108].

In case of severe pneumonia or disseminated disease in immunocompromised patients, antifungal treatment must be started as soon as diagnosis samples have been obtained. A broad-spectrum antifungal regimen is required and recent guidelines recommend as initial treatment one of the amphotericin B formulations in case of severe pneumonia or disseminated disease [102, 104, 105]. As immunosuppressive drugs are frequently tapered during severe FI, physicians must be aware of the risk of development of immune reconstitution inflammatory syndrome, especially during cryptococcosis and histoplasmosis. In case of histoplasmosis following TNF-α antagonist treatment, immune reconstitution inflammatory syndrome has indeed been observed after treatment discontinuation among 42% of patients [109].

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### Table 2. Major Web Sites for Travel Medicine Proposing Specific Recommendations Regarding Immunocompromised Travelers (Last Accessed 25 November 2012)

<table>
<thead>
<tr>
<th>Web Sites</th>
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<tr>
<td>• World Health Organization: <a href="http://www.who.int/ith/en/">http://www.who.int/ith/en/</a></td>
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<tr>
<td>• Public Health Agency of Canada: <a href="http://www.phac-aspc.gc.ca/tmp-pmv/">http://www.phac-aspc.gc.ca/tmp-pmv/</a></td>
</tr>
<tr>
<td>• Health Protection Agency (United Kingdom): <a href="http://www.hpa.org.uk/">http://www.hpa.org.uk/</a></td>
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routinely recommended for at-risk populations during travel [112]. It may, however, be discussed in some particular cases, such as HIV-infected patients expatriating to Southeast Asia with a CD4 T-lymphocyte count <200 cells/μL and therefore requiring primary prophylaxis, such as itraconazole, as the susceptible local patients do (oral suspension, 200 mg/day during the time of exposure) [113]. Finally, travelers should be aware of the symptoms requiring medical attention during or after travel: fever, respiratory, or neurologic symptoms as well as appearance of cutaneous lesions.

In conclusion, infectious disease physicians in charge of immunocompromised travelers should consult travel medicine websites (Table 2). They also should be aware of the major clinical patterns of travel-acquired FI occurring in immunocompromised hosts, as well as the fungi involved, risk factors, and diagnostic strategy according to the geographical area visited.

Note
Potential conflicts of interest. O. L. is a member of the Merck Sharp & Dohme (MSD) board, is a consultant for Astellas and Gilead Sciences, and received speaker’s fees from MSD, Astellas, Gilead Sciences, and Pfizer; C. C. received travel grants in 2011 and 2012 from Astellas for international conferences; D. L. received a travel grant in 2009 from Schering-Plough for an international conference. All other authors report no potential conflicts.

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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