Opportunistic Fungal Infections, Part 1: Antifungal Treatment and Prophylaxis

Michelle A. Barron, MD and Nancy E. Madinger, MD

Fungal infections are a major cause of morbidity and mortality in immunosuppressed hosts, such as patients with HIV-1 infection and those who are otherwise neutropenic. Thus, antifungal prophylaxis has become important in the care of patients with AIDS, transplant recipients, persons receiving chemotherapy, and other at-risk persons. This first installment in a 3-part series on opportunistic fungal infections in the immunocompromised person reviews the pathogenesis of opportunistic fungal infections in select at-risk populations and the pharmacotherapeutic armamentarium available for prophylaxis and treatment.

Key words: Fungal infections ■ Immunosuppression ■ Transplant

Patients with advanced HIV-1 infection, those who are receiving chemotherapy for malignancy, and transplant recipients (both hematopoietic stem cell transplant [HSCT] and solid organ transplant [SOT]) are among the populations of immunosuppressed patients at risk for fungal infections. The fungal infections acquired by these patients are a consequence of immunological deficits associated with the underlying disease or complications of therapy.

Diagnosis of fungal infections remains problematic. It is often based on clinical signs and symptoms in an at-risk person, and invasive procedures are frequently required for confirmation. Treatment options have improved with the introduction of newer antifungal classes and medications; however, the optimal treatment for certain infections, such as invasive aspergillosis and infections caused by other invasive moulds (eg, *Fusarium* species and *Zygomycetes*) remains controversial.

Prevention of fungal disease is dependent on minimizing exposure and having a functioning immune system. Because these conditions may not be possible to achieve in at-risk patients, antifungal prophylaxis has become an important part of care. Development of fungal vaccines remains inherently challenging, given that most vaccine technology relies on host immunity; however, novel approaches are being investigated and may be available in the future.

**PATHOGENESIS**

**HIV-1–associated fungal disease**

HIV-1 infection is characterized by the decline in CD4+ cell counts.1 The most common fungal pathogens are *Candida albicans* and *Cryptococcus neoformans*.2 Active infection with *C albicans* results from overgrowth of the patient’s endogenous flora, whereas other fungal infections are associated with exposure to conidia (probably through inhalation). In addition, HIV-1–infected patients are at risk for endemic mycoses, including those caused by *Histoplasma capsulatum*, *Coccidioides immitis*, *Coccidioides posadasii*, *H capsulatum var duboisii*, and *Penicillium marneffei*. Pulmonary aspergillosis was more common before the advent of potent antiretroviral therapy. Affected patients typically had low CD4+ T-cell counts (less than 50/µL) and neutropenia, and a history of corticosteroid use, exposure to broad-spectrum antimicrobial therapy, and previous pneumonia or underlying pulmonary disease.3
Malignancy and neutropenia

Neutropenia (defined as an absolute neutrophil count [ANC] of less than 500/µL or less than 1000/µL in a patient who is clinically deteriorating) often develops in patients who receive chemotherapy for treatment of a malignant neoplasm.

A nadir neutrophil count and protracted neutropenia (defined as an ANC of less than 500/µL for 10 days or more) are strong determinants of the development of opportunistic infection. Fever is often the only clinical sign. Although virtually any fungus with low intrinsic virulence may infect patients with severe neutropenia, Candida and Aspergillus species are the most frequently identified organisms.

HSCT

HSCT infusion of progenitor cells is typically performed to reestablish bone marrow components after ablative therapy. Allogeneic HSCT recipients have a profound impairment of host immune function during the first 4 to 5 months after engraftment, regardless of the type of graft, the underlying disease, the conditioning regimen or the presence of acute graft-versus-host disease (GVHD). Immune reconstitution in most healthy long-term survivors is accomplished 1 to 2 years after engraftment, whereas the same process in patients with GVHD is delayed.

Risk of fungal infection is greatest during periods of neutropenia and GVHD. *C. albicans* poses the greatest risk and is thought to result from unopposed growth at mucosal surfaces, leading to fungemia.

SOT

Infections in SOT recipients are dependent on exposure to the pathogens and the net state of immunosuppression. Colonization with yeasts and moulds occurs frequently both in transplant candidates and recipients. Donor-related transmission of fungal infections to the organ recipient is uncommon but often involves an undetectable or quiescent infection in the donor’s bloodstream or transplanted organ.

The initial immunosuppressive medication used for antirejection therapy are similar in all forms of organ transplant and typically include cyclosporine or tacrolimus (Table 1). The risk of fungal infection varies depending on the type of organ transplant, with lung transplant recipients at the highest risk followed by heart, liver, and kidney transplant recipients.

**Antifungal classes**

Antifungal therapy is a mainstay of both prophylaxis against and treatment of fungal infections in immunocompromised persons. The medications differ in their spectrum of activity against major pathogens and in adverse effects. The major classes of antifungal medications are reviewed below and summarized in Table 2. Disease-specific indications for antifungal therapy will be reviewed in parts 2 and 3 of this series of articles.

**Polyenes**

Amphotericin B deoxycholate was introduced in 1959. Because of the severe toxicity associated with this medication (most notably renal toxicity), lipid-based amphotericin B formulations are most commonly used today. These formulations are delivered to the site of inflammation and have excellent tissue and body fluid penetration, and high concentrations are achieved at the site of inflammation.

**Triazoles**

The triazoles include fluconazole, itraconazole, voriconazole, and posaconazole. These medications exert their activity by inhibiting the production of ergosterol, a key component of the fungal cell membrane. Fluconazole and itraconazole are licensed for the treatment of a variety of fungal infections, including candidiasis and aspergillosis.

**Azoles**

The azoles include ketoconazole, posaconazole, and itraconazole. These medications exert their activity by inhibiting the production of ergosterol, a key component of the fungal cell membrane. Ketoconazole is not currently approved for use in the United States, and itraconazole is commonly used for the treatment of systemic mold infections.

**IgM antibodies**

IgM antibodies are produced in response to fungal infections and can be used as a diagnostic tool to detect the presence of fungal antigens.

**Table 1 – Immunosuppressant drugs and mechanisms of action**

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<thead>
<tr>
<th>Immunosuppressant drug</th>
<th>Mechanism of action</th>
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<tr>
<td>Glucocorticoids</td>
<td>Reduce neutrophil accumulation</td>
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<td>Cytotoxic drugs (eg, methotrexate, azathioprine, cyclophosphamide)</td>
<td>Induce neutropenia, monocytopenia</td>
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<tr>
<td>Calcineurin inhibitors (eg, cyclosporine, tacrolimus, sirolimus)</td>
<td>Inhibit T-cell function</td>
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<td>Mycophenolate mofetil</td>
<td>Interrupt DNA replication of T cells</td>
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<tr>
<td>IL-2 receptor antibodies</td>
<td>Inhibit IL-2 receptor signaling</td>
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<tr>
<td>Antithymocyte antibodies</td>
<td>Inhibit intracellular signaling of T cells</td>
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<tr>
<td>IL-2 receptor antagonists</td>
<td>Inhibit IL-2 receptor</td>
</tr>
<tr>
<td>Interleukin (IL) antibodies</td>
<td>Inhibit T-cell function</td>
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<tr>
<td>Anti-TNF antibodies</td>
<td>Inhibit TNF-alpha activity</td>
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<td>Anti-CD20 antibodies</td>
<td>Inhibit B-cell function</td>
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**Table 2 – Antifungal drugs and mechanisms of action**

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<thead>
<tr>
<th>Antifungal drug</th>
<th>Mechanism of action</th>
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<tr>
<td>Amphotericin B deoxycholate</td>
<td>Inhibits fungal cell membrane synthesis</td>
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<tr>
<td>Fluconazole</td>
<td>Inhibits fungal cell membrane synthesis</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Inhibits fungal cell membrane synthesis</td>
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<tr>
<td>Voriconazole</td>
<td>Inhibits fungal cell membrane synthesis</td>
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<tr>
<td>Posaconazole</td>
<td>Inhibits fungal cell membrane synthesis</td>
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The initial immunosuppressive medications used for antirejection therapy are similar in all forms of organ transplant and typically include cyclosporine or tacrolimus (Table 1). The risk of fungal infection varies depending on the type of organ transplant, with lung transplant recipients at the highest risk followed by heart, liver, and kidney transplant recipients.
### Table 2 – Available antifungal agents

<table>
<thead>
<tr>
<th>Antifungal class</th>
<th>Mechanism of action</th>
<th>Agent</th>
<th>Route</th>
<th>Approved dosing</th>
<th>Spectrum of activity</th>
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<tr>
<td>Polyenes</td>
<td>Inhibit cytoplasmic membrane synthesis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Amphotericin B deoxycholate</td>
<td>IV</td>
<td>0.1 mg/kg qd</td>
<td>Candida species, Aspergillus species, Blastomyces dermatitidis, Cryptococcus species, Histoplasma capsulatum, Zygomycetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amphotericin B lipid complex</td>
<td>IV</td>
<td>5 mg/kg qd</td>
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<td>Liposomal amphotericin B</td>
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<td>Empirical therapy: 3 mg/kg qd Systemic fungal infections: 3–5 mg/kg qd Cryptococcal meningitis in HIV-1–infected patients: 5 mg/kg qd</td>
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<tr>
<td>Triazoles</td>
<td>Disrupt cytoplasmic membrane synthesis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fluconazole</td>
<td>IV and PO</td>
<td>Adults: 200–400 mg/d for prophylaxis; 800 mg/d loading dose followed by 400 mg/d for treatment of systemic candidiasis Children: 3 mg/kg/d after the age of 1 year</td>
<td>Candida species (except Candida glabrata and Candida krusei), Cryptococcus neoformans, B dermatitidis, Coccidioides species, H capsulatum, Sporothrix schenckii</td>
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<tr>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>PO</td>
<td>Histoplasmosis: 200 mg qd; if no improvement or progression, dose should be increased to 200 mg bid</td>
<td>Aspergillus species, Candida species, C neoformans, Trichophyton species, B dermatitidis, H capsulatum, Coccidioides species, Paracoccidioides brasiliensis, Penicillium marneffei, S schenckii</td>
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<td></td>
<td></td>
<td>Voriconazole</td>
<td>IV and PO</td>
<td>IV: 2 loading doses of 6 mg/kg q12h, followed by a maintenance dosage of 4 mg/kg q12h PO: &gt; 40 kg body weight: 2 doses of 400 mg q12h, then 200 mg q12h; &lt; 40 kg body weight: 2 doses of 200 mg q12h, then 100 mg q12h</td>
<td>Aspergillus species, Candida species, B dermatitidis, Coccidioides immitis, H capsulatum, hyaline moulds (including Fusarium species, Scedosporium apiosperum, Alternaria species)</td>
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<sup>a</sup> Synthesis of sterols in the plasma membrane of fungi is inhibited, which induces cellular leakage and death.<sup>b</sup> Eukaryotic cytochrome P450 14α-demethylase is inhibited, which prevents fungal ergosterol synthesis from lanosterol.
in the cerebrospinal fluid (CSF) are achieved. Current dosing recommendations are given in Table 2.

**Triazoles**
Triazole antifungals were introduced almost 30 years ago. They include fluconazole, itraconazole, voriconazole, and posaconazole. Their mechanism of action involves inhibition of a fungal cytochrome-dependent enzyme that converts lanosterol to ergosterol, an essential molecule of the fungal cell membrane. Posaconazole is structurally similar to itraconazole, and voriconazole is structurally similar to fluconazole. The antifungal spectrum of the agents differs depending on the compound. Drug-drug interactions are common with this class.

Fluconazole has excellent in vitro activity against a wide variety of yeasts, including Candida species, with the exception of Candida krusei, which has intrinsic resistance to fluconazole, and Candida glabrata,
which has decreased susceptibility to the drug. Fluconazole has limited activity against moulds.

The antifungal is very well absorbed by the GI tract (bioavailability of over 80%) and is available in oral and intravenous formulations. It has excellent diffusion into body fluids and tissues and achieves concentrations in the CSF that are at least 70% of blood levels even in the absence of inflamed meninges. Hepatic cytochrome P-450 (CYP) 2C9 plays a minor role in its metabolism. Dose adjustments for renal impairment are required. Ocular penetration of the antifungal is good as well.

Fluconazole is metabolized via the liver and CYP isoenzymes; therefore, potential drug interactions must be considered. Dose reduction of tacrolimus, cyclosporine, and warfarin may be necessary when these drugs are coadministered with fluconazole. Levels of these drugs need to be monitored closely when they are used with fluconazole.

Itraconazole has excellent in vitro activity against a wide variety of yeasts and moulds. Its absorption is more variable than that of fluconazole. The capsule is best absorbed with food, and the oral solution is better absorbed in a fasting state. It also has an intravenous formulation; however, it is no longer available in the United States.

Itraconazole does not penetrate the CSF. It is a substrate of strong inhibitor of CYP3A4, so drug-drug interactions are common.

Voriconazole is a second-generation azole antifungal that has excellent in vitro activity against a wide variety of yeasts and moulds. This drug is approved for the treatment of invasive aspergillosis and for the treatment of infections attributed to Pseudallescheria boydii, Scedosporium apiospermum, and Fusarium species in patients who are intolerant or refractory to other antifungal therapy.

Bioavailability of voriconazole following oral administration of either tablet or solution is 96%. Oral absorption is decreased by 22% when taken with food. There is also an intravenous formulation.

Voriconazole penetrates the blood-brain barrier, and CSF concentrations are approximately 46% of serum levels. Dose adjustment should be made in patients with mild to moderate hepatic disease, and the intravenous formulation should be used with caution in patients with a creatinine clearance of less than 50 mL/min/1.73 m². The potential for drug interactions with voriconazole is high because of its metabolism by CYP isoenzymes. Dose reduction of tacrolimus, cyclosporine, and warfarin is necessary when any of these drugs are coadministered with voriconazole. Levels of these drugs should be monitored closely.

Posaconazole is a triazole antifungal with a spectrum of activity that includes yeastlike fungi, such as Candida and Cryptococcus species; many moulds, including Zygomycetes; and some endemic fungi. Posaconazole is approved for the treatment of oropharyngeal candidiasis and as prophylaxis for Aspergillus and Candida infections in persons at high risk for development of these infections (HSCT recipients with GVHD or hematological malignant neoplasms with prolonged chemotherapy-associated neutropenia).

Posaconazole is available only as a suspension for oral use. Absorption is increased when taken with food, especially a fatty meal. Optimal absorption of the drug occurs when it is administered 4 times daily. Dose adjustment is not needed for patients with renal or hepatic dysfunction. Posaconazole inhibits hepatic CYP isoenzymes; therefore, when it is coadministered with tacrolimus or cyclosporine, the doses of the latter should be reduced to approximately three-fourths and one-third, respectively, of the original doses, and serum levels should be monitored closely.

Echinocandins

The echinocandins are noncompetitive inhibitors of (1,3)-β-glucan synthase, which results in the selective inhibition of glucan, an essential component of the cell wall of many pathogenic fungi. All currently available echinocandin preparations are intravenous and are poor substrates for CYP enzymes.

The antifungal spectrum of this class is restricted to Candida species and Aspergillus species, with few exceptions. This class is inactive against Zygomyces, C neoformans, Fusarium species, and Trichosporon species. It may have some activity against C immitis, Blastomyces dermatitidis, H capsulatum, and Scedosporium species, but at this time, there is a lack of clinical data to support the use of echinocandins in diseases caused by these organisms.

In general, this class has limited penetration into the CSF and urine. To date, acquired resistance to echinocandins in susceptible fungal yeastlike species has been extremely rare. Currently, there are 3 FDA-approved drugs in this class: caspofungin, micafungin, and anidulafungin. Subtle differences exist between each of these drugs, although there is no indication that one is clinically superior to the other.

Caspofungin was the first drug in the echinocandin class to receive FDA approval for the treatment of mucosal and invasive candidiasis and invasive aspergillosis. It is also approved for the empirical treatment of febrile neutropenia. No dose modifications are required in patients with renal insufficiency, and the drug is not discontinued during hemodialysis. Dose reduction is recom-
metabolized. No dose modifications are required in patients with renal insufficiency or mild to moderate hepatic impairment.

Coadministration of micafungin with cyclosporine mildly inhibits cyclosporine metabolism; thus, monitoring of cyclosporine levels is prudent. Micafungin increases serum concentrations of sirolimus and nifedipine by 21% and 18%, respectively. Monitoring of drug levels is important to prevent toxicity.

Anidulafungin is the newest echinocandin antifungal to be approved by the FDA for the treatment of esophageal candidiasis, candidemia, and deep tissue candidiasis. It is unique among the echinocandins because it slowly degrades in human plasma, undergoing a process of bio-transformation rather than being metabolized. No dose modifications are required in patients with renal insufficiency or any degree of hepatic impairment.

**PROPHYLAXIS AND TREATMENT**

**Febrile neutropenia**

Caspofungin has been shown to be as effective as amphotericin B for empirical antifungal therapy in patients with persistent febrile neutropenia (defined as an ANC of less than 500/µL for at least 96 hours and temperature of greater than 38.0°C [100.4°F]). In a randomized double-blind trial of 1095 patients who were selected to receive either caspofungin or liposomal amphotericin B in a 1:1 ratio, the overall success rates were 33.9% for caspofungin and 33.7% for liposomal amphotericin B. Among patients with baseline fungal infections, 51.9% who were treated with caspofungin had a successful outcome compared with 25.9% of patients treated with amphotericin B (P = .04). Rates of breakthrough fungal infections and resolution of fever during neutropenia were similar in the 2 groups.

Voriconazole has also been evaluated as empirical antifungal therapy in patients with persistent febrile neutropenia. In this large, multicenter, randomized trial, patients were selected to receive voriconazole (n = 415) or liposomal amphotericin B (n = 422). Overall success rates were 26% for the voriconazole arm and 30.6% for the liposomal amphotericin B arm. Fewer documented breakthrough fungal infections were seen in patients treated with voriconazole than those who received liposomal amphotericin B (1.9% versus 5%; P = .02). However, the voriconazole group did not meet the pre-defined composite end point for noninferiority, compared with the liposomal amphotericin B group in relation to overall response to therapy. Because of this, the FDA did not approve voriconazole for empirical treatment of fungal infections in febrile neutropenic patients. The results of the trial as well as the FDA decision remain controversial.

**Prophylaxis in high-risk patients**

Fluconazole prophylaxis has been a mainstay of therapy in allogeneic HSCT recipients. When no prophylaxis is administered, invasive fungal infections, mainly due to *C. albicans* and other *Candida* species, can be expected to develop in 16% to 18% of patients. Two randomized placebo-controlled trials in allogeneic bone marrow transplant recipients showed that fluconazole, given at a dosage of 400 mg qd, significantly reduced the incidence of superficial fungal infections, invasive fungal infections, and mycosis-related mortality. However, the benefits of fluconazole prophylaxis in high-risk patients with leukemia were less conclusive.

In SOT, liver transplant recipients should be stratified according to their risk factors for invasive fungal infections. It is recommended that those at high risk receive fluconazole prophylaxis.

Several studies have evaluated the use of itraconazole as prophylaxis, given its extended spectrum of antifungal activity, which includes *Aspergillus*. In a study of allogeneic HSCT recipients in which itraconazole was compared with fluconazole, fewer invasive fungal infections were detected in the itraconazole arm (9%) than in the fluconazole arm (25%). In addition, itraconazole was compared with fluconazole as prophylaxis in liver transplant recipients. However, unlike the findings seen in HSCT recipients, the rate of proven invasive fungal infections was not statistically different between the 2 arms (9% in the itraconazole arm versus 4% in the fluconazole arm [P = .25]). Use of itraconazole for prophylaxis has been limited because of issues regarding absorption and drug-drug interactions.

The only echinocandin that has been studied in the context of prophylaxis to date is micafungin, which proved to be more effective than the study comparator, fluconazole. Micafungin (50 mg qd) was compared with fluconazole (400 mg qd) as prophylaxis in 882 adult and pediatric patients undergoing autologous or allogeneic HSCT in a randomized double-blind trial. Overall...
success was 80% in the micafungin arm and 73.5% in the fluconazole arm ($P = .03$). Frequency of invasive fungal infections was similar between the 2 groups, with a trend toward reduced frequency of invasive aspergillosis in allogeneic HSCT recipients in the micafungin arm.

Findings from 2 studies examining posaconazole prophylaxis suggest that the drug is safe and effective in patients at high risk for invasive fungal infections. In the first trial, HSCT recipients with GVHD were randomly selected to receive either posaconazole (n = 301) at a dosage of 200 mg tid PO or fluconazole (n = 299) at a dosage of 400 mg qd PO. There was no significant difference in the incidence of proven or probable fungal infections in the posaconazole arm (5.3%) compared with the fluconazole arm (9%; $P = .07$) at the end of 112 days; however, fewer invasive fungal infections were observed in the posaconazole arm than in the fluconazole arm (7 cases vs 22 cases; $P = .004$). No significant differences in mortality were seen between the 2 groups, but the observed rate of mortality attributed to invasive fungal infection was significantly lower in the posaconazole arm than in the fluconazole arm (1% vs 4%, respectively; $P = .041$).

In the other trial, which was open label, prophylactic posaconazole (200 mg tid PO) was compared with either fluconazole (400 mg qd PO) or itraconazole (200 mg qd PO) in 602 patients who were receiving myelo-suppressive chemotherapy for hematological malignant neoplasms. Seven (2%) invasive fungal infections were identified in the posaconazole arm compared with 25 (8%) in the comparator arm ($P < .001$). Despite the lack of clinical trial data, voriconazole is often used as prophylaxis for HSCT recipients in lieu of fluconazole, given its broader antifungal spectrum.

Findings of a small double-blind trial investigating prophylactic voriconazole versus placebo in patients with acute myelogenous leukemia suggest that the drug is valuable in this setting. Ten patients received voriconazole 200 mg bid and 15 received placebo. The primary end point was the detection of lung infiltrates or resolution of neutropenia. The incidence of lung infiltrates up to day 21 was 0% (in the voriconazole group) and 5 (33%) in the placebo group. A randomized double-blind clinical trial that compared the effectiveness of voriconazole with that of fluconazole in HSCT recipients has recently been completed and will provide further data regarding the value of voriconazole as prophylaxis against invasive fungal infections in high-risk patients.

**Therapeutic agents mentioned in this article**

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<thead>
<tr>
<th>Amphotericin B</th>
<th>Cholesterol sulfate complex</th>
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<tbody>
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<tr>
<td>Amphotericin B deoxycholate</td>
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<td>Methotrexate</td>
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<td>Voriconazole</td>
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<td>Warfarin</td>
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**REFERENCES**

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Invasive Aspergillosis Presenting as a Neck Mass in a Person With HIV/AIDS

A 38-year-old HIV-infected man with a CD4+ cell count of 4/µL and an HIV RNA level of more than 750,000 copies/mL was admitted to the hospital after 1 month of painful right neck swelling and 1 week of dysphagia. His history was also notable for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia, which occurred 2 months earlier; adrenal insufficiency; chronic hepatitis C; remote Cytomegalovirus retinitis; and recurrent bacterial pneumonia.

The patient had started antiretroviral treatment with efavirenz and coformulated abacavir/lamivudine/zidovudine 10 months before admission but discontinued therapy on his own after 7 months. At the time of admission, his medications were daily valganciclovir, dapsone, and prednisone and weekly azithromycin.

On physical examination, the patient had a fever (temperature, 37.5°C [99.5°F]) and a swelling in the right side of his neck. Findings from the remainder of his physical examination were unremarkable. A CT scan of the neck demonstrated multiple low-density masses with rim enhancement in the right side (Figure 1). A CT scan of the orbits demonstrated abnormal soft tissue involving the right pterygopalatine fossa with destruction of the posterosuperior right maxillary sinus wall (Figure 2, area marked by arrow).

CT-guided aspiration of the neck fluids yielded pus. Gram stains suggested the presence of fungal elements. Calcofluor white stain demonstrated a mould with septate hyphae that was morphologically consistent with Aspergillus (Figure 3). Culture confirmed the presence of Aspergillus fumigatus, characterized by short conidiophores with conidia forming long chains (Figure 4; lactophenol cotton blue stain, original magnification ×100).

The right maxillary sinus was the likely site of the primary infection, with subsequent spread of the infection to the neck. Otolaryngologists were consulted; they decided not to operate because of the unacceptably high morbidity of any procedure in this patient.

The patient was treated with voriconazole. Caspofungin was added when his health did not improve. The patient’s antiretroviral therapy was not restarted. After 1 month of antifungal therapy, the patient died as a result of invasive aspergillosis.
Images in Infectious Disease

DISCUSSION
Surprisingly, invasive aspergillosis is uncommon in HIV-infected patients, and the diagnosis is commonly not made until autopsy. Most patients described in the literature have CD4+ cell counts that are less than 50/µL and are vulnerable to immunosuppression because of hematological malignancy, neutropenia, corticosteroid use, or prolonged antibacterial use.

The most common pathogen isolated among HIV-infected patients is *A fumigatus* followed by *Aspergillus flavus* and *Aspergillus niger*. The respiratory tract is the most common site of the disease, with the brain as the next most common site. Other sites include the sinuses, kidneys, thyroid, liver, pancreas, spleen, and skin. We were unable to identify any previous report in the literature of invasive aspergillosis presenting as a neck mass in an HIV-infected patient.

The diagnosis of invasive aspergillosis requires a high index of suspicion and appropriate staining to visualize the pathogen. On Gram stain, the hyphae of *Aspergillus* can appear as unstained negative images or they can be invisible. *Aspergillus* is best visualized by using calcofluor, Gomori methenamine-silver, or periodic acid-Schiff stain. *Aspergillus* appears in tissue as septate hyphae with acute-angle branching. Because *Aspergillus* is indistinguishable from *Scedosporium* and *Fusarium* species, cultures using Sabouraud dextrose with brain-heart infusion agar, usually with 5% sheep blood, are needed to make a definitive diagnosis. If specimens are obtained from non-sterile sites, chloramphenicol and gentamicin should be added to the media. Immunohistochemical identification of *Aspergillus* species using monoclonal antibodies can also be used on tissue sections.

Persons with HIV/AIDS are routinely treated with surgery and amphotericin B or itraconazole. Median survival in these patients has been only 3 months after diagnosis. The role of newer azole and echinocandin antifungal agents needs further evaluation.

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The case and images were submitted by Dmitri Iarikov, MD, a first-year fellow in infectious diseases at Baystate Medical Center, Tufts University School of Medicine in Springfield, Mass; David Robertson, MD, a second-year resident in medicine/pediatrics at Tufts University; and Eric Granowitz, MD, and Daniel Skiest, MD, who are associate professors of medicine in the infectious diseases division at Tufts University.

REFERENCES

Therapeutic agents mentioned in this article

| Abacavir/lamivudine/zidovudine | Efavirenz |
| Amphotericin B | Itraconazole |
| Azithromycin | Prednisone |
| Caspofungin | Valganciclovir |
| Dapsone | Voriconazole |
A 52-year-old woman presented with a 12-day history of diarrhea and mild stool incontinence that began 2 to 3 hours after a routine screening colonoscopy. Six or 7 bowel movements of liquid, orange-yellow feces occurred each day for 12 days. The patient reported that associated nausea, flatulence, and severe abdominal cramping were relieved by the bowel movements. She also reported that a small amount of mucus was occasionally observed in the stool and that bright red blood streaks appeared on used toilet paper, although the stool itself was not bloody. She was able to tolerate a full diet, although food exacerbated the urgency. She was afebrile during this illness.

The patient had eaten shrimp 3 days before the onset of her symptoms. She denied any significant travel, contact with an aquatic environment, or sick contacts. She otherwise had been in good health.

The physical examination was significant only for hyperactive bowel sounds. Initial laboratory tests revealed the following values: sodium, 142 mmol/L; potassium, 4.2 mmol/L; chloride, 103 mmol/L; bicarbonate, 30 mmol/L; blood urea nitrogen, 14 mg/dL; and creatinine, 0.8 mg/dL. Total bilirubin level was 0.5 mg/dL (normal, 0.1 to 1.2 mg/dL); aspartate aminotransferase, 36 U/L; alanine aminotransferase, 68 U/L (normal, 0 to 35 U/L); and alkaline phosphatase, 54 U/L (normal, 30 to 120 U/L). The white blood cell count was 7300/µL, with 68% neutrophils, 18% lymphocytes, 12% monocytes, and 1% eosinophils. The thyroid-stimulating hormone level was within normal limits.

A stool specimen revealed numerous bacteria, but no white blood cells were seen. Stool specimens were sent for culture, and the patient was discharged from the clinic. The importance of adequate hydration was stressed, and the patient was instructed to go to the emergency department if signs or symptoms increased in severity.

**DIFFERENTIAL DIAGNOSIS**

Dr Steele: This patient has acute gastroenteritis. Unfortunately, there are no clear clinical clues as to the cause.

During the colonoscopy, biopsy specimens were obtained, which would explain blood in the stools, but the procedure itself would not cause persistent diarrhea.

The absence of fever suggests infection with a viral pathogen such as rotavirus, norovirus, enteric adenovirus, coronavirus, astrovirus, or calicivirus. On the other hand, the presence of blood almost rules out rotavirus and is most frequently observed in *Shigella* infection, which characteristically causes a very high fever.

The patient experienced nausea but not vomiting. Vomiting is common with *Salmonella* infection and most viral causes of gastroenteritis, but it is unusual in infections caused by other bacterial pathogens, such as *Shigella*, *Yersinia*, and *Campylobacter*. The dysenteric form of amebiasis is
not look for unusual pathogens unless the diarrhea worsens or persists for longer than 3 weeks.

HOSPITAL COURSE
Stool cultures contained a heavy growth of Aeromonas hydrophila. There was no evidence of C difficile, Salmonella, Shigella, Campylobacter jejuni, Vibrio cholerae, Yersinia, or E coli 0157:H7. A hydrophila is susceptible to ciprofloxacin; therefore, the patient was given a 5-day course, 500 mg bid. Symptoms improved: the frequency of diarrhea decreased and no associated nausea, flatulence, or abdominal cramping was experienced. A repeated stool culture was negative for A hydrophila as well as other potential stool pathogens. The incidence of passing loose stools continued to lessen until a solid bowel movement occurred 32 days after the onset of symptoms.

FINAL DIAGNOSIS
Acute gastroenteritis caused by Aeromonas hydrophila

DISCUSSION
Although Aeromonas species have been implicated as a cause of diarrhea in both healthy children and adults, the clinical significance of these organisms as stool pathogens remains controversial. A hydrophila was isolated from the stool of our patient, who presented with acute gastroenteritis that slowly responded to currently recommended antibiotic therapy.

A hydrophila is a gram-negative, flagellated bacterium that is widely distributed in freshwater, estuarine, and marine environments worldwide. Some strains are capable of causing illness in fish and amphibians as well as in humans who may acquire infections through open wounds or by ingestion of a sufficient number of the organisms in food or water. A variety of manifestations ranging from wound infections to bacteremia have been associated with Aeromonas species, but these organisms are most commonly isolated from the human GI tract. The virulence of Aeromonas species is, most likely, multifactorial. Possible virulence factors include toxins (cytotoxic and cytolytic); proteases; hemolysins; lipases; adhesions; agglutinins; pili; enterotoxins; various enzymes; and outer membrane arrays, such as an S-layer and capsule. In addition to the presence of virulence factors, the host immune response to the infection influences the severity of the infection.

The role of this organism in causing GI disease in healthy persons has been debated; Aeromonas strains have been recovered in up to 3.2% of stool specimens from persons without obvious GI disease. Studies exist, however, that support the contention that Aeromonas can be an intestinal pathogen in healthy persons. In a 1-year prospective study of children with diarrhea, A hydrophila was isolated from 10.2% of symptomatic persons and from only 0.6% of controls. In a retrospective review, Aeromonas was isolated from 2.8% of adults with diarrhea. In fact, it was more commonly isolated than Salmonella, Shigella, and Campylobacter.

Other supportive evidence comes from a large study that identified Aeromonas as a cause of traveler’s diarrhea in 2% of patients, and a study that found that 4.7% of 3501 diarrheal stool samples from patients hospitalized during 2000-2001 were positive for Aeromonas. Aeromonas infection is associated with a variety of symptoms. The most widely reported is a mild, self-limited, watery, non-bloody, non-mucoid diarrhea, which is commonly seen in children during the late spring, summer, and early fall. Adults, in particular, may present with a protracted, non-bloody diarrhea.

A pathogen of increasing concern is Escherichia coli 0157:H7. This strain causes hemorrhagic uremic syndrome (HUS). Infection with E coli 0157:H7 is much more common in children younger than 5 years but can develop in adults. Many laboratories now routinely screen for the causative pathogen. If E coli infection is suspected, it is important to withhold antibiotics until a definitive diagnosis is made and infection with E coli 0157:H7 is ruled out. Use of antibiotics in the presence of E coli 0157:H7 increases the risk of HUS development.

With any episode of bloody diarrhea, we must consider Clostridium difficile infection, but there is no mention of the patient receiving antibiotics, and the mild nature of the diarrhea does not warrant oral metronidazole or vancomycin therapy. Therefore, I would wait before sending a stool specimen to be tested for C difficile toxin.

Other organisms that once were not thought to be significant stool pathogens but may be the cause of this patient’s symptoms include Cryptosporidium, Dientamoeba fragilis, Balantidium coli, Aeromonas, and Pleisomnus shigelloides. For completeness, infection with the parasite Giardia intestinalis, another common cause of diarrhea in children but unusual in adults, should be considered in the differential diagnosis.

With the exception of providing symptomatic therapy, I would wait to receive results from the routine examination of stool specimens before instituting treatment, and I would consider examining a stool specimen to be tested for trophozoites.
rheal illness that is without signs of colitis and lasts several weeks. Most cases of suspected Aeromonas-associated diarrhea are apparently self-limited. Although therapy may be helpful, no controlled clinical trials have been performed that clearly show benefits of antibiotic therapy. Nevertheless, it has been suggested that initial empirical therapy for suspected A. hydrophila infection should include a fluoroquinolone or trimethoprim/sulfamethoxazole, pending species identification and susceptibility testing. Therapy with ampicillin or a first-generation cephalosporin is not appropriate.

The infection in the patient described in this report fits the pattern of A. hydrophila gastroenteritis. The most likely cause was the ingestion of seafood. (Iatrogenic inoculation by the colonoscope is unlikely given the time between the procedure and the onset of symptoms, but it remains a possibility.) The organism has been associated with shrimp.

One study, conducted in India, that examined the bacterial flora associated with freshwater shrimp found that Aeromonas constituted 38% of surface and GI flora. Treatment of this patient with a fluoroquinolone resulted in a fairly rapid clearing of the organism and cessation of flatulence, cramping, and nausea, but there was slow resolution of diarrhea. This observation also has been reported by Palfreeman and colleagues.

This report supports the view that Aeromonas may act as a GI pathogen in healthy persons and should be included in the differential diagnosis in relation to examination of stool cultures from patients presenting with acute diarrhea.

REFERENCES

Cerebral Phaeohyphomycosis Caused by *Fonsecaea monophora* in a Renal Transplant Patient

Javier Tello, MD and Thomas Otal, MD, PhD

**Fonsecaea** species have been reported as causative agents of chromoblastomycosis, eumycetoma, and fungal pneumonitis. However, *Fonsecaea* rarely involves the CNS, with few cases of cerebral infection reported in the literature. *Fonsecaea monophora* may have greater neurotropic potential than other species of this genus. We describe a rare presentation of brain abscess caused by *F monophora* in an immunocompromised renal transplant patient. [Infect Med. 2008;25:469-473]

**Key words:** Phaeohyphomycosis ■ Dematiaceous fungi ■ Neurotropic infection ■ Cerebral abscess

Phaeohyphomycosis, which manifests as a variety of clinical syndromes, is caused by dematiaceous fungi. One such manifestation is chromoblastomycosis, which is a chronic infection of skin and soft tissue. It is characterized by the presence of sclerotic bodies. Another manifestation is eumycetoma, which is a chronic deep tissue infection that usually occurs in the lower extremities and is characterized by the presence of mycotic grains and sinus tracts. Other clinical presentations of phaeohyphomycosis include superficial colonization of the skin, keratitis, subcutaneous cyst formation, allergic sinus disease, and fatal disseminated infections, including brain abscess.

The presence of melanin within the fungal cell wall may play a role in the pathogenic potential of dematiaceous fungi. Melanin, which has been shown to be an important factor in determining the virulence of other fungi, such *Cryptococcus, Histoplasma, Paracoccidioides*, and *Sporothrix*, may confer an advantage in evading host defenses. Infection can occur through surgical contamination, trauma, or inhalation, and it can spread to distant sites, such as the heart (causing endocarditis) or the brain (causing fungal abscess).

**Case report**

A 67-year-old African American man who had received a cadaveric kidney graft presented with a 2-day history of right-sided hemiparesis and a seizure episode. A CT scan of the brain revealed a 2-cm mass in the left frontal lobe, and MRI of the brain showed a ring-enhancing mass in the posterior left frontal lobe. The patient underwent craniotomy and resection of a left frontal brain mass. Pathological examination of the mass revealed focally necrotic tissue with acute and chronic inflammation and fibrotic response. The tissue was infiltrated with light brown septate hyphae and rare sclerotic bodies (Figure). Cultures revealed *Fonsecaea* species. DNA sequencing confirmed *Fonsecaea monophora*.

The patient’s immunosuppressive regimen consisted of prednisone 5 mg PO qd, tacrolimus 1 mg bid PO, and mycophenolate mofetil 250 mg PO bid. He also was receiving phenytoin at a dosage of 100 mg tid to control seizures. In light of the diagnosis of fungal brain abscess, prednisone was switched to dexamethasone during the perioperative period; eventually, the dosage was tapered down and the drug was discontinued. The tacrolimus also was discontinued to decrease the level of immunosuppression. Treatment with amphotericin B lipid complex (ABLC) in combination with voriconazole was started. After 7 days, the patient was transferred to...
the rehabilitation unit to improve his functional skills.

On arrival at the unit, the patient was alert and had mild right hemiparesis and mild cognitive deficits. Functional improvement was noted, but he had a focal seizure, necessitating adjustment in the phenytoin dosage. After 3 weeks, the patient was discharged to an outpatient facility to complete 6 weeks of ABLC and voriconazole therapy. An MRI scan showed a small residual lesion at follow-up 4 weeks after discharge.

Discussion

Primary phaeohyphomycosis of the CNS can occur in immunocompetent and immunocompromised persons. The clinical management of this infection is problematic because it responds poorly to standard antifungal therapy and requires debridement or surgical excision for cure. The hematogenous route is the most likely source of infection, presumably from an initial subclinical pulmonary focus associated with inhalation of pathogenic environmental dematiaceous fungi.

Twenty-four fungal species have been implicated in cerebral phaeohyphomycosis. Most of these species cause secondary cerebral infection following development of infection in other sites (most often the sinuses). Four species can be considered to cause primary neurotropic infection: Cladophialophora bantiana, Exophiala dermatitidis, Ramichloridium mackenziei, and Ochroconis gallopavum. Fonsecaea infection usually causes lesions confined to the skin and subcutaneous tissue. The organism is ubiquitous in soil and usually gains access to the body cutaneously through a wound. Therefore, a history of exposure to soil or organic material is a risk factor for Fonsecaea infection. Invasion of underlying structures and metastatic spread to distant sites through the lymphatic vessels or via hematogenous dissemination is extremely rare. Cases of cerebral lesions caused by Fonsecaea pedrosoi with primary infection of the paranasal sinus and skin have been reported.

Isolation of Fonsecaea (particularly F. monophora) from a cerebral abscess in the absence of cutaneous or adjacent paranasal disease, as described in our case report, suggests that this organism also may be a neurotropic dematiaceous fungus. The neuroinvasive property of Fonsecaea species appears to be relatively low. Felger and Friedman noted cerebral invasion in mice only after intracerebral inoculation. Cortisone and antibiotic medication were administered to encourage proliferation of spores that were introduced intravenously so that a virulent cerebral infection would develop. Polak obtained similar results when he inoculated mice that had been intravenously pretreated with cortisone with F. pedrosoi, which resulted in a chronic infection characterized by black lesions in the skin and subcutis with sclerotic bodies resembling human chromomycosis and also lesions in the brain and other organs.

Because of the rarity of cerebral phaeohyphomycosis, there is no consensus concerning appropriate treatment. It is generally agreed that a combination of medical and surgical treatment is required. For a single brain abscess, surgical debridement is probably essential for cure. Although complete surgical removal of a brain abscess may not be possible, even partial debulking of the brain mass is helpful. In the case of brain abscess, it is probably wise to use adjunctive medical therapy.

Polyene drugs demonstrate modest antifungal activity in vitro against dematiaceous fungi. They have been used in treatment of some disseminated infections. The azoles are commonly chosen in treatment strategies for phaeohyphomycosis because they exhibit moderate to excellent activity against dematiaceous fungi and can be given safely for long periods. Among the available agents, itraconazole and voriconazole have the most consistent and potent activity. Itraconazole poorly penetrates cerebrospinal fluid, although high levels of the drug are achieved in brain tissue. In contrast, voriconazole achieves good penetration of both cerebrospinal fluid and brain tissue.

In vitro studies of drug combinations generally show either additive or synergistic activity. The initial antifungal regimen for this patient included ABLC, chosen because it is a broad-spectrum agent that penetrates the brain. Voriconazole was also selected because of its known activity against dematiaceous fungi and its clinical usefulness in cerebral phaeohyphomycosis. The level of immunosuppression was decreased, with adjustment of the corticosteroid and tacrolimus therapy. In this case,
surgical excision, combined antifungal therapy with ABL and voriconazole, and reduction of immunosuppression led to a relatively uneventful clinical recovery. After 6 weeks of combined therapy, voriconazole was then continued for several months to eliminate any residual infection.

Therapeutic agents mentioned in this article
Amphotericin B lipid complex
Cortisone
Dexamethasone
Itraconazole
Mycophenolate mofetil
Phenytoin
Prednisone
Tacrolimus
Voriconazole

REFERENCES

INFECTIONS
Importation and Laxity in Vaccine Coverage May Repatriate Measles

ALTHOUGH ENDEMIC MEASLES transmission has been eliminated thanks to vaccination efforts, measles outbreaks nevertheless are becoming increasingly common because of importation of measles via international travel and a growing population of unvaccinated children in the United States. That the number of reported cases of measles in the first half of 2008 was the highest year-to-date since 1996—131 cases—is a cause for alarm. The CDC noted that measles is one of the first diseases to reemerge when rates of vaccination coverage decline. In its report and commentary in the August 22 issue of *Morbidity and Mortality Weekly Report* (Update: Measles—United States, January-July 2008. MMWR. 2008;57:893-896), the CDC suggested that these outbreaks reflect a trend among parents to opt out of having their children vaccinated for either religious or philosophical reasons.

Most of the cases reported between January 1 and July 31 occurred in school-aged children, and most (99, or 76%) were epidemiologically associated with cases characterized as importations. Of the 17 cases that were imported, 9 occurred in US citizens who had traveled abroad and 8 occurred in foreigners who had visited the United States. The source of 15 cases (11%) could not be determined.

The CDC reiterated the importance of childhood vaccinations, explaining that robust vaccination rates (greater than 90% for 1-dose coverage among preschoolers and greater than 95% for 2-dose coverage among school-aged children) are essential to maintain immunity against measles in the general population. Because measles is still common in Europe and elsewhere, 100% eradication in the United States would be unrealistic. Laxity in vaccination coverage, however, in which communities exist with large numbers of unvaccinated persons, is perilous to public health, as evidenced by the trend reported in the MMWR. The CDC expects this trend to worsen, leading to a return of endemic measles epidemics, unless vaccination coverage rates can be improved.

Combined HBV/HAV Vaccine May Rescue Nonresponders to the HBV Vaccine

PERSONS WHO ARE unresponsive to the standard hepatitis B virus (HBV) vaccine regimen may benefit from a revaccination series using a double dose of the combined hepatitis A virus (HAV) and HBV vaccine, according to a study published in the August issue of the *Journal of Infectious Diseases*. Researchers from the Karolinska Institute in Sweden administered the combined vaccine to 48 persons who were nonresponsive and to 20 persons who were naive to the standard HBV vaccine. The combined vaccine was administered at baseline, at 1 month, and at 6 months. Hepatitis B surface antigen (HBsAg) antibodies and HAV antibodies were analyzed before vaccination and 1 month after each vaccine dose.

HBsAg antibody levels of 10 mIU/mL or greater developed after the first vaccine dose in 26 (59%) of the 44 nonresponders who completed the study. After administration of the second dose, the cumulative number of nonresponders in whom HBsAg antibody levels of 10 mIU/mL or greater were achieved increased to 35 (80%); after administration of the final vaccine dose, the cumulative number of nonresponders who achieved target antibody levels increased to 42 (95%). HBsAg antibody titers of greater than 100 mIU/mL were achieved in 80% of nonresponders after receipt of the full revaccination series.

The study authors concluded that this strategy might be highly beneficial in protecting nonresponders to the HBV vaccine who are not already immune to HAV. The citation for this study is Cardell K, Akerlind B, Sällberg M, Frydén A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis.* 2008;198:299-304.
Impact of Changing Demographics of HIV/AIDS on the Role of Primary Care

William M. Valenti, MD

Because widespread use of highly active antiretroviral therapy has made it possible for persons with HIV infection to live longer, the epidemiology of HIV/AIDS has shifted in several ways. The number of persons 50 years and older living with HIV/AIDS has risen in recent years, and there has been a substantial increase in common comorbidities associated with aging in this population. These changes place new emphasis on the important role of primary care in HIV/AIDS management. [Infect Med. 2008;25:477-480]

Key words: HIV/AIDS ■ HIV epidemiology ■ Antiretroviral therapy

Interventions in respect to current epidemiology
Interventions are recommended in 2 broad areas: HIV care and primary and preventive health care. Clinicians who provide HIV care should continue to focus on testing persons aged 13 to 64 years who seek medical attention in primary care, emergency department, and urgent-care settings. The aging baby-boomer population and young adults should be tested even if they do not perceive themselves to be at risk for HIV infection; if they are HIV-positive, they can be referred for clinical care promptly.

The CD4+ T-cell count continues to be the strongest predictor of both HIV-related and non-HIV-related deaths. Therefore, prompt referral for HIV care is an essential component of universal HIV testing. Once patients begin an antiretroviral regimen, adherence to treatment is crucial for good outcomes.

Manfredi was probably the first to report that the life expectancy of HIV-positive persons who receive highly active antiretroviral therapy approximates that of HIV-negative persons. Metabolic complications may be an issue in this population,
although some researchers believe that the cause and characteristics of metabolic conditions such as diabetes, hypertension, and hyperlipidemia in the HIV-infected person differ from those associated with metabolic diseases in noninfected persons.6,7

To reduce the risk of cardiovascular disease in persons with HIV infection, a combination of lifestyle changes and lipid-lowering agents is a priority. Addressing modifiable risk requires special attention but includes the standards established for primary health care, such as encouraging smoking cessation and good dietary and exercise habits. Although the use of lipid-lowering agents may play a role in reducing cardiovascular risk, the activity of such agents in persons with HIV/AIDS appears to be less predictable than in noninfected persons, highlighting the importance of lifestyle changes.6,7

How advancing age affects immune system function is a debatable point and the focus of much research. The goals of antiretroviral therapy remain the same regardless of patient age: restoring immune function as measured by increased CD4+ T-cell counts and viral load suppression.

Results from the AIDS Clinical Trial Group (ACTG) 384 study showed that an age of 40 years or younger, female sex, higher baseline viral load, and virological suppression were associated with greater increases in CD4+ T-cell count at 48 weeks of treatment.8 When stratified by age, patients who were 40 years and younger had significantly higher CD4+ T-cell counts while receiving treatment than those who were older than 40 years.

A study by Silverberg and colleagues9 showed that within 1 year of starting highly active antiretroviral therapy, patients 50 years and older were more likely to achieve an HIV RNA level of fewer than 500 copies/mL after adjusting for co-morbidities than those younger than 50 years. These results appeared to be determined more by greater levels of adherence in older patients than immune system function alone. Thus, if immune system reconstitution is better in younger patients than in older patients, this disparity may be overcome by improved adherence in older patients, as suggested by ACTG 384.

**Point of care**

Who should provide care for persons with HIV infection has been a topic of discussion since the earliest days of the HIV/AIDS epidemic. There is no one correct answer. The best answer is "It depends"—on the patient, the provider’s resources and capacity, and access to care.

The ideal care provider is one experienced in HIV medicine who also offers primary care. Collaboration between primary care providers and specialists in HIV medicine is another option. With the new paradigm in which persons with HIV infection live longer and in whom common age-related conditions develop, both primary and specialty care need to be addressed.10 Regardless of the treatment model, continuity of care and communication among providers are essential.

**New epidemiology and therapeutic options**

To date, no antiretroviral agent or regimen has been shown to be more effective in older persons than in younger adults, and treatment recommendations are the same for both age groups. However, when choosing an antiretroviral regimen, the clinician needs to consider potential toxicities as well as pill count, convenience, and tolerability. For example, the thymidine analogues zidovudine and stavudine are no longer

![Table — Causes of death and mortality rates in HIV-positive persons, 1990-2003](image-url)
recommended as first-line therapy in the United States because of their association with mitochondrial toxicity. Instead, other agents, such as tenofovir and abacavir, are now recommended for nucleoside analogue–backbone regimens.

Anecdotally, most providers have developed their own strategies to assess patients for antiretroviral therapy and select regimens based on their experience and preferences. The critical issue is to ensure close follow-up of patients to monitor adverse events and adjust regimens accordingly. Clinical judgment still plays a pivotal role in treatment decisions.

There is no reason to withhold antiretroviral therapy in older patients, especially if they are able to adhere to treatment. The critical issues are proper regimen selection and follow-up. Furthermore, there are no data on antiretroviral dosing adjustments for older patients. The standard recommendations for selecting antiretroviral agents or making dose adjustments based on renal or hepatic function determine treatment.

There are no guidelines that are age-specific. However, in addition to the guidelines cited above, the Infectious Diseases Society of America (IDSA) has issued 2 worth mentioning: guidelines for the management of lipid disorders and cardiovascular risk in persons with HIV infection who receive antiretrovirals and guidelines for the management of chronic kidney disease in HIV-positive patients.

For lipid management, the IDSA recommends that HIV-infected adults should undergo evaluation and treatment on the basis of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III Guidelines. The NCEP recommends that nonpharmacological interventions be given a thorough trial before consideration of drug therapy. The recommendations also stipulate that intensive therapy with lipid-lowering medications should be used in persons with metabolic syndrome. This includes aggressive treatment of hypertension, diabetes, and dyslipidemia. The NCEP also emphasizes the importance of smoking cessation, weight reduction, increased physical activity, and a salubrious diet. The fundamental message still is that physicians must treat HIV infection first. The choice of antiretroviral therapy depends on many patient-specific factors, of which cardiovascular risk is only one.

The IDSA renal guidelines are quite specific in terms of their recommendations that all patients at the time of HIV diagnosis be assessed for existing kidney disease with a screening urinalysis for proteinuria and a calculated estimate of renal function (creatinine clearance or glomerular filtration rate). This renal function estimate also allows the physician to properly prescribe antiretroviral agents and other commonly used medications that require renal adjustment. Therapy for HIV-associated renal disease should be individualized to the patient’s clinical circumstances and to the underlying renal histology findings. The guidelines also recommend ongoing evaluation of renal function, for example, measuring baseline renal function with serum creatinine and urinalysis, during antiretroviral therapy.

**Therapeutic agents mentioned in this article:**
- Abacavir
- Stavudine
- Tenofovir
- Zidovudine

**Conclusion**

The epidemiology of HIV/AIDS is changing as patients live longer and are at risk for more common age-related comorbidities. In the era before potent antiretroviral therapy was the standard of HIV care, primary care needs were shorter-term because most HIV-positive persons did not live long enough for diabetes or cardiovascular disease to develop. In the current era, these shifts reinforce the important role of primary care in addition to the specialty management of HIV/AIDS.

At minimum, patients with HIV infection need primary and specialty care. There are many options for ensuring that patients have both. The ideal is a seamless model of primary care and HIV/AIDS care by the same providers in the same setting. However, this will not always be possible for many reasons, including patient preference, provider expertise and resources, and reimbursement constraints.

When treatment is divided between a primary care provider and an HIV/AIDS care specialist, both providers need to establish a communication path to share information such as progress notes, medication lists, and reports from consultants and laboratories. This approach can help manage costs, prevent duplication of effort and, most important, contribute to better patient outcomes.

**REFERENCES**


Another version of this article was originally published in the August 2008 issue of The AIDS Reader.

Erratum
An editorial error appeared on page 364 of August issue in the article “Emerging Pathogens and New Recommendations in Travel Medicine.” The passage should read:

“Routine adult vaccine guidelines have been updated to include varicella-zoster vaccination of adults 60 years and older who have evidence of past varicella immunity. Evidence of past varicella immunity is described in the 2008 ACIP Adult Immunization Schedule. All adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine unless they have a medical contraindication.”

Apologies to the authors and readers for this oversight.

In addition, the authors would like to amend the last statement in Table 3 to read as follows:

“Persons who suspect that they were exposed to TB should be advised to seek medical evaluation because treatment for latent disease with isoniazid may be required. Because of the increased incidence of MDR-TB and XDR-TB, those with test conversion or signs and symptoms of TB associated with international travel should seek care from experts in infectious disease or pulmonary medicine.”
A zoonosis is any disease—bacterial, mycotic, viral, or parasitic—that is transmissible from an animal to a human. More than 200 zoonoses have been identified. The newly emerging zoonosis that has achieved star status in the medical press is avian influenza. Another emerging threat is Nipah virus, which is transmitted from pigs to humans in the agricultural setting and causes encephalitis. But animal to human transmission of zoonoses are multimodal: from exposure to animal secretions in the agricultural setting, to transmission through insect vectors and ingestion of contaminated animal products, to more insidious routes, such as petting or being scratched or nipped at by one’s pet dog, bird, cat, lizard, or other creature. A few interesting cases are presented here.

Tularemia
An infected 3-cm laceration on the lateral aspect of the right leg of a 25-year-old construction worker (Figure 1) was accompanied by flu-like symptoms and a painful, right-sided inguinal lymph node. The patient only complained of fever and the enlarged node, which was 3 times its normal size and exquisitely tender. The lesion went unnoticed at the initial visit, during which the patient was uncooperative about examination procedures. He denied having symptoms of venereal disease or problems with his right leg or the right side of his body. Because he was uncooperative and refused further examination, he was given a single intramuscular injection of penicillin G benzathine, 1,200,000 U, and a prescription for double-strength trimethoprim/sulfamethoxazole (TMP/SMX).

On questioning, it was learned that the patient had gone hunting the previous week and that he had sustained a cut on his leg sometime before then. During his hunting foray, he killed 2 jackrabbits and 2 cottontails. He placed them in a sack and tossed the sack over his shoulder. He later noticed that blood from the kill had leaked out of the sack and down his leg, seeping through a hole in his jeans and into the leg wound.

Tularemia, transmitted to the patient from a rabbit infected with *Francisella tularensis*, was suspected. The suspicion was confirmed by bacteriological identification from a biopsy of the node. On the recommendation of an epidemiologist, a 10-day course of streptomycin at a dosage of 1 g was given intramuscularly twice daily. Five days later, recurring fever mandated a second, 6-day course of the antibiotic. The patient was lost to follow-up.

*F. tularensis* is a nonsporulating, nonmotile, aerobic gram-negative coccobacillus that is usually transmitted to humans from infected rabbits and other small animals via ticks, fleas, or deer flies or by direct contact. Infection was more commonly seen in the United States before World War II; the incidence then declined and in recent years has been between 0.05 and 0.15 cases per 100,000.

The incubation period averages 3 to 5 days but ranges...
from 1 to 21 days. The most common presentations are ulceroglandular and typhoidal diseases. The first type of presentation makes up 21% to 87% of cases in the United States and is the result of skin or mucosal inoculation. Patients present with localized enlargement and tenderness of lymph nodes and 1 or more painful ulcerative skin lesions as illustrated in this case. The second type of presentation results from aerosol exposure and is notable for fever, headache, prostration, cough, and substernal pain, without lymphadenopathy.

The diagnosis is usually made by serological methods (tube agglutination, microagglutination, and enzyme-linked immunosorbent assay [ELISA]) several weeks after the onset of illness. The greatest impediment to a rapid diagnosis may be the lack of clinical suspicion in a patient with either primary pneumonia or typhoidal disease and no apparent traditional animal exposures. Streptomycin is the drug of choice and gentamicin is an effective alternative.

Cystic echinococcosis

Echinococcosis is a zoonotic infection caused by the cestode species of the genus *Echinococcus*. Three species of *Echinococcus* cause hydatid disease in humans: *Echinococcus granulosus*, the most common variety, which causes cystic echinococcosis; *Echinococcus multilocularis*, which causes alveolar echinococcosis; and *Echinococcus vogeli*, which causes polycystic echinococcosis. Endemic foci are found in eastern, western, and southern Europe; the Middle East; North and South Africa; Australia; and New Zealand.

The adult tapeworms (3 to 6 mm long) inhabit the small intestine of carnivorous hosts, such as dogs, coyotes, and wolves. The cystic stage occurs in herbivorous intermediate hosts, such as sheep, cattle, goats, camels, pigs, and horses, and in humans.

In the typical dog-sheep cycle, dogs ingest viscera that contain echinococcal cysts with protoscolices (tiny tapeworm heads) inside. Protoscolices attach to dogs’ intestines and develop into adult tapeworms capable of producing infective eggs. Tapeworm eggs are passed in the feces of an infected dog and may be ingested by grazing sheep. They hatch and migrate to specific sites where they develop into echinococcal cysts.

Humans, like sheep, become infected by ingesting tapeworm eggs either through direct contact or from food or water contaminated by fecal material that contains tapeworm eggs. Larvae migrate mainly to the liver (63%) and lungs (25%) and less frequently to the muscles (5%) and bones (3%).

Although echinococcosis is uncommon in the United States, transmission of *E. granulosus* in the dog-sheep cycle occurs in the western states, principally California, Arizona, New Mexico, and Utah. In Arizona and New Mexico, echinococcosis is seen in American Indians who belong to the Zuni, Navajo, and Santo Domingo tribes. Members of these tribes generally live in close proximity to their animals.

The CT scan shows a large cystic lesion with multiple internal septations (Figure 2). It developed in an asymptomatic, healthy, 40-year-old woman who had hepatomegaly and reported having a sensation of fullness in the upper abdomen for many years. The woman had been raised on a farm in Greece and moved to the United States at age 24 years. Based on ultrasonography, CT, and laboratory test results and the patient’s history (exposure to farm dogs or sheep dogs in areas where *E. granulosus* is endemic), echinococcosis was suspected. Results of an indirect hemagglutination test and an ELISA were positive for IgG antibodies against *Echinococcus*.

Albendazole and mebendazole are the only anthelminthic agents effective against cystic echinococcosis. Albendazole, which is more effective for liver cysts, is dosed at 400 mg bid for 6 to 12 months. Mebendazole is dosed at 10 mg/kg/d. Both agents are contraindicated in pregnancy. With drug treatment, cysts disappear in up to 30% of patients; in 30% to 50%, cysts degenerate or shrink significantly; and in 20% to 40%, cysts remain morphologically unchanged.

The treatment choices presented to the patient were surgery, percutaneous puncture of the cyst, and chemotherapy. The patient chose chemotherapy. Thus, a regimen of albendazole 400 mg bid was begun. After 6
months of therapy, an abdominal CT scan showed a 30% reduction in the size of the cyst. An additional 6 months of therapy with regular follow-up was recommended.

**Unusual manifestation of brucellosis**

Brucellosis is another zoonotic infection that occurs in persons who have direct contact with domestic animals. Historically, it was also spread by consuming unpasteurized milk and contaminated cheese. Clinical symptoms include intermittent fever, chills, headache, profound weakness, arthralgia, myalgias, and weight loss. This infection is associated with orchitis and epididymitis in men and miscarriage in women.

The nonpruritic, nonhemorrhagic, maculopapular rash that had developed on the arms, legs, and trunk of a 49-year-old farmer is an unusual presentation of brucellosis (Figure 3). The patient was hospitalized because of a 3-week history of intermittent fever, fatigue, anorexia, generalized myalgias, and malodorous sweating. The reddish lesions of the rash were less than 1 cm in diameter. There was no history of antibiotic or antipyretic drug therapy, and no other abnormalities were found on physical examination.

Results of a complete blood cell count were normal except for a hematocrit value of 40% and a platelet count of 410,000/µL. The erythrocyte sedimentation rate was 35 mm/h. The patient’s C-reactive protein level was 24 mg/dL, and the results of a rheumatoid factor test were negative. Biochemical parameters were normal except for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, which were twice the upper normal limit.

An ECG, a chest film, and abdominal and transthoracic heart ultrasonograms showed no abnormalities. A tuberculin skin test yielded negative results, as did serological tests for syphilis, brucellosis, leptospirosis, rickettsiosis, mycoplasmosis, and toxoplasmosis, as well as for infection with Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, HIV, and hepatitis C virus. The patient was immune to hepatitis B. Urinalysis results were normal, and urine and blood cultures were negative for pathogens.

Bone marrow for cultures was obtained on admission; the cultures were positive for *Brucella melitensis*, which is the strain found in sheep and goats. The patient was given doxycycline 200 mg/d and rifampin 900 mg/d for 6 weeks. The skin lesions disappeared a few days after therapy was initiated.

**Cutaneous leishmaniasis**

Cutaneous leishmaniasis was one of the souvenirs of a 6-week trip to the rain forests of Peru for a 28-year-old, female graduate student (Figure 4). The lesion began as a raised papule that enlarged over a 3-week period. It was nontender and did not itch. Lymphadenopathy was absent. A Giemsa-stained touch preparation of the skin...
biopsy specimen revealed amastigotes within macrophages, consistent with leishmaniasis (Figure 5). Culture was thwarted by yeast overgrowth, but a companion of the patient also had the same kind of lesion; culture of a biopsy sample from that lesion revealed *Leishmania braziliensis*.

On the basis of these findings, a presumptive diagnosis of cutaneous *L braziliensis* infection was made. The patient was treated with 20 mg/kg/d of intravenous sodium stibogluconate for 20 days. She experienced myalgias and mild elevations in serum ALT, AST, amylase, and lipase levels, which normalized after cessation of therapy. After completion of therapy, the lesion decreased in size and scarred over.

*Leishmania* organisms are obligate intramacrophage protozoa. Numerous Old World and New World species exist, and areas of endemicity are the tropics and subtropics. Thus, patients presenting with leishmaniasis in the United States typically have a history of recent travel, although rare cases have been reported in Texas.²

Cutaneous leishmaniasis is transmitted by the bite of an infected female phlebotomine sandfly, which itself becomes infected by feeding on the blood of infected mammals, including humans. Leishmaniasis also can be transmitted congenitally and through parenteral exposure to infected blood (ie, blood transfusion or needle-sharing). Lesions can range from being small, dry, and crusted to being large, deep, disfiguring, and ulcerous. They may be single or multiple and usually develop on exposed areas of skin (eg, face, arms, and legs). Other symptoms may include regional lymphadenopathy, malaise, anorexia, weight loss, and low-grade fever.

Diagnosis is made on the basis of patient history and clinical presentation and is often confirmed by Giemsa staining of a skin biopsy specimen. Most cases resolve within several weeks to 3 years without treatment. Systemic treatment with sodium stibogluconate, available in the United Kingdom but an investigational drug in the United States and only available through the CDC, is indicated for infections caused by the *L braziliensis* species complex and is used to help prevent mucosal leishmaniasis and decrease morbidity associated with the chronicity of the skin lesion.

**REFERENCES**

**Case Report**

**Pasteurella Pneumonia Associated With Cutaneous Trauma**

Smitha Daka, MD and Latha Rajagopal, MD

Community-acquired pneumonia is a frequent cause of hospital admission in adults. It usually results from infection with pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma*, and *Chlamydia*, among others. In a few cases, pneumonia develops from infection with unusual pathogens, such as *Pasteurella multocida*, a gram-negative organism commonly found in the mouths of cats and dogs. We report a case of *P multocida* pneumonia associated with skin trauma caused by cat scratches in a woman with a history of chronic obstructive pulmonary disease. [Infect Med. 2008;25:487-489]

**Key words:** Community-acquired pneumonia ■ *Pasteurella multocida* infection ■ Chronic obstructive pulmonary disease

**Case report**

A 63-year-old woman with a history of chronic obstructive pulmonary disease (COPD) presented to the emergency department with concerns of fever, productive cough, shortness of breath, weakness, left-sided pleuritic chest pain, nausea, and light-headedness. The symptoms reportedly had persisted for a week. She denied hemoptysis, vomiting, and other systemic symptoms and had no previous history of pneumonia. She was an active smoker (1.5 packs a day for 45 years), but she denied alcohol and injection drug abuse. The patient had 2 cats.

The patient was allergic to sulfa drugs, penicillin, aspirin, codeine, and ibuprofen. Her past medical history included gastric carcinoma, which was diagnosed 20 years earlier, and bladder cancer, which was diagnosed 1 month earlier. The patient weighed 107 lb. Examination of the skin and extremities revealed scratches on the right thigh and the fingers of both hands, which reportedly were caused by one of the patient’s pet cats.

During the initial examination, the patient’s temperature was 39.9°C (103.9°F). Her pulse rate was 104 beats per minute. Blood pressure was 124/74 mm Hg, respiration rate was 24 breaths per minute. Arterial blood gas analysis on admission showed significant hypoxemia (pH was 7.44, PaCO₂ was 34 mm Hg, PaO₂ was 39 mm Hg, bicarbonate level was 23 mEq/L, and oxygen saturation was 76% on room air). The leu-

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kocyte count was 7100/µL, and it increased to 15,200/µL, with 40% bands, in 48 hours. Results of the basic metabolic panel, coagulation profile, and liver function tests were normal. Chest auscultation revealed decreased breath sounds in the left lung base and dullness to percussion in the left midlung. A chest radiograph showed increased density in the left lingular area and a small left pleural effusion. A CT scan of the chest showed a lingular infiltrate with compressive atelectasis and left pleural effusion (Figure 2). A 2-dimensional echocardiogram showed no vegetations. The patient was given moxifloxacin 400 mg IV daily and aztreonam 2 g IV q8h. Blood cultures grew gram-negative rods, which were identified as P multocida. Following a 10-day course of antibiotic therapy, clinical improvement was seen. The patient was discharged home. Radiographs obtained 3 months later showed resolution of the previous infiltrate and no pleural effusion.

Discussion
Respiratory tract colonization by P multocida in humans is known to occur. In most cases, infection manifests as upper or lower respiratory tract disease, such as chronic sinusitis, bronchiectasis, pharyngitis, epiglottitis, tracheobronchitis, pneumonia, emphysema, or lung abscess. In addition, Pasteurella infections also include skin and soft tissue infections, bone and joint infections, meningitis, endocarditis, and septicemia. Most patients with P multocida respiratory tract infections have underlying lung diseases, such as COPD, which was the case with our patient. Bacteremia is found in 55% of the patients in whom blood cultures are obtained, and overall mortality is 29%.

The clinical course of Pasteurella respiratory tract infections is nonspecific. Common symptoms include fever, malaise, dyspnea, and pleuritic chest pain. Onset of disease may be gradual or abrupt. In patients with pneumonia, chest examination will reveal localized findings, such as dullness, rhonchi, or wheezing. The chest radiograph commonly shows lobar consolidation, but multilobar and diffuse infiltrates have been described. Pasteurella may be mistaken for H influenzae, M catarrhalis, Neisseria species, or Acinetobacter on sputum Gram stain. It is susceptible to a number of antibiotics, including penicillin G, amoxicillin/clavulanic acid, piperacillin/tazobactam, doxycycline, fluoroquinolones, carbapenems, and advanced cephalosporins. Penicillin is the drug of choice. Patients who are allergic to penicillin may be treated with oral quinolones or doxycycline. Infections caused by β-lactamase–producing strains can be treated with extended-spectrum cephalosporins (cefuroxime, cefpodoxime) or trimethoprim/sulfamethoxazole.

REFERENCES
1. Grehan M, Muller F. The oxidase reaction of Pasteurella multocida strains cultured on Mueller-

Figure 1 – A posteroanterior radiographic view of the chest shows increased density in the lingular area and a small left pleural effusion.

Figure 2 – A CT scan of the chest with contrast shows a lingular infiltrate with compressive atelectasis and left pleural effusion.

Therapeutic agents mentioned in this article
Amoxicillin/clavulanic acid
Aspirin
Aztreonam
Cefpodoxime
Cefuroxime
Codeine
Doxycycline
Ibuprofen
Moxifloxacin
Penicillin G
Piperacillin/tazobactam
Trimethoprim/sulfamethoxazole

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