A Decade of Advances and Challenges

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**Key words:** Pediatric infectious disease medicine ■ Vaccines ■ Highly active antiretroviral therapy ■ Antibiotic resistance

**Many advances and challenges have occurred in the field of pediatric infectious disease medicine during the past 10 years. Because this is the 10th anniversary of this column, a summarization of what, in my opinion, are the most clinically significant developments is presented here.**

Development of new vaccines, monoclonal antibodies, immunization policies, and guidelines for chemoprophylaxis represent impressive advances in preventive infectious disease medicine. New vaccines include those against infections caused by *Streptococcus pneumoniae*, rotavirus, human papillomavirus, *Neisseria meningitides*, varicella, influenza, and pertussis.1,2

As for the contribution of monoclonal antibodies, significant decreases in morbidity and mortality and associated respiratory syncytial virus infection in at-risk infants have been associated with the widespread prophylactic use of palivizumab.3 In addition, the implementation of guidelines aimed at universal prenatal screening and intrapartum prophylaxis has resulted in a dramatic decrease in the incidence of early-onset group B streptococcal disease among neonates.4

We also have witnessed a significant expansion in the field of molecular diagnostics. Many tests within this category, such as those for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, Enterovirus, herpes simplex virus, HIV, and *Bartonella henselae* infections, are now routinely requested in most clinical settings. New molecular techniques also have resulted in the discovery of pathogens such as human metapneumovirus and bocavirus, which now appear to be common causes of pediatric disease.5,6

One of the most significant achievements from the therapeutic standpoint has been the ability to use highly active antiretroviral therapy effectively in children infected with HIV. It has resulted in a significant reduction in mortality in this population. Indeed, in industrialized countries, the incidence of perinatally acquired HIV infection has decreased dramatically because of the use of highly active antiretroviral therapy during pregnancy.7-9 Progress also has been made in the development of antiviral therapy aimed at infections such as influenza, Cytomegalovirus infection, and herpes simplex.

Among new challenges is the growing epidemic of infections caused by community-associated methicillin-resistant *Staphylococcus aureus*, which has become the most common bacterial cause of hospitalization in children in many areas of the United States. Emergence of significant antibiotic resistance among other common pediatric pathogens, such as *Streptococcus pyogenes*, *S pneumoniae*, and enteric gram-negative organisms, also has become a major concern.10 Although many new antimicrobials have been developed and licensed for adults, studies aimed at assessing the safety and efficacy of these agents in children have been lacking, and thus the antibiotic armamentarium in the pediatric population is currently not up to par.11 In addition, the success of immunization programs has been compromised by the development of misconceptions about vaccine administration in the public sector and a decrease in public awareness about the deleterious effects of vaccine-preventable diseases.12

New and emerging threats seen during the past decade include the severe acute respiratory syndrome epidemic, a potential new influenza pandemic, and the resurgence of invasive pneumococcal disease in children. Worldwide, elimination of measles and poliomyelitis remains a challenge, and many developed countries still lack the resources to effectively treat and prevent pediatric GI infections, tuberculosis, and HIV infection. Nevertheless, new discoveries and technological advances...
aimed to improve children’s health will emerge as we address these and other current challenges and, of course, future challenges in the years to come.

REFERENCES
**Opportunistic Fungal Infections, Part 2: Candida and Aspergillus**

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

Morbidity and mortality attributed to *Candida* and *Aspergillus* infections can be quite high in immunocompromised hosts. The epidemiology and clinical manifestations as well as clinical pearls on prevention of infections caused by *Candida* and *Aspergillus* are discussed in this second installment of a 3-part series on opportunistic infections in immunosuppressed patients. [*Infect Med.* 2008;25:498-505]

**Key words:** Candidiasis ■ Aspergillosis ■ Opportunistic infections ■ Immunocompromise

*Candidiasis* and aspergillosis are the most common fungal infections in immunocompromised hosts. The spectrum of disease ranges from superficial and mucosal infections to invasive tissue infections. Morbidity and mortality attributed to infections with *Candida* and *Aspergillus* can be quite high; therefore, timely identification and treatment are important.

**Epidemiology**

*Candida* is ubiquitous, with more than 200 described species. About 10% of the species are responsible for human disease, with *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata* being the most commonly isolated. *Candida krusei* and *Candida lusitaniae* are seen less frequently. Significant risk factors for candidal disease include neutropenia, use of antibiotics, the presence of an indwelling vascular device, and prolonged stay in the ICU.

Infections attributed to *Candida* species can be divided into 3 categories: hematogenous (eg, candidemia, hepatosplenic candidiasis, and osteomyelitis), nonhematogenous superficial (eg, cutaneous candidiasis, oropharyngeal candidiasis, and vaginitis), and nonhematogenous deep-seated (eg, esophageal candidiasis, cystitis, peritonitis, and tracheitis/bronchitis). It is noteworthy that *Candida* is the fourth leading cause of nosocomial bloodstream infections in hospitalized patients.1 Immuno-compromised patients are at high risk for the development of any of these infections.

In HIV-1–infected patients, oro-pharyngeal and esophageal candidiasis are common and are recognized as an indicator of immunosuppression. These types of candidiasis are seen most commonly in patients with CD4+ T-lymphocyte counts of less than 200/µL.2 Other types of infections with *Candida* can certainly occur in this population but are usually associated with other concurrent risk factors. Although *C albicans* is still the predominant species that is isolated, the emergence of fluconazole-resistant species has been observed, usually in the setting of previous fluconazole exposure.

Patients with hematological malignancies and hematopoietic stem cell transplant (HSCT) recipients are at high risk for development of invasive candidiasis (IC), which is a major cause of morbidity and mortality. The portal of entry is typically the gut mucosa, and less commonly, the integument. Although oral and esophageal infections occur, fungemia is the most serious clinical syndrome observed.3 In addition, although *C albicans* still accounts for most invasive *Candida* infections, non-*albicans* *Candida* species have emerged with increasing frequency, particularly *C glabrata* and *C krusei*. Bloodstream infection with these species has been associated with higher rates of crude mortality.4

Most invasive fungal infections
following organ transplant are also due to *Candida* species. These infections are typically related to complications of surgery and usually appear near the end of the first month posttransplant. Liver and pancreas transplant recipients are at especially high risk for invasive *Candida* infections in the first month following transplant.4

Aspergillus species are also ubiquitous in the environment and are found in soil, water, and decaying vegetation worldwide. Portals of entry include the respiratory tract and damaged skin or operative wounds. Reports suggest that *Aspergillus* infections occur in 4% to 20% of bone marrow transplant (BMT) recipients, with neutropenia being the most important risk factor for infection.5 A recent prospective trial evaluating the cumulative incidence (CI) in 4261 HSCT recipients during a 22-month period found a CI of 0.5% after autologous HSCT and 2.3% after allogeneic transplant. Mortality following the diagnosis of invasive aspergillosis ranged from 53.8% to 84.6%.8 The incidence of disease in HSCT recipients has a bimodal distribution, occurring in the early engraftment stage (around day 30) and then again after 180 days posttransplant, which probably reflects the presence and treatment of graft versus host disease.

In organ transplant, *Aspergillus* infections are most common in heart and lung transplant recipients (1% to 15% and 3% to 15%, respectively) and less common in liver transplant (1% to 8%) and kidney transplant recipients (0.7% to 4%). More than half of the *Aspergillus* infections in liver transplant recipients occur in the first 3 months after transplant. In contrast, 72% of cases of invasive aspergillosis (IA) are identified in the first 3 months after heart transplant, and 50% occur in the first 5 months after lung transplant.8

**CLINICAL MANIFESTATIONS**

In immunocompromised hosts, the clinical presentation of fungal infection is often nonspecific. Fever is a common symptom, as are pulmonary symptoms of cough and dyspnea. Suspicion for fungal infection should be based on host risk factors, including the underlying immunological state and current treatments (including medications), as well as on epidemiological exposures. (See Figure 1 for a diagnostic pathway.)

**Oropharyngeal candidiasis**

Oropharyngeal candidiasis is often asymptomatic and manifests as a painless, creamy white, plaque-like lesion on the tongue or buccal or oropharyngeal mucosa. Patients who have esophageal candidiasis often present with fever, retrosternal burning pain or discomfort, and odynophagia. Endoscopic examination reveals white plaques such as those observed with oral candidiasis that may progress to superficial ulcerations of the esophagus.2

**Invasive candidiasis**

IC usually presents in a nonspecific manner, with fever as the major finding. Maculopapular, erythematous skin lesions may occur, but biopsy and histopathological examination are required for diagnosis.7 Blood cultures will be positive when the infection is associated with an endovascular catheter; however, when disease is limited to visceral organs, blood cultures are often negative. *Candida* endophthalmitis as a complication of candidemia occurs in 3.7% to 25% of candidemia cases and can be detected on funduscopic examination. However, signs may not manifest in neutropenic patients until after neutrophil recovery; therefore, ophthalmological examination should be repeated after neutropenia has resolved.3

**Aspergillosis**

Most patients (80% to 90%) who are infected with *Aspergillus* will present with pulmonary disease. However, other manifestations include rhinosinusitis; disseminated cutaneous infection (especially in children with leukemia); and disseminated disease with CNS involvement—primarily brain abscess related to mycotic aneurysm. The most immunocompromised patients are the least likely to have symptoms, and their disease rapidly leads to death. The most common symptoms, seen as the disease progresses, are fever and cough. In addition, hemoptysis occasionally is present. Patients who are receiving corticosteroids may be afebrile; however, low-grade chest pain is common.10

Chest radiographs with nodular or diffuse pulmonary infiltrates are suggestive of the disease but are very nonspecific. Cavitation and wedge-shaped lesions are the most distinctive signs of IA; however, other invasive fungal infections can cause similar effects. Characteristic radiographic findings such as the halo sign or crescent sign are the result of vascular invasion, which causes thrombosis, infarction, or necrosis of the surrounding tissue.11

**Aspergillus rhinosinusitis**

Early symptoms of acute invasive *Aspergillus* rhinosinusitis are also nonspecific and can be mistaken for bacterial infection. Fever, cough, epistaxis, and headache are common. Findings from an examination may be unremarkable, but an eschar can sometimes be visualized using direct endoscopy. CT scans will show fluid opacification of the sinus, often with bony erosion. MRI is also diagnostically useful. Diagnosis is dependent on clinical signs concurrent with a culture positive for *Aspergillus* or tissue biopsy results suggestive of fungal invasion.10

continued*
Cutaneous aspergillosis
Primary cutaneous aspergillosis is most commonly seen at or around intravenous catheter insertion sites (Figure 2) or is associated with adhesives, such as tape or occlusive dressings, or infections resulting from trauma or surgical wounds. Secondary cutaneous aspergillosis is associated with disseminated disease and may be due to direct extension or embolic disease. Necrosis is common, and a biopsy is often necessary to make this diagnosis.

Cerebral aspergillosis
Cerebral aspergillosis can present as cerebral hemorrhage secondary to fungal invasion of the surrounding blood vessels. It occurs in 10% to 20% of all cases of IA. A characteristic finding on a CT scan of the head is 1 or more hypodense, well-demarcated lesions. A biopsy is required for definitive diagnosis.

LABORATORY DIAGNOSIS
Candida species grow readily in standard blood culture media, but blood cultures are negative in up to 56% of autopsy-proved cases of IC. Microscopic features show important species-related variations. Most produce pseudohyphae that are long, branched, or curved. On tissue histopathological examination, this feature distinguishes *Candida* from *Aspergillus*.

Pathogenic *Aspergillus* species generally grow easily and relatively quickly on routine bacteriological and mycological media in the laboratory; however, a higher yield of organisms is achieved on mycological media. Fluid from bronchoalveolar lavage (BAL) or endotracheal aspiration should be processed for microscopic or cytological examination and for fungal culture. Culture of *Aspergillus* from an infected sterile...
site provides definitive proof of disease and is important in making therapeutic decisions. Definitions of invasive fungal disease are generally based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group definitions that have recently been revised.14

Serological testing using the galactomannan (GM) assay or (1→3)-β-D-glucan (BG) assay is reviewed further on in this article. Histopathological findings of IA show filamentous septated hyaline hyphae with acute angle branching (Figure 3).

**Non–culture-based diagnostics**

The current conventional diagnostics for the detection of fungal infections include antigen or antibody testing as well as routine culture methods. Culture-based methods for diagnosis of *Candida* and *Aspergillus* infection can be problematic. The sensitivity and specificity of culture of *Candida* and *Aspergillus* are low, especially when the organisms are recovered from nonsterile sites.16

The diagnostic value of a culture positive for *Aspergillus* depends on the risk status of the patient. In a retrospective analysis of 1209 patients with *Aspergillus*-positive cultures, mostly from nonsterile respiratory secretions, 148 cases of definite (n = 90), probable (n = 49), or possible (n = 9) IA were identified. Patients were stratified into high risk, intermediate risk, or low risk for IA on the basis of underlying disease. Among high-risk patients (allogeneic HSCT recipients or patients who were neutropenic or were being treated for a hematological malignancy), a culture positive for *Aspergillus* was associated with IA in 50% to 65% of cases, whereas in those at low risk (patients with cystic fibrosis or other connective-tissue disease), a positive culture result rarely represented invasive disease. In the intermediate-risk group (for example, autologous BMT or solid organ transplant recipients or patients with diabetes or HIV infection), the association between a positive culture result and IA was 8% to 28%.17

For these reasons, alternative non–culture-based diagnostic tests are being developed, including GM antigen testing, polymerase chain reaction (PCR) assay, and BG antigen testing.

GM is a highly immunogenic antigen found in the cell wall of *Aspergillus* species and is released by the fungus into serum during its growth in tissues.18 Enzyme-linked immunosorbent assay for GM has been validated as a surrogate marker for detection of IA in both animal models and humans.16-23 It is reported as an index of optical density (GM index [GMI] test), and results are considered positive when the index is 0.5 or more from 2 aliquots of the same sample.24 False-positive tests have been associated with the use of certain antibiotics, including piperacillin/tazobactam and amoxicillin/clavulanate,25-28 and they also may be seen in patients who have histoplasmosis.29

A recent review by Miceli and colleagues24 investigated the correlation between the GM assay followed sequentially and clinical outcomes in patients with hematological malignancies using data derived from 27 published studies. Their findings showed a strong correlation between GMI and aspergillosis outcome. Specifically, a normal GMI was associated with a favorable outcome, whereas a positive GMI was associated with death. Although these results are quite interesting, caution should be used in interpreting them in regard to treatment decisions.

Recently published guidelines from the Infectious Diseases Society of America regarding the treatment of aspergillosis suggest that resolution of GM antigenemia should not be used as a sole criterion for discontinuation of antifungal therapy.23 The role of GM in BAL fluid as a tool for

**Figure 3** - This is a Gomori methenamine-silver stain of *Aspergillus* in a biopsy specimen of the lung of an allogeneic hematopoietic stem cell transplant recipient. Note the acute angle of branching hyphae that is characteristic of moulds (not specific to *Aspergillus*). *Mucor* tends to have a 90-degree branch angle, whereas *Fusarium* and *Aspergillus* tend to have a 45-degree branch angle.
early diagnosis of IA has been examined, and findings are promising; however, this diagnostic method remains investigational.\(^{2,3,10-12}\)

Serial monitoring of GM in conjunction with thoracic high-resolution CT scanning in high-risk neutropenic patients also has been evaluated. The investigators found that this approach led to improved preemptive and empirical antifungal therapy in patients in whom invasive fungal infections were later diagnosed.\(^{11}\) This approach may be useful in screening patients at high risk for infection, since a routine chest radiograph alone usually will not detect disease early enough.

BG is a component of the cell wall of most fungi except for Zygomycetes and Cryptococcus neoformans.\(^{12}\) The presence of BG in the serum is indicative of fungal invasion, including IC, IA, and other invasive fungal infections, but is not specific to 1 particular organism.\(^{23}\) False-positive results for BG assays have been reported in several contexts, including patients treated with immunoglobulin, patients exposed to glucan-contaminated blood collection tubes, patients undergoing hemodialysis using cellulose membranes, and patients receiving certain antibiotics (specifically, ampicillin/sulbactam, carbapenems, and some cephalosporins).\(^{23,33,35}\)

The Fungitell (formerly Glucatell) \(^{23}\) BG detection assay (Associates of Cape Cod, Inc, East Falmouth, Mass) is approved by the FDA for the diagnosis of invasive mycosis.\(^{15,23,36}\) Several studies have evaluated this assay in patients with acute myelogenous leukemia and myelodysplastic syndrome,\(^{36}\) in patients with proven or probable invasive fungal infection,\(^{15}\) and in patients with IC.\(^{34}\) It was found to be sensitive and specific in the early detection of fungal disease.

Results of the BG assay are usually positive in patients with invasive \textit{Fusarium} infections, but the assay is not specific to this mould. However, the combination of a positive BG assay result and a negative GM test result in a highly immunocompromised patient with a mould infection is suggestive of fusariosis, although it also can be seen with IC (specifically, hepatosplenic candidiasis).\(^{37}\)

A recent study used the BG assay in the evaluation of neutropenic patients with acute leukemia.\(^{38}\) BG was measured twice weekly in the absence of fever and daily in the presence of fever during 190 neutropenic episodes in 95 patients. An invasive fungal infection was diagnosed in 60 neutropenic episodes (9 proven, 21 probable, and 30 possible). Proven cases included 5 instances of pulmonary IA and 4 of IC. Sensitivity of the assay for diagnosis of proven or probable invasive fungal infection was 63% and 96%, respectively. The time interval between onset of fever as a first sign of invasive fungal infection and a positive BG assay result was 0.5 day, preceding positive microbiology or histopathology and positive radiological findings in most cases. More research is required to determine whether routine monitoring with this assay is appropriate.

PCR-based diagnosis of fungal infections has shown considerable promise. There have been several studies that evaluated the use of PCR in the diagnosis of fungal infections using universal fungal PCR primers that allow for the potential detection of both yeasts and moulds.\(^{19,38-43}\) Sensitivity and specificity vary depending on the assay. Head-to-head comparisons of fungal PCR assays have been lacking because most of the PCR assays are developed in-house and use different fungal DNA targets and different protocols for sample selection and preparation. The issue of contamination is also important given the ubiquitous nature of moulds in the environment.\(^{16}\) Overall, PCR-based fungal testing is investigational at this point. Its use remains limited because of lack of standardization of the assays and lack of their commercial availability.

**PROPHYLAXIS AND TREATMENT OPTIONS**

**Esophageal candidiasis**

Systemic therapy is required for effective treatment of esophageal candidiasis (EC). A 14- to 21-day course of either oral or intravenous fluconazole (100 to 200 mg qd) or oral itraconazole (200 mg qd) is highly effective and is the recommended first-line treatment.\(^{3}\) Alternative drugs for fluconazole-resistant infections include voriconazole, posaconazole, and echinocandins (caspofungin, micafungin, and anidulafungin).

Results of a double-blind multicenter study comparing voriconazole 200 mg bid with fluconazole 200 mg/d for treatment of EC in 391 immunocompromised patients (most with AIDS) showed equivalency of treatment effect. The cure rate was 98.3% for patients who received voriconazole and 95.1% for those who received fluconazole.\(^{44}\)

As for the echinocandins, 3 randomized trials demonstrated the efficacy of caspofungin in the treatment of patients with mucosal candidiasis.\(^{45-47}\) The vast majority of these patients had AIDS. Amphotericin B deoxycholate was the comparator in 2 of the studies. The incidence of drug-related adverse events was significantly lower in the caspofungin arm.\(^{45,46}\) Studies also showed that the efficacy of micafungin and anidulafungin was equivalent to that of fluconazole.\(^{48,49}\)

**Invasive candidiasis**

If feasible, initial nonmedical management should include removal of all indwelling central venous catheters. Initial therapy depends on the clinical status of the patient, the
physician’s knowledge of the epidemiology of Candida species at his or her institution, and previous antifungal exposures. Therapeutic choices include an amphotericin B preparation, fluconazole, voriconazole, or an echinocandin. Treatment duration should be for a minimum of 14 days from the last positive blood culture. Fluconazole dosed at 6 mg/kg intravenously or 400 mg qd orally is appropriate when concerns about non-albicans Candida species are minimal.

Although amphotericin B was the preferred initial treatment for many years because of its broad spectrum of activity, the safety and good clinical outcomes of drugs in the echinocandin class favor their use as empirical therapy.

Micafungin recently received FDA approval for the treatment of IC at the 100-mg daily dose. In an open-label, noncomparative study of micafungin for the treatment of candidemia in 119 patients (101 adults and 18 children), overall treatment success was found in 83.2% of patients and was similar in patients with and without neutropenia. In a randomized double-blind study comparing micafungin 100 mg qd, micafungin 150 mg qd, and caspofungin at a conventional dosage (a 70-mg IV loading dose, then 50 mg qd IV) in 595 patients with IC, treatment success was achieved in 76.4% of patients in the 100-mg group, 71.4% in the 150-mg group, and 72.3% in the caspofungin group, demonstrating noninferiority.

A success rate of 75.6% also was achieved in patients with IC given anidulafungin in a randomized double-blind trial that compared it (at a loading dose of 200 mg followed by 100 mg qd) with fluconazole (at a loading dose of 800 mg followed by 400 mg qd) in 261 patients. The success rate in the fluconazole arm was 60.2%.

### Invasive aspergillosis

In patients with a likely diagnosis of IA, antifungal therapy should be started while diagnostic evaluations are being performed. Voriconazole is approved for the treatment of IA and is recommended as primary therapy for invasive pulmonary aspergillosis.

For patients who are intolerant or refractory to voriconazole, a formulation of amphotericin B is an appropriate alternative. Available data indicate that the lipid forms of amphotericin B are as effective as amphotericin B deoxycholate but are associated with less nephrotoxicity. The optimal dosage for treatment of IA has not been defined for any of the lipid forms of amphotericin B. Higher doses of these formulations are often used, but data on their use are lacking. A recent study that compared 2 doses of liposomal amphotericin B (3 mg/kg/d and 10 mg/kg/d) for the primary treatment of proven or probable IA in 201 patients found similar overall response rates (50% for the 3 mg/kg/d regimen and 46% for the 10 mg/kg/d regimen; P > .05) and similar survival rates (72% and 59%, respectively; P > .05).

Caspofungin has been FDA-approved for salvage therapy in adults with IA on the basis of findings from a trial in which a favorable response was achieved in 44.6% patients of who were refractory or intolerant to amphotericin B, lipid formulations of amphotericin B, or triazoles. Mortality directly related to aspergillosis was 12.1%.

Combination therapy for IA has not been studied in a randomized controlled fashion. In a retrospective analysis of HSCT recipients who had received either voriconazole or voriconazole and caspofungin as salvage therapy for IA, an improved survival rate was observed in the combination arm compared with the voriconazole-alone arm (hazard ratio, 0.42; P = .048). Recently published guidelines for the treatment of IA do not recommend routine administration of combination therapy; however, in the context of salvage therapy, the addition of another antifungal agent may be useful. Randomized clinical trials are currently being developed to address this issue.

**Therapeutic agents mentioned in this article**

- Amoxicillin/clavulanate
- Amphotericin B
- Amphotericin B deoxycholate
- Ampicillin/sulbactam
- Anidulafungin
- Caspofungin
- Fluconazole
- Itraconazole
- Liposomal amphotericin B
- Micafungin
- Piperacillin/tazobactam
- Posaconazole
- Voriconazole

**PREVENTION**

In the hospital, patients at risk for IA, including neutropenic patients, should not be given pepper or tea that has not been sterilized because standard preparations of such substances have high counts of Aspergillus. For similar reasons, fresh flowers and potted plants should not be allowed in patient care areas.

Local construction work is a major factor for the acquisition of IA and has been associated with outbreaks in transplant centers. The use of high-efficiency particulate air (HEPA) filters along with positive air pressure in patient rooms reduces...
this risk but does not eliminate it entirely. Barriers between patient care areas and renovation or construction areas are highly recommended, along with adjunctive monitoring of the air for spore counts on the HSCT unit.57

A vaccine for Candida infection has been evaluated in mice and appears protective against otherwise-lethal disseminated candidiasis; however, development for clinical testing in humans faces many challenges,58-60 and it is unlikely to be available for many years. A vaccine for Aspergillus infection would be desirable, but the likelihood of one being developed at this time is low.61

REFERENCES


Herpes zoster is a painful, blistering rash that typically manifests in a dermatomal distribution and is caused by reactivation of varicella-zoster virus infection. A classic presentation of herpes zoster involving the right T4 dermatome is illustrated in Figure 1. The patient was a 90-year-old man who experienced severe pain on the right side of his neck and chest followed by development of maculopapular lesions. The lesions, which ranged from macular to vesicular, resolved with no scarring or postherpetic neuralgia following 10 days of therapy with oral acyclovir and intramuscular injections of \textit{\textgamma}-globulin.

Figure 2 also depicts herpes zoster involving the T4 dermatome, but the T10 dermatome is involved as well. Typically, a single dermatome is affected; involvement of 2 distinct dermatomes is rare. This case occurred in a 66-year-old man who had been hospitalized because of left-sided chest pain. Cardiac evaluation revealed no abnormalities. The patient was discharged; however, that evening, painful, vesicular lesions on erythematous bases simultaneously began to develop along the left T4 and T10 dermatomes. The pain and rash resolved within a week of management with acyclovir at a dosage of 800 mg qid.

Another unusual case of herpes zoster is depicted in Figure 3. When vesicles developed on the right sole of a 35-year-old man, he thought he was having a recurrence of athlete’s foot. The pain and tenderness in the area suggested herpes zoster. Note that the vesicles and erosions correspond to the S1 dermatome.

The diagnosis of herpes zoster was confirmed by the presence of multinucleated giant cells in a Tzanck smear taken from the floor of the vesicle. The pain and rash promptly resolved following administration of acyclovir.

The unusual presentation of herpes zoster and the relatively young age of the patient raised suspicion of immunocompromise. Indeed, a presentation such as the one described here can be the first sign of HIV infection, although no underlying immunosuppressive disease was found in this patient.

\textbf{Herpes zoster ophthalmicus}

The course of herpes zoster is usually benign, but serious complications can occur. One such complication is blindness, which can result (in severe cases) when herpes
Involvement of the ophthalmic branch of the trigeminal cranial nerve (associated with the V1 dermatome), as illustrated in Figure 4. This nerve is involved in about 10% of herpes zoster cases. Lesions on the tip of the nose (Hutchinson sign) are an important clinical and prognostic clue indicating that the nasociliary nerve and possibly the eye are affected. Indeed, ocular complications develop in about 50% of patients with herpes zoster ophthalmicus. Typically, the conjunctiva is red and swollen, and keratitis manifests. Rarely, uveitis develops, leading to secondary glaucoma. In addition to loss of vision, ocular complications include neuroparalytic keratopathy, Adie pupil caused by ciliary-ganglion damage, ophthalmoplegia, and optic nerve involvement.

Figure 3 – This presentation of herpes zoster resembles athlete’s foot. (Image and case supplied by Mark Popkin, MD.)

Figure 4 – This illustration of herpes zoster ophthalmicus shows the telltale involvement of the nasociliary nerve (Hutchinson sign). (Image and case supplied by Sunita Puri, MD.)
The case of herpes zoster ophthalmicus developed in an otherwise healthy 40-year-old woman. She presented with an asymptomatic rash on her forehead and nose that had developed 2 days earlier and erythema of the right eye. Antiviral therapy was started immediately, and the patient was referred to an ophthalmologist for evaluation and intervention regarding optical injury.

Despite the proximity to the eye, the herpes zoster rash shown in Figure 5A that developed in a 73-year-old woman did not include ocular involvement. Complicating the diagnosis, however, was the presence of a rash on the woman’s forehead, which was determined to be molluscum contagiosum (Figure 5B). (Note the classic umbilicated papules, not to be confused with herpetic vesicles.)

The rash, which developed near the right eye, was pruritic and painful and had a somewhat ruddy, vesicular appearance. It could have been mistaken for acne rosacea or the type of rash that can occur in patients with systemic lupus erythematosus, although those types of rashes usually have a bilateral distribution. The patient was found to have an elevated herpesvirus titer. The rash resolved following acyclovir therapy. ❖
Posaconazole: A New Triazole Antifungal

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Key words: Posaconazole ■ Antifungal therapy ■ Triazole ■ Fungal infections

Posaconazole, indicated for prophylaxis of invasive Aspergillus and Candida infections in immunosuppressed patients aged 13 years or older and for treatment of oropharyngeal candidiasis (Table 1), is like other triazole antifungals in that it blocks ergosterol biosynthesis. Its chemical structure is most similar to that of itraconazole (Figure), which may confer efficacy even against strains resistant to fluconazole and voriconazole.

Posaconazole has a broad spectrum of activity. It has been shown to be active in vitro against most Candida species (with approximately 97% of isolates susceptible at a minimal inhibitory concentration [MIC] of less than 1 µg/mL), demonstrating more activity than itraconazole or fluconazole. Similar to voriconazole, posaconazole is active against Aspergillus species. In limited in vitro studies, posaconazole has been shown to have activity against the dimorphic fungi, Histoplasma, Blastomyces, and Coccidioides. It also has in vitro activity against Penicillium, Paracoccidioides, Paecilomyces, and Cryptococcus. Variable activity against Scedosporium and Fusarium have been reported. Posaconazole has been shown to have activity against Zygomycetes, giving it a potential niche for use over voriconazole. However, it is important to note that its potency is variable among Zygomycetes species, that clinically relevant MIC breakpoints for Zygomycetes are lacking, and that it may be less active than amphotericin B.

The agent, which is available only as an oral suspension, has excellent bioavailability that is enhanced by food. One study showed that a nonfat meal and a high-fat meal enhanced the oral bioavailability of the posaconazole suspension by 168% and 290%, respectively, without significantly affecting the rate of absorption. It has also been shown that divided daily dose administration (every 6 to 12 hours) significantly increases posaconazole exposure under fasting conditions. In healthy adults, oral posaconazole exhibits dose-proportional pharmacokinetics up to a dosage of 800 mg/d; absorption of posaconazole is not increased at dosages exceeding 800 mg/d. Dosages up to 1600 mg/d are well tolerated. Excretion is 71% fecal and 13% urinary.

CLINICAL EFFICACY

Oropharyngeal/esophageal candidiasis
A multicenter blinded trial comparing posaconazole with fluconazole, each dosed at 200 mg once followed by a dosage of 100 mg/d for 13 days, for treatment of oropharyngeal candidiasis in patients with HIV infection demonstrated greater than 90% efficacy with either agent at day 14. A second study that evaluated the efficacy of posaconazole in 199 HIV-infected patients with oropharyngeal candidiasis or esophageal candidiasis refractory to oral fluconazole or itraconazole found response rates of approximately 75%.

Prophylaxis for neutropenia and graft versus host disease
A randomized, multicenter trial compared prophylactic posaconazole (200 mg tid) with fluconazole (400 mg once daily) or itraconazole (200 mg bid) in patients 13 years or older with prolonged neutropenia. Proven or probable invasive fungal infections occurred in 2% of patients in the posaconazole arm and in 8% (combined) in the fluconazole arm and itraconazole arm (absolute risk reduction, −6%; 95% confidence interval [CI], −9.7% to −2.5%;
In regard to secondary outcomes, invasive aspergillosis (IA) developed in only 1% of patients in the posaconazole group and in 7% in the comparator groups. There was also significant survival benefit among patients in the posaconazole group ($P = .04$), with a relative reduction in mortality of 33% (number needed to treat to prevent 1 death = 14).20

A second multinational trial compared posaconazole (200 mg bid) with fluconazole (400 mg/d) for prophylaxis of invasive fungal infections in patients 13 years or older who had undergone allogeneic hematopoietic stem cell transplant and were at high risk for graft versus host disease.21 No statistically significant difference in proven or probable invasive fungal infection (5.3% in the posaconazole group vs 9.0% in the fluconazole group; odds ratio [OR], 0.56; 95% CI, 0.30 to 1.07; $P = .07$) was noted, but only 46% of patients who received posaconazole and 41% of patients who received fluconazole com-

### Table 1 – Indications for use of posaconazole

<table>
<thead>
<tr>
<th>Indication</th>
<th>FDA approved</th>
<th>Efficacy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharyngeal/ esophageal candidiasis</td>
<td>Yes</td>
<td>&gt; 90%18</td>
<td>&gt; 70% effective for isolates resistant to either fluconazole or itraconazole19</td>
</tr>
<tr>
<td>Prophylaxis against invasive Aspergillus and Candida infections in high-risk patients ≥ 13 years old</td>
<td>Yes</td>
<td></td>
<td>In neutropenic patients: rate of invasive fungal infection was 5% vs 11% in patients receiving either fluconazole or itraconazole ($P = .003$); relative risk reduction in mortality was 33%20</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>No</td>
<td>Partial or complete response in &gt; 40%22,23</td>
<td>Has not been compared with voriconazole yet</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>No</td>
<td>Partial or complete response in = 60%22,23</td>
<td>Data from compassionate use trials for salvage therapy in patients mostly treated with amphotericin B</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>No</td>
<td>Response in &gt; 70%27</td>
<td>Has been shown to be well tolerated for treatment &gt; 6 months</td>
</tr>
<tr>
<td>Fusariosis</td>
<td>No</td>
<td>Partial or complete response of salvage therapy in = 30% of patients with disseminated infection and = 60% with localized infection24</td>
<td>Small number of patients studied</td>
</tr>
</tbody>
</table>

GVHD, graft versus host disease.
completed the full 16 weeks of treatment. Secondary, on-treatment analysis (mean prophylaxis for about 7 weeks) showed fewer breakthrough fungal infections in the posaconazole group (2.4% vs 7.6%; \(P = .0004\)). Posaconazole was also associated with fewer cases of IA (2.3% vs 7.0%; OR, 0.31; 95% CI, 0.13 to 0.75; \(P = .006\)). Although there was no statistical difference in overall mortality, there was a significant improvement in mortality from invasive fungal infections with posaconazole use (1% vs 4%; \(P = .041\)).\(^{21}\)

**Other invasive fungal infections**

Much of the other published clinical experience is from expanded-access program use of posaconazole for the treatment of refractory invasive fungal diseases. Two publications reported the results from open-labeled, non-randomized, multicenter trials that evaluated oral posaconazole (800 mg/d) for salvage therapy in 91 patients with zygomycosis.\(^{22,23}\) Partial or complete response was noted in 60% of patients, while stable disease was noted in 21% patients.

Posaconazole (800 mg/d) has also been studied as salvage therapy for patients with refractory invasive fusariosis.\(^{24}\) Complete or partial response was seen in 10 of 21 patients (48%). Of these, response was achieved in 3 of 10 patients with disseminated infection (with or without pulmonary involvement). For patients with a localized site of infection (including pulmonary infection alone), the response rate ranged from 57% to 75%.

In another trial, the outcome for patients with refractory IA who received posaconazole was compared with that for historical controls who received an amphotericin B–based regimen; complete or partial response was achieved in 42% of the posaconazole-treated group and in 26% of the control group (OR, 4.06; 95% CI, 1.50 to 11.04; \(P = .006\)). Results remained significant when evaluated by site of infection, underlying medical condition, and reason for enrollment.

Posaconazole has been studied for treatment of nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. Posaconazole 400 mg/d in 20 such patients resulted in a satisfactory response in 85% after a median duration of 173 days of therapy.\(^{26}\) A second study showed that posaconazole was also effective in patients with chronic coccidioidomycosis whose disease was refractory to more than 40 days of other appropriate therapy (median duration of other therapy was 306 days).\(^{27}\)

Restrepo and colleagues\(^{28}\) described successful clinical
outcomes in 6 patients with refractory histoplasmosis after 6 to 34 weeks of posaconazole use. An additional study showed that posaconazole may be effective for CNS fungal infections and specifically found that 14 of 29 patients (48%) with cryptococcal meningitis had at least a partial response to posaconazole, including 8 patients whose disease was refractory to standard therapy.29

SAFETY, TOLERABILITY, AND COST
Posaconazole is well tolerated, even during periods of prolonged treatment (ie, more than 6 months).17,20 Typical adverse reactions include elevated levels of liver-associated enzymes (3%), nausea (8%), and vomiting (6%) at rates similar to those seen with fluconazole use.20,21 Prolongation of the QTc interval occurred in 1% of patients but did not require drug discontinuation.

It is important to note that in both of the large randomized trials, patients with significant renal and liver impairment have been excluded. Currently, no specific dose adjustments are recommended for preexisting hepatic or renal disease. It is recommended that posaconazole be used with caution in patients with hepatic impairment. The manufacturer also recommends that patients with severe renal impairment should be monitored.

Table 2 – Potential drug interactions with posaconazole

<table>
<thead>
<tr>
<th>Drug class/name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum/magnesium hydroxide antacid preparations</td>
<td>No clinically significant effect in absorption of posaconazole</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Can cause 2-fold reduction in posaconazole levels; avoid using together (unless benefit outweighs risks)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Since metabolized by CYP3A4, posaconazole may impair the clearance of benzodiazepines; consider reducing midazolam dose</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Can cause 2-fold reduction in posaconazole levels; avoid using together (unless benefit outweighs risks)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Can cause 2-fold reduction in posaconazole levels and an increase in phenytoin levels; avoid using together (unless benefit outweighs risks); if used, consider reducing phenytoin dose and monitoring levels</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Reduce cyclosporine dose to 75% of original dose</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Reduce tacrolimus dose to 33% of original dose</td>
</tr>
<tr>
<td>Zidovudine, lamivudine, ritonavir, and indinavir</td>
<td>No clinically significant effect described</td>
</tr>
<tr>
<td>Terfenadine, astemizole, cisapride, pimozide, and quinidine</td>
<td>Can cause prolonged QTc interval; coadministration is contraindicated</td>
</tr>
<tr>
<td>Ergot alkaloids (ergotamine, dihydroergotamine)</td>
<td>Can increase levels of the ergot alkaloids, and may lead to ergotism; coadministration is contraindicated</td>
</tr>
<tr>
<td>Vinca alkaloids (vincristine, vinblastine)</td>
<td>Can increase levels of the vinca alkaloids and may lead to neurotoxicity; recommend dosage adjustment of vinca alkaloid</td>
</tr>
<tr>
<td>Statinsa metabolized through CYP3A4</td>
<td>Can increase statin concentration in plasma, which can be associated with rhabdomyolysis; consider dose reduction of statins</td>
</tr>
<tr>
<td>Calcium channel blockers metabolized through CYP3A4</td>
<td>Frequent monitoring for adverse events and toxicity related to calcium channel blockers; dose reduction of calcium channel blockers may be necessary</td>
</tr>
</tbody>
</table>

CYP, cytochrome P-450.

a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.
closely for breakthrough fungal infections. Because posaconazole inhibits cytochrome P-450 3A4, it may increase levels of other drugs that are substrates for this enzyme; the package insert describes medications that are contraindicated or with which precautions are necessary (Table 2). 17

Posaconazole is pregnancy class C. The excretion of posaconazole in human breast milk has not been investigated and therefore the manufacturer recommends that it should not be used by nursing mothers unless the benefit to the mother clearly outweighs the risk to the infant. 17 The cost of a 105-ml bottle (40 mg/ml) of posaconazole is approximately $600. 31

IN SUMMARY

Posaconazole has been shown to be effective for prophylaxis against invasive fungal diseases in high-risk patients and for use in oropharyngeal candidiasis resistant to other azoles; it has also been shown to have a broad spectrum of activity against other pathogens in vitro. The agent shows promise as salvage therapy for zygomycosis, aspergillosis, fusariosis, histoplasmosis, and coccidiodomycosis. Its availability as an oral agent is beneficial, but the necessity to take it with food or nutritional supplementation to enhance its bioavailability may limit its use in severely ill patients. Thus far, it has been shown to be generally well tolerated, even with prolonged use. Although there is a need for additional studies, the promising results seen so far suggest that posaconazole is a useful new addition in the antifungal armamentarium. ❖

REFERENCES

Prophylactic Antibiotics for Postpartum Perineal Tears

by Gilles R. Monif, MD

[Infect Med. 2008;25:516]

Key words: Perineal tears ■ Perineal wound infection

Third-degree perineal lacerations reputedly occur in 2.2% to 19% of vaginal deliveries in the United States. Breakdown of a third- or fourth-degree perineal repair can lead to incontinence of stool or flatus, rectovaginal fistula, or sexual dysfunction. Infection at the operative site occurs in up to 12% of cases, and a key factor in successful anal sphincter repair is the absence of infection.

Duggal and colleagues conducted a prospective, randomized, placebo-controlled study to assess whether prophylactic antibiotics at the time of third- or fourth-degree perineal tear repair after vaginal delivery would prevent site-specific wound infection and breakdown. One hundred forty-seven patients were enrolled. Eighty-three patients received placebo and 64 received either 1 dose of a second-generation cephalosporin (1 g of cefotetan or cefoxitin) or 900 mg of intravenous clindamycin. Forty patients did not return for their 2-week follow-up appointment. The criteria used to diagnose a perineal wound complication were (1) the identification of purulent discharge and (2) the presence of an abscess at the repair site.

Analysis of the 107 patients who returned for their 2-week follow-up appointment revealed that a perineal wound infection developed in 4 of the 49 patients (8.2%) who received antibiotics and in 14 of the 58 patients (24%) who received placebo. The repair site in 21 patients who missed their 2-week visit but presented for their 6-week postpartum checkup was free of infection. Inclusion of these patients altered the overall results slightly such that infection developed in 7.3% of women who received antibiotic therapy and in 19.2% of women who received placebo. A significant decrease in the amount of purulent discharge from the repair site was noted in women who had received antibiotics compared with women who had received the placebo (4% vs 17%).

The study was well designed and attempted to control most variables. The observations were numerically sufficient to demonstrate a trend but not sufficient to document statistical significance. Better insight might have been attained if observations were given for the 14 patients in each group with fourth-degree perineal tears. The success of an anal sphincter repair was significantly influenced by the skill of the operating surgeon.

The data could have profited from separating the cases performed by an attending physician from those performed by a resident. The data also could have profited from subcategorizing outcomes by the type of antibiotic used. The absence of bacteriology forces one to presume that the resultant repair site infections were the consequences of anaerobic progressions, which—to circumvent antibiotic prophylaxis—would have had to have focal hematomas or dead spaces.

Antibiotics appear to exert a beneficial effect in preventing repair site infections, but equal or greater emphasis must be given to operative site hemostasis. Because this was a well-designed, randomized, placebo-controlled study of antibiotic prophylaxis for third- and fourth-degree perineal tears, this study is currently the best data that we have.

REFERENCES

A 55-year-old man with no past medical problems presented with headache, difficulty in walking, and loss of balance of 3 days’ duration. Physical examination findings and laboratory test results were unremarkable except for lethargy, slurred speech, positive Romberg sign, hyponatremia, and leukocytosis with left shift.

A noncontrasted CT scan of the head showed large areas of cerebellar vasogenic edema with pressure on the fourth ventricle and aqueduct, causing mild hydrocephalus. An MRI scan of the head revealed ring-enhancing lesions with surrounding edema without midline shift (Figure 1). A contrast-enhanced CT scan of the chest showed soft tissue thickening along the bronchoalveolar margin of the superior segment of the right lower lobe. Lung cancer with metastases to the brain was suspected, but after lack of enhancement was seen on positron emission tomography, the diagnosis fell into doubt.

Suboccipital craniotomy for resection of the cerebellar lesions was performed. The lesions were found to be capsular, with purulence noted on incision. Hematoxylin and
eosin, Gomori methenamine-silver, and acid-fast bacilli stains of brain tissue revealed Nocardia farcina (Figure 2). A 6-week treatment regimen with intravenous ceftriaxone and oral trimethoprim/sulfamethoxazole (TMP/SMX) was started. Two weeks after treatment was started, an MRI scan showed enlargement of existing lesions and development of new lesions (Figure 3). The intravenous antibiotic was switched to imipenem/cilastatin, and the treatment was continued for 6 weeks. Serial MRI scans of the head demonstrated shrinkage of the lesions, and clinical improvement occurred.

Discussion
In the case described here, multiple brain abscesses in an immunocompetent patient were misdiagnosed as metastatic lung cancer. After initial treatment with intravenous ceftriaxone and oral TMP/SMX failed, a correct diagnosis of N farcina infection was made. Treatment with a combination of imipenem/cilastatin and TMP/SMX led to complete clinical and radiological improvement.

The case and images were submitted by Ashar Luqman, MD, a resident in internal medicine at the University of Tennessee Health Science Center in Memphis, Tenn, and Saurabh Dhawan, MD, a fellow in cardiology at Emory University in Atlanta.
**Mycobacterium goodii** Infection of a Total Knee Prosthesis

Jason C. Tompkins, MD, MPH, Mark S. Harrison, MD, and Richard S. Witzig, MD, MPH

*Mycobacterium goodii* infection is uncommon and probably occurs via disruption of skin and bone integrity or the introduction of a foreign body into viscera, namely implantation of a prosthetic device. We describe a case of nosocomial, total knee arthroplasty-associated *M goodii* infection that required combined antibiotic and surgical therapy for clinical management. An infection control investigation revealed that the source of the organism might have been the water in the operating room scrub faucets. [Infect Med. 2008;25:522-525]

**Key words:** *Mycobacterium goodii* ■ Prosthesis-related infection ■ Infection control

*Mycobacterium goodii* was first characterized in 1999 as biochemically distinct but closely related to the rapidly growing *Mycobacterium smegmatis.* Although the environmental sources of *M goodii* are not known, those of *M smegmatis* are known to be water and hospital dust. Clinical cases are rare. We report the first case of a nosocomial *M goodii* infection in Michigan. The nosocomial nature of this pathogen is explored by examining all previously identified case reports.

**Case report**

A 63-year-old woman with type 2 diabetes mellitus and morbid obesity underwent elective right total knee arthroplasty for degenerative osteoarthritis at a small, rural Michigan hospital that performs approximately 4 total joint replacements a year by a single surgeon. Wound healing was rapid and complete. Five months later, the patient presented with a 2-week history of erythema, warmth, and dehiscence of the skin overlying her right knee. She recalled no trauma or soil contact to the knee. In the outpatient clinic, a right knee arthrocentesis through unaffected skin was performed, and the patient was hospitalized to receive intravenous vancomycin and nafcillin for treatment of overlying cellulitis.

The patient’s laboratory workup was remarkable for a C-reactive protein level of 16.68 mg/dL and an erythrocyte sedimentation rate of 31 mm/h. The white blood cell count and differential were normal. A CT scan of the right knee revealed a low-density soft tissue mass anterior to the tibial tuberosity, with the bone at this level demonstrating mild irregularity (Figure 1). Triple-phase, technetium-99m bone scanning showed intense delayed uptake in the right patella and tibia (Figure 2). The cellulitis was treated with vancomycin and nafcillin until culture results were negative for bacteria.

During her hospital stay, an infectious diseases (ID) consultation was requested. Because the orthopedic service had only requested bacterial cultures, the ID consultant requested that mycobacterial and fungal stains and cultures also be performed on the fluid aspirated from the knee. Nafcillin was discontinued, but vancomycin was continued. Five days after hospital admission, the culture results were negative for bacteria and the overlying cellulitis had nearly resolved; therefore, the patient was discharged without antibiotics. However, the next day, a rapidly growing *Mycobacterium* was isolated from the arthrocentesis fluid. The culture was nonpigmented, but after a week of growth in darkness at 37°C...
(98.6°F), it demonstrated a yellow pigment. To obtain a species-level identification and extended-panel sensitivities, the organism was sent to the National Jewish Medical and Research Center in Denver.

Several weeks passed before species confirmation was made. In the meantime, empirical therapy that consisted of oral moxifloxacin 400 mg daily and clarithromycin 500 mg bid was started. Four days after initiation of this therapy, an MRI scan of the right lower leg with and without gadolinium showed a fluid collection but no definite osteomyelitis. By the following week, culture results from the fluid collection were negative for bacteria, fungi, and mycobacteria.

The organism ultimately was identified as *M. goodii*. Because of the results of drug susceptibility testing, clarithromycin was discontinued, doxycycline 100 mg bid was initiated, and moxifloxacin was continued. The patient continued to receive moxifloxacin 400 mg daily and doxycycline 100 mg bid as suppressive therapy for 9 months, then treatment with doxycycline alone was maintained for the life of the retained prosthesis, which was fully functional and asymptomatic at the time of this report.

**Discussion**

*M. goodii* is a rapidly growing mycobacterium found in soil and water. It shows growth on Middlebrook 7H10 agar and trypticase soy agar at 30°C, 35°C, and 45°C within 2 to 4 days. Cultures demonstrate smooth to mucoid, off-white to cream-colored colonies. Yellow to orange pigment is produced in 78% of all strains after 10 to 14 days’ incubation. When the organism was originally called *M. smegmatis* strain 2 or *Mycobacterium wolinskyi*, Brown and colleagues sequenced its DNA and demonstrated species-level differences. Brown and colleagues’ original strains showed susceptibility to amikacin, ethambutol, and sulfamethoxazole.

The clinical spectrum of disease includes skin and soft tissue infection from penetrating trauma, respiratory disease associated with lipid pneumonia or achalasia and, notably, an association with surgically implanted devices. Nosocomially associated cases are a recent clinical theme in the literature. In a case of *M. goodii* bursitis, Friedman and Sexton theorized that *M. goodii* was introduced into the bursal sac “during intrabursal injections or during subsequent surgery.” In another case, *M. goodii* was associated with an infected prosthetic inguinal hernia repair mesh, which was removed to achieve a cure. Nosocomially associated *M. goodii* infection in a total hip arthroplasty, a hernia patch, and a total knee replacement also have been reported, although the Epidemic Intelligence Service of the CDC failed to find a conclusive mechanism of surgical contamination for any of these cases.

In addition to reported cases of post-breast reduction surgery, soft tissue infection, and intravascular catheter–associated sepsis, a ventriculoperitoneal shunt was nosocomially infected; its removal and pro-

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**Figure 1** – A CT scan of the right knee demonstrates a low-density soft tissue mass anterior to the tibial tuberosity. The bone demonstrates mild irregularity.
longed antibiotic treatment were required to achieve a cure.\textsuperscript{5} \textit{M. goodii} has also been implicated in an infection of an intraocular lens implant\textsuperscript{6} and of a pacemaker lead\textsuperscript{7}; these cases required removal of the lens and of the pacemaker lead for cure.

Therapy for the patient described here initially was empirical and based on published in vitro data and case reports; however, when the National Jewish Medical and Research Center reviewed the drug susceptibility data, the most appropriate treatment was selected.

The \textit{M. goodii} isolate was susceptible to doxycycline, imipenem, linezolid, and trimethoprim/sulfamethoxazole. It also was susceptible to the fluoroquinolones (ciprofloxacin, moxifloxacin, and gatifloxacin) and to select injectable aminoglycosides (tobramycin, amikacin, and kanamycin). It was resistant to the oral macrolides azithromycin and clarithromycin but susceptible to injectable tigecycline.

Intermediate susceptibility was demonstrated to cefoxitin and full resistance to amoxicillin/clavulanate. Perhaps the lack of activity against \textit{M. goodii} of routinely administered perioperative antibiotics, such as \textbeta-\text{lactams and vancomycin}, is a factor in the recent increase in clinically recognized cases. Nevertheless, a wide range of oral and injectable antibiotics have in vitro activity against \textit{M. goodii}, and treatment with doxycycline and moxifloxacin led to full clinical suppression of infection in our patient.

An infection control investigation was conducted to trace the source of infection. It was learned that the sterilizer load used in the operating room was intact, and no quality control alarms had been triggered. Biological controls indicated no problems with the sterilization process.

The manufacturer of the prosthetic implant was contacted. No other problems with sterilization had been documented, and no other reports of atypical mycobacterial infection had been reported.

The hospital environmental services removed all air ducts that led into the operating room, recovery room, and ICU where the patient had stayed postoperatively. No standing water was noted. The humidity controls and filters for the forced-air system were clean and functional. Dust samples from the air ducts from 6 locations were collected by a commercial certified industrial hygienist and processed by a commercial pathogen-control laboratory; the samples were cultured at 37°C (98.6°F). All cultures results were negative for pathogens.
The operative record showed no breaches in sterile protocol. One infection control nurse who was in the operating room during the surgery noted no variances.

Samples of hot and cold water from the 3 scrub sink faucets outside the operating room also were cultured. A total of 6 samples were incubated at 37°C (98.6°F) and 45°C (113°F) for 6 weeks. None of the cultures grown at 45°C demonstrated mycobacteria. The cultures grown at 37°C from samples taken from the left sink’s hot water, center sink’s cold water, and right sink’s hot water all grew mycobacteria that were subsequently unidentifiable because of fungal overgrowth. Nevertheless, the suspicion arose that the source of M. goodii might have been the scrub sinks. However, because of the ubiquitous nature of environmental mycobacteria in tap water, the source of this patient’s infection could not be definitively proved.

Given the low pathogenicity of M. goodii, either disruption of skin and bone integrity or introduction of foreign material is probably necessary for infection. Isolation of M. goodii from prosthetic material should spur the initiation of empirical therapy with antimicrobials that are active against this species and should prompt a review of infection control practices and an investigation into nosocomial water and environmental sources of the organism.

Acknowledgments:
The authors thank Sandra Claborn, RN, and Sandra Burton, RN, for their infection-control investigation assistance.

REFERENCES

Therapeutic agents mentioned in this article
Amikacin
Amoxicillin/clavulanate
Azithromycin
Cefoxitin
Ciprofloxacin
Clarithromycin
Doxycycline
Ethambutol
Gatifloxacin
Imipenem
Kanamycin
Linezolid
Moxifloxacin
Nafcillin
Sulfamethoxazole
Tigecycline
Tobramycin
Trimethoprim/sulfamethoxazole
Vancomycin

Interested in placing an ad in INFECTIONS in MEDICINE?
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A 28-year-old man presented with a 1-year history of nodular, plaque-like, nontender, pruritic lesions on his face, ears, elbows, and feet. He was born in Mexico but had been residing in the United States for the past 6 years. He worked in construction, was an active smoker, and denied use of alcohol or illicit drugs. The patient had not been taking any oral medications and had no recent history of trauma.

Six months before this presentation, the patient presented to a different clinic and received a prescription for a topical corticosteroid. After 6 months of use, the lesions were more numerous and extensive, prompting him to seek further medical attention.

Findings from the physical examination were remarkable for nodular, plaque-like lesions localized to the forehead, elbows (Figure 1), knees, feet, and ears. Leonine facies, a facial characteristic associated with leprosy, and ulcerative lesions at the nares with no associated bleeding were evident (Figure 2). The skin on his forehead was diffuse, thickened, smooth, and shiny, and alopecia of the eyebrows and eyelashes was noted. All lesions were nontender or hypoesthetic. There were no hypertrophied nerves, and the neurological examination findings were remarkable for right-sided weakness on handgrip.

A chest radiograph and laboratory findings, including an HIV test, were unremarkable. Biopsy material from the ears and nose and scrapings from nasal lesions demonstrated acid-fast bacilli (Mycobacterium leprae) with Wade-Fite staining (Figure 3, magnification ×400).

After a brief hospitalization, the patient was discharged home on a standard regimen of 12-month therapy for multibacillary leprosy. This consisted of oral dapsone, 100 mg daily; clofazimine, 50 mg daily; rifampin, 600 mg monthly; and clofazimine, 300 mg monthly. Follow-up consultation with an infectious disease specialist was scheduled.

First described in 1873, leprosy is caused by an M leprae infection. This chronic granulomatous disease primarily affects the skin, mucous membranes, and peripheral nervous system. Areas in which leprosy is endemic include various locations throughout Asia, Africa, and Central and South America. In the United States, 166 cases of leprosy were reported in 2005. In early 2006, 219,826 cases of leprosy were reported globally.

M leprae is an obligate, intracellular, slow-growing mycobacterium that survives optimally at 27°C (80.6°F) to 33°C (91.4°F). Humans are the primary reservoir of M leprae, but animal reservoirs, such as armadillos and certain primates, have been identified. The definite route of transmission for leprosy is unknown, although many experts believe that transmission occurs via aerosol spread from infected nasal secretions to nasal and oral mucosa. It is usually not spread by direct contact, but close contacts may be more vulnerable to the disease. Risk factors in-
to the median and ulnar, common peroneal, and posterior peroneal nerve and manifest as loss of sensation.

Peripheral neuropathies most commonly affect the posterior peroneal nerve and manifest as loss of sensation to temperature, light touch, pain, and pressure. Damage to the median and ulnar, common peroneal, and posterior or tibial nerves can result in clawhand, footdrop, or claw-toes, respectively. Loss of eyebrows and eyelashes is not uncommon.

Acid-fast and modified Wade-Fite staining of skin scrapings or biopsy specimens are the preferred methods to confirm a diagnosis of leprosy. Up to 70% of patients with leprosy can have a negative skin test result. Polymerase chain reaction and antiphenolic antibody assays can also be used to help confirm the diagnosis.

Treatment depends on the type of disease, patient allergies, comorbidities, and patient’s place of residence. A multidrug regimen is the standard of care for leprosy worldwide. For paucibacillary disease, a 6-month course of oral dapsone, 100 mg daily, and oral rifampin, 600 mg monthly, is recommended. However, patients with leprosy diagnosed in the United States tend to have more active disease than those presenting in other areas of the world and often receive daily rifampin in addition to oral dapsone and an extended treatment course of 1 year. For multibacillary disease, the recommended treatment is oral dapsone, 100 mg daily; clofazimine, 50 mg daily; and monthly doses of rifampin, 600 mg, and clofazimine, 300 mg. The treatment duration for multibacillary disease is 12 months.

Roughly 25% of patients with borderline and lepromatous types of leprosy experience an adverse reaction to treatment. There are 2 types of adverse reactions that can occur. A reversal reaction (type 1 reaction) is characterized by erythema and edema of skin lesions with neuritis and occasional ulceration. If neuritis occurs, prednisone should be initiated immediately to prevent permanent nerve damage. Another adverse reaction is erythema nodosum leprosum (type 2 reaction), which is an immune complex disorder characterized by fever and multiple erythematous tender nodules. Neuritis, edema, arthralgia, leukocytosis, iridocyclitis, peritonsillar abscess, and nephritis may also be present. Thalidomide, 300 to 400 mg daily, typically lessens the type 2 reaction within 48 hours.

Although infrequent in the United States, leprosy is an important disease worldwide. Given the diverse US population, recognizing typical features of leprosy is crucial for accurate diagnosis and early treatment.

REFERENCES

Because it has excellent activity against Aspergillus species, voriconazole is being used with increasing frequency in patients with prolonged neutropenia or following hematopoietic stem cell transplant (HSCT). Use of voriconazole may be selecting for mould infections from pathogens such as Zygomycetes and Scedosporium species. We report a case in which disseminated Fusarium infection developed in an HSCT recipient who was receiving voriconazole therapy.

Key words: Voriconazole, Fusarium, Immunosuppression, Hematopoietic stem cell transplant, Disseminated infection

Disseminated Fusariosis Following Cutaneous Injury From Contact With a Palm Tree

Ana Paula Velez, MD, John N. Greene, MD, Ramon L. Sandin, MD, MS, and Albert L. Vincent, PhD

Opportunistic fungal infections are increasingly common in patients who undergo hematopoietic stem cell transplant (HSCT). Voriconazole is frequently used in allogeneic SCT recipients who receive immunosuppressant therapy for graft versus host disease to prevent invasive aspergillosis. Indications for voriconazole use include invasive aspergillosis, candidemia, Scedosporium apiospermum infection, and fusariosis. We describe a case in which disseminated Fusarium infection developed in an HSCT recipient who was receiving voriconazole therapy. [Infect Med. 2008;25:528-530]

While planting a palm tree, the patient’s left hand was lacerated by a frond. After several days, he noticed that a pink papular lesion had developed at the site of the injury. The patient was referred by his primary care provider to a dermatologist who performed a biopsy. Treatment was deferred pending biopsy results.

The lesion enlarged over the next several weeks. At the time of the injury, the man had been receiving voriconazole, acyclovir, trimethoprim/sulfamethoxazole, mycophenolate mofetil, tacrolimus, and prednisolone for both prophylaxis of opportunistic infection and treatment of GVHD.

The patient presented to our clinic 6 weeks after being injured and 6 months after having undergone HSCT. Physical examination revealed a 3 × 5-cm papulonodular erythematous lesion with scarring on the dorsal aspect of the left hand. The patient had no other systemic symptoms. Given his severe immunosuppression and history of gardening injury, a CT scan of the chest was ordered because it was suspected that symptoms were related to a disseminated mould infection.

Findings from the physical examination were otherwise unremarkable. The total white blood cell count was 3900/µL (absolute neutrophil count less than 1000/µL); hemo-
globin, 11.9 g/dL; platelet count, 42,200/µL; creatinine, 1.3 mg/dL (improved from 1.4 mg/dL); alkaline phosphatase, 114 U/L; aspartate aminotransferase, 114 U/L; and alanine aminotransferase, 386 U/L. Blood cultures were negative.

A CT scan of the chest and abdomen revealed multiple 1- to 2-cm hypodense nodular lesions in the lungs, liver, and kidneys (Figure 1). Histopathological examination of a biopsy specimen from the hepatic nodules revealed septate hyphae with ballooning, which is characteristic of Fusarium (Figure 2). A culture of urine, liver, and skin biopsy specimens grew Fusarium (Figure 3). A test for species determination was not available.

Despite 6 weeks of treatment with intravenous liposomal amphotericin B at a dosage of 5 mg/kg/d and oral posaconazole at a dosage of 200 mg qid, the liver lesions persisted and new lesions appeared in the kidneys. The patient died of disseminated infection; no autopsy was performed.

Discussion
The epidemiology of fungal infections in HSCT recipients has changed since the introduction of fluconazole prophylaxis. An increased incidence of invasive mould infections such as aspergillosis and fusariosis has correlated with a decline in Candida infections. Fusarium species are important plant pathogens that cause diseases such as crown rot, head blight, and scab in cereal grains. The fungus is widely distributed in the soil and in both subterranean and aerial plants. Different species of Fusarium have also been isolated from palm trees.

Fusarium species that are most often implicated in human infection are Fusarium solani, Fusarium oxysporum, and Fusarium moniliforme. Second to Aspergillus, Fusarium has become the most frequent cause of mould infection among patients with underlying hematological malignancy and in those who have undergone either intensive

![Figure 1](image1.png) - A CT scan of the chest (A) revealed multiple 1- to 2-cm nodular lesions typical of a Fusarium infection. A CT of the abdomen (B) and of the abdominal pelvic region (C) revealed multiple hypodense liver and kidney lesions consistent with disseminated Fusarium infection, which was confirmed by a liver biopsy and urine culture.

![Figure 2](image2.png) - Hematoxylin and eosin stain of a biopsy specimen from the liver nodule revealed septate hyphae with ballooning, which is characteristic of Fusarium.
cytotoxic chemotherapy or HSCT. Risk factors for development of disseminated *Fusarium* infections include prolonged neutropenia, use of corticosteroids and broad-spectrum antibiotics, and indwelling intravascular catheters. Clinical signs and symptoms include myalgias, fever, skin lesions, sinopulmonary infections, and fungemia with subsequent dissemination to the liver, spleen, and other viscera. The skin lesions are initially macular with central pallor and may progress to ecchyma gangrenosum-like nodular necrotic lesions.

Blood cultures are positive for *Fusarium* in up to half of all cases, and histopathological examination of involved tissues may support the diagnosis of disseminated infection. Diagnostic techniques using polymerase chain reaction methods are being developed.

The mainstay of treatment for invasive *Fusarium* infections is high-dose lipid formulations of amphotericin B. Voriconazole has been approved by the FDA for use as salvage therapy for patients in whom other therapies fail or for those who are intolerant to other therapies. Successful responses to voriconazole have been described in case reports, but confirmatory prospective studies have not yet appeared.

Posaconazole also has demonstrated activity against *Fusarium* infections in patients with hematologic malignancy. Breakthrough infections have been described during amphotericin B therapy in which *Fusarium* appeared to be resistant in vitro. Combination therapy with a lipid formulation of amphotericin B and a newer-generation azole, such as voriconazole or posaconazole, may be more effective in eradicating infection than monotherapy. Although the lungs, sinuses, feet, and toes are the usual entry points for *Fusarium* organisms in immunocompromised cancer patients, our case illustrates another portal of entry, the skin. Specifically, even minor trauma involving plants or soil that disrupts the skin’s integrity may cause a life-threatening fungal infection.

Optimal treatment of *Fusarium* infections remains an unresolved issue. Further identification of *Fusarium* species and their susceptibilities are needed to elucidate the best treatment for these infections. The increasing use of prophylactic voriconazole in immunosuppressed patients may exert a selection pressure for fungi such as Zygomycetes and *Scedosporium* and *Fusarium* species, which are resistant to voriconazole. Minor trauma incurred by immunosuppressed HSCT patients while handling plants can result in disseminated infections that are refractory to treatment and can be fatal.

**REFERENCES**