Fungal Infections

Richard Paula

host defenses allow varying types of infection. Candidal infections offer a clear example of this point. Granulocytes primarily prevent bloodborne candidiasis, and this becomes apparent in neutropenic patients, who are at greater risk to develop Candida-induced fungemia and sepsis. Contrast this situation with the T-cell–mediated defense that prevents mucosal Candida proliferation. This property explains why almost 90% of patients with human immunodeficiency virus (HIV) infection have oropharyngeal colonization, and more than half develop clinical thrush. Some fungal organisms, such as Histoplasma capsulatum and Coccidioides immitis, change form during active infection of the host, and others remain exclusively in the yeast form. This adaptation allows Histoplasma and Coccidioides to infect healthy individuals.

ANATOMY
Fungal disease may occur in any organ system (central nervous system [CNS], cardiovascular system, respiratory system, skin, eyes); no system is spared. The type of infection is often associated with a specific risk factor or endemic exposure. The anatomic location of infection may be noted by the presenting symptoms. A particular area of infection may help to identify a specific deficiency in a patient’s immune system. Certain immune deficiencies are associated with specific fungal disease manifestations.

PRESENTING SIGNS AND SYMPTOMS
No specific presenting signs or symptoms are pathognomonic of fungal infection. Certain patient populations are more likely to contract fungal infections (Table 176.1).

Depending on the site of infection, presenting symptoms vary. The important signs of fungal infection are indicated by indirect evidence found in the patient’s history. Patients who have a history suggestive of greater risk for fungal infection should be evaluated and treated more extensively. For example, when a patient with acquired immunodeficiency syndrome (AIDS) presents to the emergency department (ED) after a recent admission for pneumonia with recurrent symptoms of pneumonia, the incidence of fungal infection, specifically Candida, is much higher. The patient needs cultures specifically for Candida and requires prompt antifungal therapy in the ED, in addition to broad-spectrum antibiotics covering health care–associated pneumonia.

KEY POINTS
- Fungi can cause significant human disease.
- Human fungal infection is overwhelmingly caused by the following organisms: Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Paracoccidioides, Sporothrix, and Zygomycetes.
- Fungal infection rates have dramatically increased after the arrival of improved diagnostic capabilities and a growing population of immunosuppressed patients.
- Invasive fungal infections carry an extremely high mortality rate, and recognition with rapid treatment by an observant emergency physician prevents morbidity.

GENERAL EPIDEMIOLOGY
The risk of fungal infections is tied to both geography and immune status. Immunocompromised individuals are exponentially more likely to suffer from fungal infection. Immunocompetent patients do acquire significant, often invasive fungal disease, especially in endemic areas. In 3 counties in the southwestern United States, coccidioidomycosis in immunocompetent patients who were more 65 years old occurred with an incidence of 40 in 100,000. In addition to the best-known endemic areas, smaller areas in Africa and Asia are known to harbor pockets with high rates of infection. Fungal infections are a scourge in hospitals, and they account for significant numbers of nosocomial infections. Previously published data showed that 10% of all nosocomial infections were fungal, and Candida was responsible for 85% of those infections.

RISK FACTORS
Outside the endemic areas of concern, the significant risk factor for fungal infection is immune dysfunction. One of the reasons for the extended life expectancy of immunocompromised patients is the ability to recognize the increased susceptibility of these patients to fungal disease. Patients with selective specific immune deficiency often contract specific fungal infections. Different weaknesses in immune-mediated
SECTION XVII
INFECTIONS

ORGAN-SPECIFIC CLINICAL FINDINGS

Pulmonary Disorders
Patients with fungal pneumonia present similarly to patients with other types of pneumonia. They have fever, dry or productive cough, fatigue, shortness of breath, or hemoptysis. The chest radiographic appearance also resembles that of other pneumonias. No specific finding is associated with particular fungal infections; lobar and interstitial infiltrates are both common. Certain fungal infections occasionally manifest with visible masslike lesions (e.g., blastomycosis, aspergillosis), and other infections form cavitary lesions (e.g., sporotrichosis), but these are the exception and not the rule. Fungal pneumonia causes varying symptoms and radiologic appearances. In one review, aspergillosis was the most common fungal cause of pneumonia in patients with cancer. Other reviews reported aspergillosis as the most common cause of pneumonia in immunocompromised patients. Healthy, immunocompetent individuals are overwhelmingly more likely to have one of the endemic fungal infections.

Central Nervous System Disorders
Almost all the common fungal pathogens can cause CNS infection. The best known is *Cryptococcus* because of its propensity to cause meningitis in 50% to 60% of infected, immunocompromised patients. CNS infections may also be seen in much lower proportions in healthy individuals. Histoplasmosis leads to meningitis in approximately 1% of symptomatic individuals. Almost all patients with fungal meningitis present after known fungal infections and are hospitalized patients with severe immunodeficiency. This is not the case in many HIV-infected patients with cryptococcal meningitis. Patients with cryptococcal meningitis have varying presentations, often including a headache for weeks, fever, nausea, or frank mental status decline. Such patients require lumbar puncture and prompt antifungal therapy.

Sepsis (PROWESS) trial demonstrated a fungal sepsis mortality rate of nearly 56% that was more than double the nonfungal sepsis mortality rate of 28% to 30%. Suspicion is necessary to identify these patients early. A patient with a history of recent hospitalization, immunosuppression from organ transplants, or abdominal surgery has a dramatically increased risk of disseminated fungal infection causing sepsis. Cultures with specific fungal organism media should be sent, followed by initiation of antifungal therapy.

Ear, Nose, and Throat Disorders
Fungal infections in the craniofacial area may be progressive and often fatal (e.g., zygomycosis), or they may be chronic and need referral for eventual diagnosis and treatment (e.g., allergic fungal sinusitis). Zygomycosis is rare, but it is also extremely invasive and may manifest as facial pain and swelling. Patients with diabetes, especially those with diabetic ketoacidosis, require a thorough craniofacial examination to look for the characteristic black exudate. Craniofacial computed tomography (CT) scanning hastens the diagnosis when zygomycosis is suspected. Most patients with fungal sinusitis present with common sinusitis symptoms: facial pressure, congestion or drainage, swelling, and allergic “shiners.” Although most of these patients may be treated conservatively, patients with ongoing symptoms, nasal polyps, or evidence of facial deformity or bone erosion on CT will need rapid ear, nose, and throat follow-up and evaluation for débridement and antifungal therapy.

Rheumatic Disorders
Patients with disseminated fungal infections often complain of polyarthritis. Specifically, sporotrichosis spreads to the elbow or knee, and blastomycosis spreads to the weight-bearing joints or spine. Patients with cutaneous evidence of sporotrichosis or blastomycosis who have joint pain and swelling need aspiration and specific fungal analysis of the synovial fluid.

Cutaneous Disorders
The most common fungal infections in humans are the superficial cutaneous fungal infections (e.g., tinea), which are

### Table 176.1 Predisposing Factors in Fungal Infections

<table>
<thead>
<tr>
<th>PATIENT RISK FACTOR</th>
<th>COMMON FUNGAL INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus infection (acquired immunodeficiency syndrome)</td>
<td>Candidiasis, cryptococcosis, aspergillosis</td>
</tr>
<tr>
<td>Recent organ transplantation</td>
<td>Candidiasis, aspergillosis</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Candidiasis, aspergillosil</td>
</tr>
<tr>
<td>High-dose steroids</td>
<td>Zygomycosis, candidiasis</td>
</tr>
<tr>
<td>Recent antibiotic treatment</td>
<td>Candidiasis</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Candidiasis, zygomycosis</td>
</tr>
<tr>
<td>Recent or ongoing hospitalization</td>
<td>Candidiasis, aspergillosil</td>
</tr>
<tr>
<td>Recent abdominal surgery or burns (especially with intensive care unit stay)</td>
<td>Candidiasis</td>
</tr>
<tr>
<td>Travel to endemic area</td>
<td>Histoplasmosis, blastomycosis, coccidioidomycosis</td>
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detailed in Chapter 184. Certain fungal species may start as cutaneous lesions and disseminate to invasive disease, or they may begin as pulmonary disease and disseminate to form cutaneous lesions. The latter type is a form of blastomycosis characterized by a primary pulmonary infection that spreads, leading to cutaneous lesions in 75% of patients with disseminated disease. Sporotrichosis behaves similarly, but in an opposite fashion, because most patients with disseminated disease initially have cutaneous lesions. Both infections manifest as raised verrucous lesions with irregular borders that are painless and are often seen on the face or neck. Either infection can develop into the verrucous form or can become an extremity ulcer. Potassium hydroxide (KOH) scraping identifies these lesions as fungal.

**Vulvovaginal Disorders**
*Candida* is well known to cause a vulvovaginal infection that is common among sexually active women. This infection is often seen after a course of antibiotics, or it may appear spontaneously. Patients describe itching, burning of the labia, and a thick, white discharge. The incidence is increased in women taking oral contraceptives and in patients with diabetes. Adequate treatment is usually provided by over-the-counter antifungal creams, but patients may require oral medication if the infection is recurrent or severe.

**DIAGNOSTIC TESTING**

Fungi are usually visible in a tissue or fluid sample with the aid of KOH solution, which destroys nonfungal cell structures. This approach identifies only fungi that are easy to sample. In cases of pneumonia or fungemia, this type of testing is not usually possible. Most fungi can be cultured, and species such as *Coccidioides* and *Candida* grow readily on most agars. Other species, such as *Histoplasma* and *Aspergillus*, are much more difficult to grow and require antigen testing such as enzyme-linked immunosorbent assay to confirm infection. *Zygomycetes* requires special stains and is often a laboratory contaminant. It may be erroneously discarded if the laboratory is not told that it is a possible pathogen. Emergency physicians should call their particular hospital or outpatient microbiology laboratory to determine the best method of identification.

**SPECIFIC Fungal INFECTIONS**

**BLASTOMYCOSIS**
Blastomycosis is caused by the fungus *Blastomyces dermatitidis*. This infection occurs primarily in healthy individuals who are exposed in one of the endemic areas (Table 176.2). Pulmonary infections are typical, especially in the acute phase, and are contracted though inhalation of the dormant form. After attaining body temperature, the organism transforms into the yeast form and develops a greater ability to infect. Many patients acquire the infection and have chronic pneumonia for years, often diagnosed as reactive airway disease, before the infection is discovered. Patients with chronic pulmonary infections often develop extrapulmonary manifestations of the disease. These patients frequently have cutaneous lesions, and frank meningitis occurs in 10% of disseminated cases. If CNS involvement is suspected, a simple lumbar puncture is inadequate because results are routinely negative; ventricular fluid collection is required to confirm the diagnosis.

**PRIORITY ACTIONS**

**Differential Diagnosis**

**Shortness of Breath or Productive Cough?**
Does the patient have evidence of pneumonia that did not respond to antibiotics?

Does the patient have a noninfectious cause of the infiltrate such as pulmonary embolism or congestive heart failure?

If not, fungal pneumonia should be suspected and treated. Although some controversy exists regarding treatment of mild fungal pneumonia with antifungal therapy, initiating therapy in the emergency department is prudent and recommended.

**Headache or Mental Status Changes?**
Does a patient with poorly controlled HIV infection have a significant or prolonged headache? Are mental status changes associated with this headache?

Does the patient have a normal brain computed tomography scan?

If so, a lumbar puncture with the patient in the lateral decubitus position should be performed. The opening pressure should be recorded and the cerebrospinal fluid examined for evidence of fungal infection along with bacterial and viral causes.

**Organ or Bone Graft Transplant Patient with a Fever?**
Does the fever have another cause? Is the patient hemodynamically stable?

If a transplant recipient has a fever while taking antibiotics or appears to have sepsis, initiating antifungal therapy after obtaining appropriate cultures is appropriate and important.

**Difficult or Painful Swallowing?**
Does the patient have evidence of an esophageal foreign body or a bacterial infection such as with streptococci?

If not, *Candida* esophagitis should be suspected in patients with HIV infection or other immunocompromised states and in healthy individuals after recent antibiotic exposure.

Patients who are not tolerating oral fluids need to be admitted for hydration and evaluation for esophagastroduodenoscopy.

**Verrucous Lesion or Extremity Ulcer?**
Does the patient work with plant material such as roses or moss?

If so, scrape the lesions and send sample for a potassium hydroxide preparation. If the patient has no sign of systemic disease, discharge with oral fluconazole and follow-up instructions.

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HIV, Human immunodeficiency virus.
Histoplasmosis is caused by the fungus *H. capsulatum*. Infections regularly occur in healthy, immunocompetent individuals. The disease is prevalent in endemic areas, but it has a much greater geographic spread than blastomycosis. *Histoplasma* is found in caves, chicken coops, and ships hulls all over the world. Pulmonary infections are typical, and infection is often contracted through inhalation of the dormant mold form. This mold form is then activated by increased body temperatures, thus causing proliferation. Histoplasmosis has a much greater affinity for extrapulmonary symptoms than blastomycosis; spreading infection causes pericarditis, rheumatologic symptoms, and CNS involvement. Active infection depends on the load of inoculation. Lighter exposures do not produce disease, and published rates of infections higher than 50% occur in endemic areas without evidence of symptoms. The common presentation of symptomatic histoplasmosis-induced pneumonia is indolent, with flu-like symptoms, malaise, fever, and headache in almost 100% of patients. Chest radiography is highly variable, and findings may be normal, but patchy alveolar infiltrates and hilar adenopathy are common. Disease disseminates in approximately 10% of patients, mostly immunocompromised persons, and it leads to pericarditis in 10%, arthritis and arthralgias in 10%, and meningitis in 10%. Symptoms in disseminated infection are associated with pancytopenia, with significant elevations in lactate dehydrogenase, and this condition must be differentiated from thrombotic thrombocytopenic purpura.

Identification of histoplasmosis is complicated. Culture is difficult because the organism is dangerous to laboratory personnel and must be held more than a month before results can be reported as negative. Antigen testing is helpful, but many individuals have been exposed, and complement fixation rates as high as 5% may suggest the diagnosis when it is not present. The polysaccharide antigen test is preferred, although it has problems because it cross-reacts with blastomycosis and coccidioidomycosis.

When treatment is discussed, to the physician should remember that most healthy patients without chronic or disseminated infections recover without any treatment. The current literature suggests a period of observation for otherwise healthy patients with symptomatic histoplasmosis. In making the decision to treat, the side effects of therapy must be weighed against the high likelihood of spontaneous recovery. Admittedly, this was much more of an issue before azole therapy because the side effects of treatment with amphotericin B (“amphoterable”) were sometimes worse than the infection itself.

Recommendations are to initiate treatment with oral itraconazole for a minimum of 6 weeks in patients who are hypoxic or who have not improved after 3 weeks of observation. Infected immunocompromised patients or patients with disseminated or life-threatening infections are treated best with lipid formulations of amphotericin B, with the addition of a steroid taper if pulmonary involvement is severe. Itraconazole has been used successfully in patients with HIV infection who have not developed AIDS.

**Coccidioidomycosis**

Coccidioidomycosis is caused by the soil fungus *C. immitis*, which is endemic to the southwestern North American continent. Famously responsible for San Joaquin Valley fever, this organism regularly infects healthy persons. A dramatic increase in infections has been observed, with more than 100,000 infections annually in the United States alone. The increase mirrors population growth within the endemic geographic area. Infection occurs through inhalation of the mold form and subsequent transformation at body temperature into a more virulent spherule. Many infections are not symptomatic, and estimates in the literature reflect that 40% to 70% of exposed individuals never show evidence of disease. Coccidioidomycosis becomes disseminated in only 10% of cases, and much of the time only to the skin, where it frequently forms abscesses. Meningitis occurs in fewer than 5% of cases. Most complications are local, with pulmonary cavitation and chronic pneumonia responsible for the 20% of cases judged as severe.

Although primary infection usually remains in the lungs, extrapulmonary symptoms are common. Fever, chills, cough, pleuritic chest pain, and malaise are hallmarks of disease. Arthralgias and rash are also common, hence the designation “desert rheumatism.” Because only 50% of symptomatic patients have abnormal chest radiographs, the diagnosis is easy to overlook. When apparent, abnormal findings include hilar adenopathy, diffuse infiltrates, and pleural effusions. Cavitation occurs in 5% of untreated patients, and it often appears as a solitary, peripheral lesion.

Identification of *Coccidioides* is significantly easier than detection of other fungi because of the rapid growth of this organism. Most growth media produce identifiable organisms.

### Table 176.2  Endemic Areas of Common Fungi

<table>
<thead>
<tr>
<th>FUNGUS</th>
<th>ENDEMIC AREA</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Coccidioides</em></td>
<td>Southwestern United States</td>
</tr>
<tr>
<td><em>Blastomyces</em></td>
<td>Mississippi, St. Lawrence, and Ohio River valleys</td>
</tr>
<tr>
<td><em>Histoplasma</em></td>
<td>Mississippi and Ohio River valleys</td>
</tr>
</tbody>
</table>
in 2 to 3 days. Mature spherules may also been seen in tissue biopsies with special stains, and antibody detection is helpful. Unlike in histoplasmosis, colonization is rare. Complement immunoglobulin M identification is considered a sign of active infection, and it disappears over time. Results of immunoglobulin G testing continue to remain positive in patients with chronic infection, but they also resolve when the infection clears.

Treatment of coccidioidomycosis is not always necessary because the infection often resolves without intervention. The Infectious Diseases Society of America (IDSA) reported that no evidence indicated that treating the mild form of pneumonia reduces morbidity or prevents chronic infection. Therefore, the recommendations are to treat only the following groups: immunocompromised patients, patients with severe pneumonia, and patients with suspected high inoculum loads such as after laboratory accidents. Certain ethnic groups, individuals with African or Filipino ancestry, are at greater risk of disseminated infection and should be considered more thoroughly for treatment. The precise definition of severe pneumonia is left to the physician’s judgment. Therapeutic options are similar to those in other fungal diseases, with azole therapy as first-line treatment. Some literature suggests a benefit of itraconazole over fluconazole. Both drugs are associated with considerable relapse rates in chronic disease, and this is why a 3-month course of therapy is recommended. Disseminated disease may still be treated with the azoles if the patient is not immunocompromised. Patients with life-threatening cases require amphotericin. Patients with CNS involvement were traditionally treated with intrathecal amphotericin B. More recently, this approach was challenged by using high-dose azole therapy, and response rates were high, at 60% to 90%. However, cure was not observed, only suppression, and current thought is that a combination of intrathecal amphotericin B and intravenous azole therapy will work best.

ASPERGILLOSIS

The Aspergillus species that infects humans is most commonly Aspergillus fumigatus, and it is responsible for 90% of infections. Aspergillus flavus is less common, but it is much more likely to cause sinus disease. Aspergillus is a saprophyte, a soil-loving species found worldwide. Aspergillosis casts a wide spectrum of disease. It can benignly colonize immunocompetent hosts, it can cause chronic allergic symptoms, or it can devastatingly lead to overwhelming fungal sepsis in immunocompromised patients. Infection is usually contracted through inhalation of the conidia form, which progresses to the hyphae form at increased body temperature. The hyphae form is much more aggressive and difficult for the human immune system to combat. Because of the pathogenicity of the hyphae form, infection occurs in normal and immunocompromised hosts.

Immunocompetent hosts who acquire aspergillosis frequently manifest disease in the form of sinusitis. The theory of the continuum of sinus disease termed allergic fungal sinusitis is controversial. Aspergillus has been recovered from 13% of adults with allergic fungal sinusitis. The origin is obscured by the finding that the evidence points in both directions, toward either inflammatory or infectious disease. What are not debated are the secondary effects. The accumulation of mucinous debris leads to nasal polyps and possibly more invasive disease, causing bone erosion and facial deformity.

Patients with nasal polyps should be promptly referred to an ear, nose, and throat specialist because surgical débridement is currently thought necessary for cure. Because of the complex nature of the disease, therapy should not be initiated until ear, nose, and throat consultation has been obtained, unless evidence of concomitant bacterial sinusitis is present. If clinical evidence of anatomic distortion is present, facial CT scanning is helpful in determining the extent of disease. Sinusitis is the most common form of aspergillosis in immunocompetent hosts, and pulmonary disease, particularly aspergillosis, often occurs in patients who are chronically diseased but not immunocompromised.

The long-recognized fungal ball or aspergilloma infects individuals with preexisting cavitary disease, such as tuberculosis, sarcoidosis, or bullous chronic obstructive pulmonary disease. These patients continue to have an infection rate of 10% to 15%. Symptoms, most commonly cough and hemoptysis, are difficult to discern from those of the chronic disease state in these patients. Aspergillomas are usually easily identified on plain chest radiography or on CT scans. Classic therapy involves surgical resection, and admission with surgical consultation is recommended.

Aspergilloma is the contained form of pulmonary aspergillosis. Invasive pulmonary aspergillosis is far more dangerous and must be addressed quickly. The immunocompromised patient, in particular the transplant recipient, is at great risk of contracting pulmonary aspergillosis. The incidence of Aspergillus in the bronchial tree of transplant recipients has been reported at 20% to 40%. Patients with AIDS have experienced an increase in invasive aspergillosis, and the current incidence has been reported at 1% to 2%. Symptoms of invasive pulmonary aspergillosis are variable, but they usually involve a combination of fever, cough, malaise, hemoptysis, and pleuritic chest pain. Heavily immunosuppressed patients present late and may have only fatigue as their first symptom, followed by massive hemoptysis or sepsis. Diagnosis in these patients is challenging, and no “gold standard” for diagnosis exists. Findings on plain radiography may be normal. Chest CT is more helpful in identifying disease, but it is not specific for aspergillosis. Serum culture for Aspergillus is highly specific, but it has a very low yield. Enzyme-linked immunosorbent assay may be better, although sensitivity has been reported to be as low as 60% and as high as 100%. Clinical suspicion is important, and even though no randomized study has proven the value of empiric therapy, initiating therapy before an official diagnosis has been confirmed is prudent and may be lifesaving. Even treated patients have a 20% to 100% mortality rate.

Therapy for invasive aspergillosis traditionally consisted of amphotericin B, but reported cure rates were as low as 40%. In 2002, a randomized study comparing voriconazole with amphotericin B demonstrated a significantly higher survival rate of 71% versus 58%, respectively. The study also reported an unfortunately high rate of adverse events that occurred with amphotericin B therapy in 24% of the trial participants, almost double the 13% rate in the voriconazole-treated group. The IDSA recommended voriconazole as first-line treatment for invasive disease in their most recent guidelines.

CRYPTOCOCCOSIS

Cryptococcus neoformans is an arboreal fungus found worldwide, with a predilection for the excrement of certain bird
species, particularly pigeons. This disease was described in the 1950s to be similar to tuberculosis in terms of progression of disease in healthy individuals. Currently, Cryptococcus rarely infects immunocompetent individuals and is mainly linked to morbidity in HIV-infected individuals. Before the AIDS epidemic, infection rates were 0.8 per million in persons who were not infected with HIV. These rates spiked to 66 per 100,000 in patients with advanced HIV infection and then dropped again in that population with the advent of highly active antiretroviral therapy. Although Cryptococcus is not responsible for significant disease in otherwise healthy individuals, it is known to cause widespread asymptomatic colonization. Most adults have serum antibodies to Cryptococcus. A study of children in New York City demonstrated seroconversion before the age of 10 years.

Infection is thought to occur through inhalation of contaminated propagules (microscopic plant material), although aerosolized pigeon dander has yielded a potentially infectious yeast form of the fungus. Patients who manifest pulmonary cryptococcosis have common pneumonia symptoms: cough, fever or chills, and pleuritic chest pain. Cryptococcus has a well-known predilection for CNS involvement, and even though infection may be through inhalation, 50% to 60% of patients with cryptococcosis have CNS involvement. Patients with cryptococcal meningitis have varying presentations: often headache for weeks, fever, nausea, or frank mental status decline. Any HIV-infected patient with significant headache or mental status changes should be evaluated by lumbar puncture for cryptococcal meningitis.

The diagnosis is made with India ink examination of infected cerebrospinal fluid. Of HIV-infected patients with infected cerebrospinal fluid, 80% have organisms visible with India ink staining. Systemic involvement is often present in these patients and may be confirmed with either serum culture or latex agglutination, although latex agglutination is more accurate, with a sensitivity and specificity of more than 90%. Latex agglutination should be added to the cerebrospinal fluid studies to increase the likelihood of diagnosis.

Treatment should begin immediately in ill-appearing patients, even before lumbar puncture. The current literature points to combination therapy for CNS cryptococcosis in immunocompromised patients. Randomized trials showed that flucytosine, in combination with either amphotericin B or fluconazole, is superior to any single agent. In less severe infection such as symptomatic pneumonia in healthy individuals, oral fluconazole as monotherapy is sufficient. Revised IDSA recommendations include newer liposomal amphotericin formulations found to be effective in severe disease. Details regarding amphotericin B lipid complex (ABLC), L-amphotericin B, and amphotericin B colloidal dispersion (ABCD) are beyond the scope of this text.

CANDIDIASIS

Candida is the most common fungal pathogen seen by physicians. It is common in healthy individuals and in immunocompromised patients, and it is a frequent cause of nosocomial infection. More than 100 species of Candida have been identified. Candida albicans remains the most common species, but a rise of other species has been reported. The increase in non-albicans species is thought to be related to improved identification methods, the longer life span of immunocompromised patients, and a significant increase in the number of patients living with implantable devices.

Candida is a ubiquitous organism, existing as a yeast form and reproducing with buds and hyphae. It lives for long periods on surfaces, especially in hospital environments, but it does not commonly cause laboratory contamination. Candida can infect any organ and is sometimes seen as having a commensal relationship with healthy humans. Candida infection is fought by multiple components of the immune system. T-cell–mediated attacks prevent mucosal overcolonization, and granulocytes help to prevent candidemia. Evidence of these mechanisms is seen in the common occurrence of thrush in patients with AIDS and of Candida sepsis in neutropenic patients. The most common infection with Candida is vulvovaginal candidiasis. Although identification of vulvovaginal and oral candidiasis is almost always made clinically, identifying candidiasis in other disease states is a challenge.

Candidiasis may be diagnosed on sight, as is often the case with thrush or vulvovaginal infections. The diagnosis may be aided by a simple scraping and KOH preparation that will show the yeast or hyphae forms of the fungus. Culture is still the most common method of identification. Candida grows on most agars and is an unlikely contaminant. Unfortunately, the specificity of the culture is not matched by the sensitivity; and although the blood culture remains important, results can be misleading. In patients with autopsy-proven systemic candidiasis, the rate of recovery from blood cultures was only 40% to 60%. Because of the low sensitivity and increased incidence of invasive candidiasis, enzyme-linked immunosorbent assay and polymerase chain reaction testing are becoming more popular. Antigen testing should be pursued when invasive disease is suspected or identification of a particular species of Candida is important, such as in organ transplantation or in recent bone graft recipients. When patients develop invasive disease, treatment should be instituted when it is suspected, not when it is confirmed.

Treatment of invasive disease is much different from treatment of mucocutaneous infection. Candida can infect any organ system and has become a deadly cause of sepsis. It is now one of the top five causative organisms in sepsis. Candida sepsis has a mortality rate of 50%. Many of these cases are nosocomial, and Candida is responsible for approximately 9% of all nosocomial infections. Along with immunocompromised patients, patients with burns, patients with recent abdominal surgery, newborns, and patients receiving total parental nutrition are at risk for invasive candidiasis. Traditional treatment of disseminated candidiasis has been with amphotericin B, but intravenous fluconazole was equally effective in randomized trials in neutropenic patients. The IDSA guidelines stated that either drug may be used. Patients with recent azole exposure may have developed resistant organisms, and caspofungin should be added to the initial therapy. No convincing studies exist to prove the value of initial treatment of septic immunocompromised patients with antifungal agents, although multiple guidelines have suggested that septic patients who are at high risk for candidemia may benefit from empiric antifungal therapy. Less invasive forms of candidiasis are much more prevalent and are commonly seen in EDs.

Oral candidiasis may occur in healthy individuals after antibiotic use or in HIV-infected patients. Initial episodes should
be treated with clotrimazole troches or nystatin. If this approach is not curative or if the condition recurs, oral azole therapy should be started. Oral fluconazole and itraconazole solutions are equivalent, and both are superior to other oral therapies. HIV-infected patients with oral thrush who complain of odynophagia or retrosternal chest pain likely have esophageal involvement and should be admitted for systemic azole therapy and culture of Candida to check for resistance.

Vulvovaginal candidiasis is a common diagnosis, and 50% of women have received the diagnosis by the age of 25 years. This disorder is common after antibiotic use and is more frequent in women taking oral contraceptives. Infrequently, it can be the first sign of diabetes, and anyone who is diagnosed with vulvovaginal candidiasis for the first time should have a spot blood glucose check as a screening examination. Vulvo-vaginal candidiasis can be diagnosed by the combination of symptoms, visual inspection of the genitals, and KOH preparation of the scraping. Although coinfection may exist, if symptoms do not resolve, further evaluation is necessary. Patients often treat vulvovaginal candidiasis with over-the-counter agents before they see the physician. If treatment has not been attempted by patients, an over-the-counter cream should be suggested as first-line therapy. When over-the-counter treatment fails, a higher-concentration prescription azole cream is second-line therapy. An alternative is single-dose oral therapy with fluconazole or itraconazole.

SPOROTRICHOSIS

Sporotrichosis, or rose cutter’s disease, is caused by the fungal saprophyte Sporothrix schenckii. The fungus is found in the soil of tropical and subtropical environments, but it can be present in more austere areas, especially in greenhouses. Sporotrichosis is almost always identified as the cutaneous form in healthy individuals, although it can become disseminated through the pulmonary or cutaneous forms in immunocompromised patients. Outbreaks do occur occasionally, especially when heavy colonization is found in packed sphagnum moss that is used to protect plants (e.g., saplings, rose bushes) during transportation. More common is the sporadic case seen in plant workers, such as rose cutters.

The noninvasive form of the disease is caused by inoculation from a thorn or a skin tear during plant handling. Symptoms usually occur 3 to 4 weeks after exposure, and they begin with a small, erythematous area, usually on the forearm or hand. The lesion becomes indurated and often verrucous, and then it spreads locally to cause lymph node swelling. The lesions are not painful, but they may become superinfected with skin flora. In healthy individuals, the lesions grow very slowly and may appear the same for months. The reason for physician visits is often the cosmetic appearance. In immunocompromised patients, these skin lesions may spread. Disseminated sporotrichosis causes arthritis, often of the elbow or knee, and immunocompromised patients with suggestive skin lesions and joint effusions should be evaluated for fungal joint disease. Smaller numbers of patients with disseminated disease have pulmonary involvement. Symptoms in these patients are similar to those in patients with other types of fungal pneumonia, with presenting productive cough and pleuritic chest pain. The chest radiograph is nonspecific; interstitial infiltrates, nodules, and cavitary lesions can be seen.

Systemic illness causes constitutional symptoms such as fatigue, weight loss, and, uncommonly, fever.

The diagnosis is made with KOH examination of the cutaneous lesion scrapings. If a more specific diagnosis is required, or if extracutaneous disease is suspected, S. schenckii is easily cultured on various media, and it is identified by latex agglutination. Sporothrix is not considered a contaminant, and its presence signifies disease.

Treatment of the cutaneous form of the disease has traditionally been with saturated solution of potassium iodide (SSKI). Although theories exist, exactly how this solution works to combat sporotrichosis is unknown. The main problem with SSKI is the side effect profile. When used for more than a month, SSKI has a disabling effect on thyroid hormone production, especially in children. Itraconazole is more efficacious and has fewer side effects. Other azoles may also be used. Therapy is long, often lasting 3 to 4 months, and it should continue for a month after resolution of lesions. Patients with disseminated disease can also be treated with intravenous azoles.

ZYGOMYCOSIS

Zygomycosis is now the preferred term for the former mucormycosis. The preference stems from the use of zygomycosis to refer to an invasive form of disease produced by any of several Zygomycetes organisms: Absidia corymbifera, Rhizomucor pusillus, and Rhizopus arrhizus. Zygomycosis is rare, and it is almost always diagnosed in immunocompromised patients. In these patients, zygomycosis is invasive, rapidly progressive, and usually fatal. The rhinocerebral form has a mortality rate of 80% to 90%. The severity of disease is likely related to the particular affinity this group of fungi has for blood vessels. These fungi have been termed angiotrophic because of the widespread invasive blood vessel disease. This predilection for blood vessel invasion leads to ischemia, necrosis, and emboli.

Zygomycosis exists predominantly in the rhinocerebral, pulmonary, gastrointestinal, and cutaneous systems, and it may disseminate. The different forms are witnessed in particular subgroups of immunocompromised patients. The rhinocerebral form is seen in diabetic patients, especially during diabetic ketoacidosis, and in patients receiving high-dose or long-term steroids. Patients with leukemia or neutropenia often have the pulmonary form. Organ transplant recipients represent the group with the fastest-growing incidence of disease; zygomycosis represented less than 1% of fungal disease in transplant recipients in 2001, and it now represents 20%.

Symptoms of the rhinocerebral form are insidious and consist of local pain or swelling, nasal congestion, headache, fever, or epistaxis. Rhizomucor leaves a distinctive black exudate, “black pus,” that is a foreboding sign of disease. Pulmonary involvement causes cough, fever, and occasional hemoptysis, and it is usually diagnosed in extremely ill-appearing patients. Gastrointestinal involvement is also seen in significantly ill patients, and it causes hematochezia, nausea, and emesis, eventually leading to intestinal ischemia.

The diagnosis is made by tissue biopsy with microscopic examination and culture. Special stains are often needed to identify the organism accurately, and the laboratory must be
made aware that the physician is looking for *Zygomycetes*. Culture is available, but these organisms are common laboratory contaminants and are not considered diagnostic unless serial cultures are combined with direct tissue examination. Treatment should not wait for confirmation. The high mortality rate demands that treatment be initiated when the diagnosis is considered.

Rapid treatment may still not prevent death. The mortality rate of general zygomycosis is 50%, with a mortality of 80% to 90% in the rhinocerebral form. Amphotericin B is the recommended first-line therapy because the traditional azoles are not effective for zygomycosis. Members of a newer class of extended-spectrum azoles, voriconazole and posaconazole, have achieved success in patients in whom amphotericin therapy has failed.

### MEDICATION

Antifungal therapy is the primary treatment for known or suspected fungal infections. Current therapy is transitioning from amphotericin B toward more potent forms of azole medications. Amphotericin B has been used for decades for nearly every type of fungal infection and is still recommended primarily in certain situations. Because of the many situations that call for antifungal therapy, recommending one particular drug over another is impossible. A newer generation of azole medications, the triazoles, is supplanting amphotericin. These medications, including voriconazole and fluconazole, have shown superior rates of improvement and cure compared with amphotericin B. In the most serious infections such as systemic aspergillosis and zygomycosis, voriconazole and posaconazole have been directly compared with amphotericin B and have had higher cure rates and lower side effects. In less serious, but symptomatic infections, fluconazole is superior or equal to amphotericin B, with a dramatically lower side effect profile.

### REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES