

**Life-Threatening Fungal Infections on the Rise**Author: Connie C. Chettle, RN, MS, MPH, CIC, COHN-S

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**Course Objectives**

The purpose of this program is to inform nurses about the two most common fungi-caused invasive diseases in critically ill and immunosuppressed patients. After studying the information presented here, you will be able to —

- Describe the two major risk factors for invasive *Candida* infections.
  - Discuss three ways patients can become infected with *Aspergillus*.
  - Explain three ways invasive *Aspergillus* infections can be prevented.
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*I first encountered Aspergillus infection as a new nurse on a bone marrow transplant unit. I remember that my patient, a woman in her late 40s with leukemia, had received a bone marrow transplant and was severely neutropenic. Her Aspergillus infection started in her sinuses and spread within days into her facial structures, eyes, and then her brain. Although she received amphotericin B and extensive surgical debridement that left her with severe facial deformities, she died of cerebral aspergillosis within a few weeks of diagnosis.*

The incidence of life-threatening invasive fungal infections has doubled during the past several decades due, in part, to an increasing population of immunosuppressed and critically ill patients.<sup>1</sup> Cancer patients with chemotherapy-induced **neutropenia** (an abnormally low number of neutrophils); transplant recipients receiving immunosuppressive therapy, such as corticosteroids or cyclosporine; patients with HIV; and patients in ICUs are at an increased risk of acquiring fungal infections. The risk of infection has increased for critically ill patients with normal immune systems, as well.

Aggressive treatments, diagnostic procedures, and complicated surgeries — along with the nearly universal use of broad-spectrum antibiotics, long-term indwelling catheters (intravascular, peritoneal, or urinary), and total parenteral nutrition — have made these patients more vulnerable to hospital-acquired fungal infections.<sup>1,2,3</sup> Nurses need to educate these vulnerable patients about the importance of infection-control protocols to reduce their risk of developing invasive fungal infections. Such patient education can save lives.

The two most important species of fungi that cause invasive disease in hospitalized patients are *Candida* and *Aspergillus*. Both are associated with high morbidity, high mortality, and a significant use of medical resources.

*Candida* species are the major cause of invasive fungal infections in both critically ill immunocompetent (normal immune system) and immunosuppressed patients. In U.S. hospitals, *Candida* species account for approximately 15% of all hospital-acquired infections, more than 72% of fungal infections, and 9% to 10% of bloodstream infections, making *Candida* the fourth most frequently isolated organism in bloodstream infections.<sup>1,2,3</sup> *Candida* bloodstream infections have the highest mortality rate of all bloodstream infections, and for invasive disease (disseminated candidiasis), the mortality rate is similar to that of septic shock, 40% to 60%.<sup>4</sup> In addition to the high mortality rates, infections with *Candida* are responsible for an extra \$1 billion in health care costs in the U.S. each year.<sup>5</sup>

Aspergillosis is the second most common fungal infection, primarily involving the lungs in patients who are severely immunocompromised. It's the leading cause of death in patients with leukemia and in those who undergo bone marrow transplants. The mortality rate for neutropenic patients with invasive *Aspergillus* infection is greater than 90%.<sup>3</sup>

**How *Candida* gets a foothold**

*Candida* are yeastlike fungi that can be found in low concentrations as normal inhabitants of the human skin and of the mucosal membranes lining the GI, genitourinary, and respiratory tracts.<sup>6</sup> The organisms rarely cause invasive disease in humans unless an interruption of the body's natural barriers, such as skin and mucosal surfaces, occurs, allowing the fungal pathogens to enter the bloodstream. This can happen when medical procedures break down skin and mucosal surfaces or when bacterial and viral infections, such as herpes simplex or cytomegalovirus; chemotherapy; radiation therapy; or graft-vs.-host disease damage the skin and mucosa. It can also occur when antibiotics suppress the body's normal bacterial microflora, allowing *Candida* to overgrow in the GI tract.<sup>6</sup> In immunocompromised patients, an overgrowth of *Candida* can lead to life-threatening infections ranging from candidemia (*Candida* species in the blood) to widespread dissemination (candidiasis, sepsis, and multisystem failure). At high concentrations, *Candida* cells are able to pass across the intact gut mucosa and enter the bloodstream. From there, they can travel to the kidneys, brain, lungs, liver, heart, spleen, and pancreas.<sup>4,7</sup>

Most *Candida* infections are thought to be endogenous (acquired through previous colonization of the mouth, GI tract, vagina, or skin). But exogenous infections are possible, acquired by crossinfection from another patient or a health care worker (especially through unwashed hands) and contaminated equipment, solutions, and surfaces. Health care workers often fail to wash their hands; in one study, 58% of nurses had *Candida* strains on their hands.<sup>8</sup>

The two major risk factors for developing invasive *Candida* infections are prolonged immunosuppression, usually as a result of highly cytotoxic chemotherapy, or an exposure to an ICU environment, where 50% to 86% of patients with extended stays become colonized with *Candida*.<sup>2,4,6,7</sup> In the ICU, the widespread use of broad-spectrum antibiotics, total parenteral nutrition, mechanical ventilation, and indwelling medical devices are especially favorable for the growth of *Candida*. Patients with indwelling medical devices are at particular risk.<sup>3</sup> *Candida* species have a special affinity for biomedical materials (e.g., plastics), and the increase in *Candida* infections during the last decades has paralleled the increased use of implanted/indwelling medical devices in patients with impaired immune systems.<sup>9</sup>

*Candida* cells are able to colonize medical devices — such as IV and central venous catheters, urinary catheters, surgical drains, feeding tubes, nasogastric tubes, pacemakers, stents, and shunts — by forming dense microcolonies of cells entrapped within a polysaccharide matrix attached to the devices. This “slimelike” material protects the *Candida* cells from the body’s immune defenses and from most of the commonly used antifungal agents.<sup>3,9</sup>

### ***Aspergillus* all around us**

**Invasive aspergillosis** is an acute, rapidly progressive, often fatal infection that primarily involves the lungs and central nervous systems of severely immunosuppressed patients. The infection is caused by *Aspergillus*, a filamentous fungus named in 1729 by a botanist who thought the fungal fruiting bodies resembled an aspergillum, a brush or perforated ball used for sprinkling holy water during church services.

Exposure to *Aspergillus* is common. The fungus is ubiquitous in soil, water, food, and decaying vegetation. In the hospital, *Aspergillus* spores (conidia) can be isolated from the air, ventilation systems, water, contaminated ceiling tiles, carpeting, food, plants, flowers, and contaminated dust during construction.

The two major risk factors for invasive aspergillosis are neutropenia and **corticosteroid therapy** (Corticosteroids are used as immunosuppressants to prevent and treat transplant rejection). Patients at highest risk include those who have had stem-cell transplants (10% to 15%); those who have received liver, lung, and heart transplants (5% to 8%); and those receiving intensive chemotherapy for leukemia (10% to 20%).<sup>10,11</sup>

Infections with *Aspergillus* nearly always occur from inhaling its spores, which then are deposited in the lungs, nose, or paranasal sinuses. When inhaled spores reach the lungs, pulmonary macrophages and neutrophils are the first line of defense against invasive disease. In the normal host, pulmonary macrophages are able to kill and ingest the spores. If a few spores escape the macrophages and germinate, neutrophils are able to use extracellular mechanisms to destroy the hyphal (branching, threadlike filaments) forms.<sup>6</sup> However, in patients with severely compromised immune systems, the spores are able to germinate, forming hyphae that can invade the lung tissues and blood vessels. The rapidly growing hyphae plug the vessels, disrupting the flow of blood. Areas of necrosis distal to the obstruction develop, and erosion into the blood vessel walls can lead to massive pulmonary hemorrhage and exsanguination. Corticosteroid therapy further increases susceptibility to invasive aspergillosis by impairing the ability of the macrophages and neutrophils to kill spores and hyphae and by increasing the growth rate of *Aspergillus* by as much as 40% and cell synthesis by more than 150%.<sup>5</sup>

The lungs are the site of 80% to 90% of invasive infections. The usual clinical presentation is nonspecific with symptoms of pleuritic chest pain, low-grade fever, cough, dyspnea, and pulmonary infiltrates. In extensive infection, multiple nodular pulmonary infiltrates surrounded by a zone of low attenuation, the “halo” sign, can be seen on chest radiographs. Over time, the nodules can create a cavity, forming a thin crescent of air near the edge, the “air-crescent” sign. Both signs are characteristic of invasive pulmonary aspergillosis.<sup>5</sup> Respiratory tract infections can disseminate to other sites, including the eyes, brain, liver, spleen, kidney, and bone.

Cerebral aspergillosis is the most lethal manifestation of invasive disease. It occurs in 10% to 20% of patients with invasive infections and nearly always causes death. The fungus is usually disseminated to the brain through the bloodstream, although it may also be a result of direct extension from the sinuses, where inhaled *Aspergillus* spores have settled in the nasal turbinates, germinated, and invaded the bone, orbit, and brain. Clinical symptoms of central nervous system infections include focal seizures, hemiparesis, cranial nerve palsies, and hemorrhagic infarcts caused by vascular invasion.<sup>12</sup> Treatment with antifungal agents is of limited efficacy because of the restricted penetration of the drugs through the blood-brain barrier.

### **Elusive clues**

Infections with *Candida* and *Aspergillus* are extremely difficult to diagnose, and many infections are confirmed only at autopsy.<sup>4</sup> The clinical symptoms of *Candida* are nonspecific. Often the only indication of infection is a gradual worsening of a patient’s clinical condition associated with a persistent, unexplained fever or sepsis that does not respond to broad-spectrum antibiotics. Fewer than 50% of patients with invasive disease have positive blood cultures.<sup>7</sup>

Early diagnosis of *Aspergillus* infection is equally difficult. Not only are the clinical signs nonspecific, but clinical presentation varies among different patient groups. Blood cultures are rarely positive, and even with focal pulmonary lesions, sputum cultures are positive only 50% of the time.<sup>12</sup> In addition, the “halo sign” and “air-crescent sign” seen on CT chest scans are relatively late findings and are not usually seen until the disease has advanced and the patient has recovered from neutropenia.

In 2003, the Food and Drug Administration approved [a noninvasive test for \*Aspergillus\* infection](#) that detects galactomannan antigen (a fungal

cell-wall antigen) in body fluids. This test is used in conjunction with other diagnostic procedures. However, for a definitive diagnosis, a biopsy showing tissue invasion by fungal hyphae is needed.<sup>12</sup>

### Treatment can't wait

Since early detection of invasive *Candida* and *Aspergillus* infections is nearly impossible, empiric antifungal therapy is typically initiated for febrile neutropenic patients who fail to respond to four to seven days of appropriate broad-spectrum antibiotic therapy.<sup>7</sup> Empiric therapy generally consists of antifungal agents active against *Candida* and *Aspergillus* species, such as amphotericin B formulations (Albecet), itraconazole (Sporanox), voriconazole (Vfend), and caspofungin (Cancidas).<sup>7</sup> Patients diagnosed with or suspected of having an invasive *Candida* infection should receive systemic antifungal therapy. In addition, all IV catheters should be removed since biofilms on catheters form a nidus (central point) for ongoing infection. Currently, the antifungal drugs most frequently used to treat candidemia are fluconazole (Diflucan) and caspofungin. Amphotericin B is used less often.<sup>7</sup>

Invasive aspergillosis is highly lethal in immuno-suppressed patients, and treatment is often initiated upon suspicion of diagnosis without definitive proof. The drugs of choice for treatment of invasive aspergillosis are voriconazole, amphotericin B (lipid formulation), and itraconazole. **Posaconazole** and ravuconazole (two new azoles) are under evaluation in clinical trials.<sup>12</sup>

### Nurses lead prevention efforts

Despite aggressive medical treatment, the mortality rate for immunosuppressed patients with invasive *Candida* or *Aspergillus* infections remains unacceptably high. For this reason, preventive measures are of major importance. Nurses need to have a clear understanding of how and where *Candida* and *Aspergillus* infections are acquired to help prevent disease. Invasive *Candida* infections are predominantly endogenous, resulting from a prior colonization of the patient's skin and mucosa. Nevertheless, with careful attention to the patient's oral, dental, skin, and perineal hygiene, nurses can help reduce or suppress *Candida* colonization. Exogenous infections also occur. Hospital-associated transmission, attributed to direct or indirect contact with environmental sources and health care workers' hands, has been documented as a source of *Candida* infections. Patients have developed invasive disease from *Candida* strains cultured from the hospital environment, including food, adjacent patients, and surfaces in patient rooms.<sup>13</sup> Nurses and other health care workers can help prevent these infections by careful housekeeping and by frequent and thorough hand hygiene.

In contrast to most *Candida* infections, infections with *Aspergillus* are exogenous. They are nearly always acquired through inhalation of airborne spores from the environment. Given the ubiquitous presence of *Aspergillus* in the environment and the uncertainty of the incubation period for infection, it is often difficult to determine whether aspergillosis was acquired inside or outside the hospital. However, because most patients undergoing chemotherapy and bone marrow and solid organ transplants spend their most vulnerable, neutropenic period in the hospital, many *Aspergillus* cases are assumed to be a result of exposure during hospitalization.

Air contaminated with *Aspergillus* spores is the major source of hospital-associated aspergillosis. Numerous outbreaks of disease have been associated with dust-laden air from hospitals or nearby construction sites. To lessen exposure to airborne *Aspergillus* spores, many neutropenic patients are placed in a protected environment during hospitalization. This environment includes rooms with —

- HEPA filtration of incoming air
- Positive air pressure relative to the corridor, toilets, anterooms, and other hospital areas
- Well-sealed walls, floors, ceilings, windows, and electrical outlets to keep out unfiltered air
- Ventilation to provide at least 12 air changes per hour
- Strategies to lower dust (e.g., no carpeting or upholstered furniture)
- Routine cleaning and disinfection using daily damp dusting
- A ban on dried or fresh flowers and potted plants in patient rooms and other hospital areas of patient exposure<sup>13</sup>

When patients leave their protected environment for diagnostic studies or treatments, they should wear N-95 respirators.

Hospital water and food have been implicated as sources of *Aspergillus* infections. Waterborne *Aspergillus* can aerosolize, especially in bathrooms, where sinks, showers, toilets, and drains are potential sources for transmission of spores. *Aspergillus* is also found in ice-making machines and refrigerator condensate trays. Although there are no specific guidelines for preventing exposure to *Aspergillus* in hospital water, it makes sense that nurses should help neutropenic patients minimize their exposure to activities that cause water aerosolization. For example, bed baths might be used instead of showering, and commercially bottled sterile water might be provided for drinking and brushing teeth instead of tap water. Nurses might also caution high-risk patients to avoid exposure to faucet water, humidifiers, and flushing toilets.<sup>14</sup>

Nurses should also explain to high-risk patients that food is another possible source of *Aspergillus* and that their physicians may place them on a neutropenic diet, which reduces pathogens in food that could cause infections in immunosuppressed patients. In a food contamination survey, *Aspergillus* was cultured from 100% of black pepper and tea bag samples; 12% to 66% of fruits, with peaches and other fruit with downy skin registering the most contamination; and 20% of freeze-dried soups.<sup>8,14</sup>

Preventing fungal infections in severely immuno-suppressed patients remains a challenge. When patients are severely immunosuppressed and isolated in a protective environment, nurses play a key role in helping them understand the need to adhere to infection-control protocols that will reduce their exposures to pathogens in the environment.

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