Managing Invasive Fungal Infections CME

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Editorial note:
Broad-spectrum antifungal agents aid in reducing the incidence of fungal sepsis in critically ill patients hospitalized in intensive care units (ICUs) where invasive candidiasis and pulmonary aspergillosis are most common. Early initiation of antifungal therapy depends on early, fast and reliable diagnostics to optimize the chances of survival as there is a lack of specificity for risk factor assessment. Even though blood cultures or histopathologic evidence is the standard to measure infection, they lack sensitivity and taking a biopsy sample may present substantial risk in patients who are critically ill. Diagnostic tools that are non-culture-based have been devised for earlier and/or more accurate detection of fungal infection. These include assays of (1-3)-β-D glucan and galactomannan antigens which yield promising predictive values, although results may not be specific. The incidence of invasive candidiasis has been stable over the past decades, but there is an alarming trend towards non-albicans Candida species. The guidelines from the Infectious Diseases Society of America (IDSA) on antifungal prevention, prophylaxis and treatment were published in 2008 and 2009 and do not include more recent data, so Medscape asked John R. Wingard, MD, Price Eminent Scholar and professor of medicine at the University of Florida Health Cancer Center in Gainesville, Florida, to comment on risk factors for invasive fungal infections (IFIs) and optimal approaches to preventing and treating these infections in critically ill patients.

Medscape: Which patients are at highest risk for invasive fungal infections?

John R. Wingard, MD: Invasive fungal infections are complications of conditions and procedures that result in immunosuppression, including transplantation, human immunodeficiency virus (HIV) infection, and treatment of malignancies. The 2 major fungal pathogens that affect hospitalized patients in the United States are *Candida* species and *Aspergillus* species. The patients at highest risk for the life-threatening infections vary, as do risk factors and epidemiology.[1,2] In general, patients at highest risk for invasive fungal infections (IFIs) in the hospital setting include those who are neutropenic; those who are undergoing solid organ or bone marrow transplantation; those receiving intensive chemotherapy regimens; those receiving broad-spectrum antibiotics, especially those with a central venous catheter and those receiving parenteral nutrition. Additionally, non-neutropenic patient in surgical or medical ICUs are also at risk, especially those who have been receiving broad-spectrum antibiotics and who are intubated; those with bladder or venous catheters; those who are septic; and neonates born prematurely and/or who are in an ICU and deemed to be high risk due to other conditions that increase their vulnerability.[2,3] In most tertiary care hospitals, the majority of IFIs occur in ICUs and are caused by *Candida* species. Invasive fungal infections also commonly occur in patients being cared for in oncology and transplant units. *Candida* species infections are much less common today, with the widespread use of antifungal prophylaxis, but the risk for *Aspergillus* species infections has increased.

Medscape: What are the specific risk factors for *Candida* infections?

Dr Wingard: *Candida* species produce a wide spectrum of diseases ranging from superficial mucocutaneous conditions to invasive illnesses. A primary risk factor is injury to the mucosal and skin barriers; this includes patients with vascular and peritoneal catheters, burn patients, and those undergoing surgical procedures. Also at risk are those with mucositis secondary to chemotherapy or radiation and those who undergo surgery or develop perforations of the intestinal tract, as well as patients with disrupted immune defenses. In particular, the latter includes cancer patients, organ transplant recipients, and patients who have autoimmune or immunocompromised medical conditions and who are on immunosuppressive therapies.[2]

An important factor related to both the clinical syndromes and pathophysiology is that *Candida* is a commensal organism, meaning that it resides on the skin and mucosal surfaces, and invasive infections are generally caused by organisms already colonizing the patient. Patients most at risk tend to be those with suppressed

bacterial flora, those who are neutropenic, those who have damage to natural barriers such as skin and mucosa, and those with indwelling catheters.

Medscape: What are the specific risk factors for *Aspergillus* infections?

Dr Wingard: In contrast to *Candida*, *Aspergillus* is an exogenous organism. It is typically inhaled and enters the body through the nasal passages and the respiratory tract. *Aspergillus* is a common cause of pneumonia, sinopulmonary, or rhino-sino-orbital infections, which occur when the organisms are deposited into the sinuses, nasal passages, or the respiratory tract. Invasive fungal infections caused by *Aspergillus* most commonly occur in allogeneic hematopoietic stem cell transplant (HSCT) recipients, in deeply neutropenic patients with acute leukemia, and less so in those undergoing solid organ transplantation. *Aspergillus* infections are occasionally encountered in patients with chronic obstructive pulmonary disease and other respiratory conditions as well as in patients with advanced stages of human immunodeficiency virus (HIV) infection. In recent years, the occurrence of *Aspergillus* infections has increased in patients in ICUs, but it is still relatively infrequent in such patients.[2,4]

Medscape: What are the basic treatment strategies for invasive *Candida* infections?

Dr Wingard: Historically, the management strategy has been to document infection and then initiate treatment. There are a number of effective therapies. The principles of *Candida* therapy are to document the infection as early as possible and remove the focus of infection, such as a contaminated catheter. When possible, immunosuppression should be reduced or stopped in order to restore the body's normal immune function. And finally, antifungal therapy should be started early -- as soon as the infection is highly suspected or documented.[5] The reason for this strategy is that a number of studies have shown that early therapy, defined as that initiated within 12 hours of a positive blood culture in patients with *Candida* fungemia, is associated with the lowest mortality.[5] However, it often takes longer than 12 hours for cultures to demonstrate growth, which means the clinician must maintain a high degree of vigilance for infection. Particularly in high-risk patient populations, it may be appropriate to initiate therapy when infection is strongly suspected and while the evaluation proceeds. The therapy can then be discontinued if the results of the evaluation do not confirm the suspicion.

There has been discussion about the necessity of removing intravenous (IV) catheters. In some retrospective studies, it has been suggested that catheter removal can result in improved outcomes, although this has been debated in recent years.[6] However, there is general agreement that catheters should be removed from patients who are fungemic and have persistent positive blood cultures despite antifungal therapy.[7]

Medscape: This is really informative. What are your thoughts on the treatment options for invasive *Candida* infections?

Dr Wingard: The antifungal therapeutic options for the treatment of *Candida* infections include the azole antifungal agents; the polyenes, including amphtotericin B deoxycholate and the lipid formulations such as liposomal or lipid complex amphotericin B; and the echinocandins, caspofungin, micafungin, or anidulafungin.[5] Fluconazole, the most commonly used azole, has gained wide acceptance as a first-line therapy. Fluconazole has a very good safety profile and can be given intravenously or orally for prolonged treatment courses. Its activity is excellent against *Candida albicans,* but it is less active against certain non-*albicans* species, especially *C krusei* and *C glabrata*.

A recent concern with the widespread use of fluconazole, particularly for prophylaxis, is the increase in non-*albicans* species, which tend to be less susceptible to the current treatment options, especially fluconazole.[8] This is particularly true for *C glabrata*, which is relatively resistant to fluconazole and in some cases, frankly resistant. The increasing rate of resistance has led some to question fluconazole as the most appropriate first-line strategy. Some of the extended-spectrum azoles, such as voriconazole, have also been shown to be effective.[5]

The echinocandins can be used as effective therapy for invasive *Candida* infections. They are well tolerated and have an excellent spectrum of activity against non-*albicans* species. A limitation to their use is the need for IV administration. Thus, for prolonged treatment courses a step-down approach to an oral azole is often used if the *Candida* species is susceptible to azoles. Amphotericin B, either deoxycholate or a lipid formulation, is also an effective treatment option. Due to its toxicity, amphotericin B deoxycholate has been replaced by the lipid formulations that are less nephrotoxic and better tolerated. Amphotericin B has a much wider spectrum of activity against the various *Candida* species than fluconazole. It is important to know the epidemiology in one's own hospital to optimally choose the most appropriate treatment strategy.

Medscape: Just to confirm, the 2009 IDSA guidelines for the treatment of candidiasis recommend fluconazole or an echinocandin as initial therapy for most adult patients who are non-neutropenic, whereas for most patients who are neutropenic, echinocandins are recommended.[5] This latter recommendation is consistent with recommendations from the 2014 NCCN guidelines on the prevention and treatment of cancer patients.[24]

What are the treatment options for *Aspergillus* infections?

Dr Wingard: Amphotericin B deoxycholate was historically the preferred treatment for *Aspergillus* species infections. The lipid formulations have largely replaced the deoxycholate formulation due to less toxicity; they permit much better tolerance of the high doses and prolonged courses of therapy needed. The introduction of extended-spectrum azoles with excellent anti-*Aspergillus* activity has changed our approach. A prospective, randomized trial comparing voriconazole with amphotericin B deoxycholate in patients with invasive aspergillosis showed that initial therapy with voriconazole led to better responses and improved survival.[9] Guidelines from IDSA indicate that voriconazole is now the preferred first-line therapy.[10] Studies also suggest that other azoles such as posaconazole and caspofungin have good activity and can be used for salvage therapy. Caspofungin has been approved in the United States for salvage therapy; posaconazole is licensed for that indication in Europe but not in the United States.

Medscape: Can you tell us how are we improving treatment for invasive fungal infections?

Dr Wingard: Treatment outcomes have improved over the years as new therapies have been approved, but many patients still have poor outcomes. Thus, there has been considerable interest in prevention and the use of assays of the galactomannan *Aspergillus* antigen and the fungal wall component, (1-3)-β-D glucan. These assays can be used on serum samples and on samples of bronchial lavage fluid,[23] thus avoiding the need for invasive biopsy procedures. Galactomannan is a cell wall constituent of *Aspergillus* that is secreted into blood during invasive infections. It is not detected in the serum of colonized or noninfected patients, but it is detected in invasive infections with reported sensitivity and specificity of approximately 80% and 80%, respectively. [11] The galactomannan antigen assay is relatively specific for *Aspergillus*, but there is some cross reactivity with other fungal pathogens[11,12] and there are occasional false-positive and false-negative tests.

The (1-3)-β-D-glucan assay detects a broader range of IFIs, including invasive *Candida*, *Aspergillus*, and other invasive fungal pathogens,[12] but false-positive and false-negative test results can occur. These assays can alert clinicians to the possibility of invasive fungal pathogens, such as in patients with a suspected infection that is not yet documented. In such cases, these diagnostic tools may allow clinicians to initiate therapy early in the course of the disease.

Medscape: As you know, the 2009 guidelines published by IDSA lay out in detail the options for prophylaxis of Candida infections. For example, several options are recommended including fluconazole, posaconazole, or caspofungin for patient with chemotherapy-induced neutropenia, and fluconazole, posaconazole, or micafungin for stem cell recipients with neutropenia.[5]

Would you please comment on *Candida* prophylaxis for high-risk patients?

Dr Wingard: A variety of studies have shown that prophylaxis can be quite useful in patients at high risk for IFIs. This was first demonstrated with *Candida*. The results of several randomized trials showed that when

fluconazole prophylaxis was used, there was a reduction in the rates of IFIs in HSCT recipients (primarily due to a reduction in *Candida* infections).[13] In some studies, there was also a survival benefit. Studies have also suggested a potential preventive role for micafungin.[13] Such studies have changed practice, and other data suggest a similar beneficial role for fluconazole or itraconazole prophylaxis in patients with acute myeloid leukemia (AML).[14] Additionally, other studies suggest that certain high-risk populations in ICUs could benefit from fluconazole prophylaxis, but this has been less well established. A consensus on the risk factors that best identify those in whom this therapy should be used has not been reached.

Medscape: The 2008 IDSA guidelines recommend posaconazole for patients with acute myeloid leukemia and neutropenia or HSCT recipients with graft-vs-host disease who are at high risk of Aspergillus infection. The 2014 NCCN guidelines on the prevention and treatment of cancer-related infections include a category 1 recommendation for prophylaxis with posaconazole in these patient populations.[10,24]

Would you please comment on *Aspergillus* prophylaxis in high-risk patients?

Dr Wingard: Initial studies of itraconazole for *Aspergillus* prophylaxis identified problems with variable bioavailability and tolerance, as the oral formulation was not well tolerated in many patients, and its use has gone out of favor. Studies of the use of posaconazole oral solution in patients receiving induction chemotherapy for AML have shown it to be associated with fewer IFIs, including *Aspergillus* infections, as well as a survival benefit when compared to fluconazole or itraconazole.[15,16] The benefit of posaconazole and voriconazole in HSCT is less clear. A trial comparing oral posaconazole to fluconazole in allogeneic HSCT patients with graft-vs-host disease showed a nonsignificant trend in reduction of IFIs and a reduction in *Aspergillus* infections compared with fluconazole; the benefit of posaconazole was most demonstrable in patients who had a positive galactomannan antigen assay at baseline.[17] Another trial comparing prophylaxis with voriconazole vs fluconazole after allogeneic HSCT showed nonsignificant trends in reductions of IFIs and *Aspergillus* infections.[18] These findings have left clinicians uncertain as to whether to routinely use the extended-spectrum azoles for prophylaxis or to continue to use fluconazole prophylaxis.

Now that galactomannan biomarker tests are available, there has been a growing interest in using biomarker-guided initiation of anti-*Aspergillus* therapy. A patient at high risk would typically be started on fluconazole prophylaxis to eliminate the threat of *Candida* infection and would have blood sampled twice weekly. A positive biomarker response would trigger the initiation of anti-*Aspergillus* therapy. Some clinicians refer to this as preemptive therapy or biomarker-driven therapy, and several studies have evaluated the efficacy of this approach in patients with acute leukemia and HSCT. The data look promising, but as yet there is not a consensus on the appropriateness of this strategy. However, it is worthy of further study.

Medscape: What new drug formulations are available?

There are 2 new formulations of posaconazole approved by the US Food and Drug Administration. Historically, posaconazole has been available in an oral solution, but it is associated with considerable variability in blood levels; low levels are unpredictable if patients are not eating well. Studies have suggested a strong association between higher serum levels and better outcomes. Both an oral tablet and an IV formulation are now licensed.[19-21] Studies with the oral tablet have suggested good patient tolerance, a very good safety profile, and more dependable blood levels, even in patients who are not eating well.

Clinicians need to be aware that the dosing schedules of the 2 formulations are different. The oral suspension is given at a dose of 200 mg, 3 times daily, and is continued until recovery from neutropenia or immunosuppression occurs. Tablets are given as a loading dose of 300 mg twice on the first day, followed by a maintenance dose of 300 mg once daily. The duration of treatment is the same as for the oral suspension. The IV formulation is designed for patients who are unable to tolerate oral therapy. The dosing schedule is similar to that for oral tablets. It is given initially in a loading dose of 300 mg, twice on the first day, and then 300 mg once daily.

There are several caveats to keep in mind about these different formulations. First, the oral solution is highly

dependent on a concomitant meal. Therefore, the take-home message is that patients who are not eating will not absorb the drug; therefore, the effectiveness of the oral solution is dependent on patients being able to take the drug concomitantly with food. The recommendation for the delayed-release tablet is that it also to be taken with food, although studies have suggested that there is less dependence on concomitant administration with food.[20] In fact, some data show that the bioavailability is about 50%, even in a fasting state.[21] Also, with the oral tablet there is less interference with antacids or drugs that block acid production, and absorption is generally very good in the presence of these agents. Another caveat concerning the IV formulation is that it should be given as an infusion, not as a bolus. Administration through a peripheral line can cause phlebitis. It is recommended that it be administered by a central venous catheter as a slow infusion of approximately 90 minutes in duration.

Oral administration is an advantage for voriconazole and posaconazole, but it is not always feasible in the ICU setting. These agents are treatment options for patients with invasive mold infections and have distinct properties that differentiate them from each other and from other members of the azole family. Each agent has a broad spectrum of activity against a wide range of yeasts and molds with one notable difference: only posaconazole is active against Zygomycetes. Posaconazole is an oral suspension that requires administration with a high-fat meal; this is often not possible in the ICU. Substituting a high-fat nutritional supplement or a dosing regimen of 200 mg given orally every 6 hours without food achieves serum concentrations similar to 400 mg given orally every 12 hours administered with food. This method provides an option for those ICU patients who are unable to eat. Although posaconazole may be administered via nasogastric tube, this method of delivery results in lower plasma drug concentrations and is still being evaluated.[22]

Medscape: Could you discuss treatment of a representative case?

Dr Wingard: A 51-year-old man presented with AML and was treated with a chemotherapy regimen consisting of idarubicin and cytarabine. He was placed on levofloxacin, acyclovir, and fluconazole prophylaxis. He developed a fever on the fourth day of induction therapy. Following the administration of broad-spectrum antibiotics, the fever resolved. Fourteen days after the start of the induction chemotherapy, the patient underwent a second bone marrow biopsy to assess his response to treatment. The biopsy showed persistent leukemia, requiring a second course of chemotherapy. After the second course of chemotherapy fluconazole was stopped and voriconazole was started as prophylaxis, since a prolonged course of neutropenia was anticipated.

After 25 days of neutropenia, the patient developed a cough and fever. A computed tomography (CT) scan of the chest showed a nodular lesion in the periphery of the right lung field. The nodule was dense and surrounded by a halo sign, which is a circular area of ground-glass attenuation that can be caused by several pathologic processes. The clinician was very suspicious that this may indicate mold pneumonia. Since the patient was being treated with voriconazole, mucormycosis was suspected (since voriconazole has no activity against the agents of mucormycosis). It was also possible that the voriconazole levels used were suboptimal to prevent the infection that was observed. Intravenous therapy was initiated with a lipid amphotericin formulation, and a pulmonologist performed bronchoalveolar lavage. A specimen was sent for galactomannan testing. The test was negative, as were the bacterial cultures. The clinician felt the diagnosis was confirmatory and continued the patient on lipid amphotericin B. Four days later, the culture was positive for *Rhizopus*. Gradually, the patient improved and the fever abated, and the neutrophil count eventually recovered. A repeat CT scan 2 weeks later showed a marked reduction in the nodule; the patient was afebrile. He was then switched to posaconazole tablets for an additional 3 to 4 weeks. Because he was in remission, he was considered for consolidation chemotherapy.

Medscape: This case nicely illustrates the range of factors, such as clinical suspicion, neutrophil levels, and results of blood cultures and assays of components of particular fungal organisms that may be involved in selecting optimal antifungal prophylaxis and treatment. Thank you for this enlightening discussion.

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Abbreviations

AML = acute myeloid leukemia
CT = computed tomography
HIV = human immunodeficiency virus
HSCT = hematopoietic stem cell transplant
ICU = intensive care unit
IDSA = Infectious Diseases Society of America
IFI = invasive fungal infection
IV = intravenous

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