Pulmonologists and intensivists often care for patients at risk for infections caused by both *Aspergillus* and *Candida*. Infection with either can lead to severe life-threatening disease. Mortality rates for invasive fungal disease often exceed 30%. Furthermore, immunosuppressed patients are at increased risk for disease caused by both pathogens. Despite these similarities, however, important differences exist between infections caused by mold as compared with those related to yeast. For mold, the lungs (in addition to the central nervous system) remain the key affected organ system, while yeast rarely are implicated as a cause of pneumonia. Conversely, colonization by *Aspergillus* has clearly different implications for the patient than does colonization with *Candida*. For both organisms, however, multiple diagnostic challenges remain. Fortunately, therapeutic paradigms are shifting, and clinicians have many new agents in their armamentarium for combating fungal infection. Given the rapidly changing literature in this broad area, it is imperative that physicians caring for the immunosuppressed patient and for the critically ill remain abreast of this evolving field.

**INVASIVE PULMONARY ASPERGILLOSIS**

Invasive pulmonary aspergillosis (IPA) represents a dreaded complication in critically ill patients. Several species of *Aspergillus* remain major causes of IPA. In particular, *A. fumigatus*, *A. flavus* and *A. niger* account for nearly all human disease. Although *Aspergillus* can lead to disease in both immunocompetent and immunocompromised hosts, the intensivist often is addressing disease in the systemically immunosuppressed patient. The pulmonologist, alternatively, may face several types of noninvasive disease such as allergic bronchopulmonary aspergillosis (ABPA), mycetoma...
formation, and chronic necrotizing aspergillosis (CNA). In these three conditions, the immune system is generally intact, and in select syndromes such as ABPA, it is the host response to infection that leads to a clinical syndrome. Invariably these three conditions are associated with local impairments of the intrapulmonary immune system as a result of local airway damage and destruction. Unless leading to hemoptysis that compromises the airway, patients who have these non-IPA syndromes usually do not require treatment in the ICU. Because of the disproportionate burden of IPA, the remainder of this discussion will focus on IPA.

Epidemiologically, the true incidence of IPA is unclear. Although certainly less common than infection with yeast, the frequency of IPA may be increasing. For example, Groll and colleagues in examining autopsy data between 1978 and 1992 noted a rise in prevalence of all invasive mycoses from 0.4% to 3.1%, and Aspergillus as the causative organism increased from 17% to 60% over the same time period. Certainly one factor driving rates of IPA is the broadening use of immunosuppressive agents. Both the types of and duration of immunosuppression related to all forms of transplant are evolving. Attendant with more extensive immunosuppression is a greater risk for IPA. Not all forms of immunosuppression appear to carry similar risks for IPA. Both the extent and duration of neutropenia represent long recognized risk factors for IPA. More recently, use of select monoclonal antibody strategies for induction of immunosuppression has been thought to heighten the chance for IPA. In hematopoietic stem-cell transplant (HSCT) subjects, the development of graft versus host disease has been linked to a greater frequency of invasive mold infections. Following any type of transplant, cytomegalovirus (CMV) disease also amplifies the potential for IPA.

Recently, Patterson and Singh described the disproportionate distribution of IPA as a function of the type of transplant. In a systematic review of over 20,000 cases of IPA, they reported that the incidence of IPA was greatest among those undergoing lung transplant, with 8.4% developing IPA. Patients receiving kidney transplants face a substantially lower risk for IPA (0.7%). The rate of IPA following either HSCT or heart transplant was approximately 6.0%. In part, this difference related to transplant type reflects both the difference in the agents used for immunosuppression (eg, renal transplant patients require much less immunosuppression) and also the fact that Aspergillus spores are inhaled. Hence, the lungs potentially are exposed to an excessive inoculum. The impact of IPA on post-transplant mortality was staggering: anywhere from 10% to 17% if all post-transplant deaths were attributed to IPA.

More recent analyses suggest that the epidemiology of IPA in the ICU may be shifting away from those traditionally considered at risk. Several recent case series have described IPA in nonimmunocompromised critically ill subjects. Samarakoon and Soubani reported five cases of IPA among chronic obstructive pulmonary disease (COPD) patients from their medical center and performed a systematic review of literature on this topic. These investigators found that among the 65 cases examined, clinical presentation was largely nonspecific, and in most (63%), radiological findings consisted of infiltrates. Although in 15 patients (23%) diagnosis was made with a bronchoalveolar lavage (BAL), in a plurality of cases (n=28, 43%) Aspergillus was recovered at autopsy. Despite treatment with antifungal agents in most cases, the mortality rate was 91%. The authors concluded that the likely risk factors in this cohort of COPD patients for IPA included chronic treatment with corticosteroids and advanced severe COPD.

Similarly, Vandewoude and colleagues described 38 individuals (incidence 4 out of 1000 ICU admissions) who had IPA cared for between 1997 and 1999. Only 17 of them (45%) had traditional risk factors, while among the remaining 21 without evidence of
immune compromise, invasive disease was a complication of their critical illness. The authors noted that while in the presence of risk factors the actual mortality was similar to that predicted by Acute Physiology and Chronic Health Evaluation (APACHE) II, in those lacking the traditional risk factors for IPA, actual mortality exceeded that predicted by APACHE. The same investigators in a case–control analysis calculated that the attributable mortality of IPA in the ICU approached 20%, finding the presence of this disease to be an independent predictor of hospital mortality among the critically ill. Finally, Meerssemann and colleagues described a 127-patient cohort of ICU patients who had IPA, of whom 89 did not have an underlying malignancy. Of these 89, 35 had COPD; nine had undergone a solid organ transplantation, and 17 were on immunosuppressive therapy. Observed mortality in this group (80%) was higher than that predicted by the Simplified Acute Physiology Score (SAPS) II (48%). Of particular interest, were five critically ill patients without any predisposition but with proven IPA. In an additional analysis addressing only critically ill patients colonized with Aspergillus, Vandewoude and colleagues concluded that nearly 50% of such subjects had invasive disease and not simply colonization. Again, despite the absence of typical risk factors for IPA, they detected the syndrome in patients, where before one might never have considered it a clinical possibility. Although thought-provoking, each of these analyses has major limitations because of essentially retrospective, single-center designs. Nonetheless, these findings, taken as a whole, suggest that the epidemiology of IPA in the ICU is shifting. In response, physicians need to remain vigilant and consider this syndrome in patients not significantly immunocompromised.

Diagnostically, IPA remains a challenge. Initially, the clinical manifestation of IPA may be nonspecific. As many as 30% of patients may be asymptomatic. Nonspecific symptoms such as dyspnea and fever are common. Radiographic manifestations of IPA also may be diverse. The classic description of cavitation associated with IPA is a late finding, and the absence of cavitation does not preclude a diagnosis of IPA. In some cases, the disease begins as small nodules that eventually coalesce. Alternatively, IPA can lead to peripheral, wedge-shaped opacities that resemble those seen after pulmonary infarction. The air crescent sign is a late finding in IPA and is caused by contraction of infarcted tissue surrounding the site of infection. Conversely, the halo sign, an area of low attenuation near the primary lesion, is an early finding that often is transient. These two signs are somewhat specific for invasive aspergillosis but lack sensitivity.

To facilitate the diagnosis of IPA, two strategies have been proposed. The first addresses the risk for IPA based on airway colonization with Aspergillus. In many syndromes, colonization with a pathogen does not increase the subsequent risk for infection necessarily. With respect to IPA, this appears not to be the case. In the review by Paterson and Singh described earlier, the authors estimated that colonization with Aspergillus correlated with an eventual risk for IPA ranging from 16% to 80%, depending on the type of transplantation. HSCT subjects faced a greater risk for IPA if they were known to be colonized (60% to 80%), while in lung recipients, a positive airway culture for Aspergillus conveyed a less than 20% chance of eventual IPA. In unselected ICU patients, recovery of Aspergillus in apparently noninfected patients may also represent a harbinger of IPA. For example, Vandewoude and colleagues performed a large cohort study of 172 patients (incidence 6.8/1000 ICU admissions) with a positive sputum culture for Aspergillus. Based on a predefined algorithm involving clinical presentation, radiographic signs, and BAL cultures, 83 cases were deemed to be IPA, while the remaining 89 were thought to be colonized with the organism. The algorithm was found to have good positive and negative predictive values for invasive disease in this population of patients.
Serologically, ELISA-based testing for the presence of galactomanan (GM), a component of the mold cell wall, has held promise as a noninvasive tool in the approach to suspected IPA. Other areas of interest for noninvasive diagnosis address 1,3 beta-D-glucan and the presence of *Aspergillus* DNA. Initial reports suggested that the GM assay was fairly accurate and could suggest the presence of IPA days before it became clinically apparent. These studies, however, were limited to mainly HSCT subjects. A meta-analysis of GM testing indicated that the assay was performed moderately well (approximate sensitivity and specificity 80%) but varied widely based on the cutoff used for defining a positive test. The many agents that can confound the GM assays, along with the fact that the assay performs less well in people receiving antifungal prophylaxis further limit the utility of this diagnostic modality.

Bronchoscopy remains a much-used tool in the approach to patients who have suspected IPA. Aggressive and early use of bronchoscopy has been shown to improve outcomes in mixed cohorts of immunosuppressed patients who have pulmonary infiltrates. Bronchoscopy, however, may not be reliable in suspected mold infections. Because *Aspergillus* may result in patchy involvement or be angioinvasive, BAL is only positive half the time in either known or probable IPA. The role for transbronchial biopsy (TBB) to increase the yield of bronchoscopy for suspected IPA remains controversial. First, many patients who have this condition are coagulopathic or thrombocytopenic, which may preclude TBB. Second, because it is patchy by nature, the bronchoscopist may simply fail to biopsy a site of involvement. In an effort to improve the diagnostic yield of bronchoscopy in IPA, Husain and colleagues proposed measuring GM titers on BAL. In an analysis of over 100 patients, they determined that this approach was fairly specific and had modest sensitivity. Confirmatory studies are necessary before broad application of this strategy.

With respect to treatment, the number of trials exploring new agents and alternatives has exploded over the last decade. Treatment options for IPA consist of the polyene amphotericin B deoxycholate (D-AMB) or its less toxic lipid formulations (L-AMB), azoles, and echinocandins (Infectious Diseases Society of America [IDSA] guideline). In selected cases, surgery may be required. The recommended first-line therapy for primary IPA is voriconazole, a broad-spectrum triazole, either intravenously or orally, depending on the underlying illness severity. This recommendation is based on the results of a multinational multicenter randomized unblinded trial comparing the efficacy, safety, and tolerability of voriconazole with D-AMB in 277 immunocompromised patients who had definite or probable IPA. Over one half of subjects randomized to voriconazole had either a complete or partial response, compared with 31.6% of the D-AMB group, meeting not only the noninferiority margin, but also showing superiority to D-AMB. More importantly, voriconazole was associated with an increased probability of intermediate-term survival. Although large and prospective, this trial has been criticized because of its open-label nature and because L-AMB was not employed as the comparator. Nonetheless, it represents the single largest randomized trial for *Aspergillus* and the only one suggesting a mortality benefit.

In the ICU, the main limitation with voriconazole has been the fact that the drug cannot be administered intravenously to patients who have impaired renal function. The carrier with the voriconazole can build up in those who have GFRs of less than 35% and lead to toxicity. Moreover, because voriconazole is an azole and can lead rarely to hepatotoxicity, coupled with the fact that it is also prone to drug–drug interactions, there are alternative strategies for treating IPA. Because several studies document the equivalent efficacy of and better safety profile for L-AMB over D-AMB, only the former is recommended by the IDSA at the dosage of 3 to 5 mg/kg daily for treating IA.
immunocompromised patients who had proven invasive disease, 201 subjects were randomized to either a standard (3 mg/kg) or high (10 mg/kg) daily dose of L-AMB for 14 days followed by 3 mg/kg/d. 21 Although efficacy outcomes were similar in both groups, the high-dose group experienced higher rates of toxicity than observed with the standard dose. 21 Caspofungin, a member of the echinocandin family, represents an option for IA treatment among those who have refractory disease or for people unable to tolerate AMB or triazoles. Maertens and colleagues, 22 in an open-label noncomparative multicenter clinical trial in patients who had probable or proven IA intolerant of treatment with AMBs or triazoles, investigated the use of caspofungin at the dose of 50 mg daily following a 70 mg loading dose on day 1. A complete or partial clinical resolution was the primary outcome of the study. Among the 83 efficacy-evaluable patients, 45% responded favorably, and only two patients were forced to discontinue caspofungin because of drug-related toxicity. The authors concluded that caspofungin is a viable salvage treatment for IA, and it is recommended as such by the IDSA. 16,22

Before trials with voriconazole, itraconazole, an older azole with activity against Aspergillus, was studied for IPA. Caillot and colleagues 23 reported the results of a trial of intravenous itraconazole followed by oral treatment for probable or definite IPA in 31 immunocompromised patients. In this single-arm open-label multicenter study, the primary outcome of complete or partial clinical resolution was met in 18 (58%) of the subjects, in the face of mostly mild-to-moderate toxicities. 23 The largest study of invasive Aspergillus was conducted by Patterson and colleagues 24 in North America and Western Europe and represented a naturalistic observational analysis examining case records of 595 patients who had IA, most of whom (56%) had IPA. This study was completed before the commercial availability of voriconazole. When looking at treatment regimens, 187 were treated with AMB alone, 58 with itraconazole alone, and 93 with a combination of the two (the remaining patients were treated with other various regimens). 24 Itraconazole resulted in a 57% rate of combined complete and partial response, similar to the combination therapy (54%) and higher than AMB alone (32%). 24 Although it boasts the largest study sample to date, rigorous randomized trials are lacking to compare the treatment of IA with itraconazole with either AMB or voriconazole. If using itraconazole, serum level measurements are needed to document adequate drug absorption. 16 Posaconazole is an additional extended-spectrum triazole available in the European Union for treating refractory disease. This monotherapy was investigated in an open-label prospective trial in 107 patients, the results of which were compared with 86 retrospectively collected historic controls. 25 Complete or partial response was achieved in 42% of posaconazole-treated patients versus only 26% of those on the comparator regimen. 25 In a logistic regression model, the authors noted that the adjusted odds ratio (OR) of response was 4.06 (95% CI, 1.50 to 11.04) for posaconazole over other salvage therapies. 25

The final drug recommended as salvage therapy for IA is micafungin, a newer echinocandin. 16 Although a treatment dose has not been conclusively established, two trials indicate its efficacy in probable or definite IA. In a 225-patient open-label single-arm study, 35.6% of all patients treated with micafungin achieved a response, with the rates even higher in the primary (50%) and salvage (41%) groups. 26 An additional open-label study investigated the efficacy of micafungin alone or in combination for treating refractory or intolerant patients. 27 Of the 98 patients enrolled in the study, eight were treated singly with micafungin, of whom three (38%) achieved a response. 27 Clearly, the experience with micafungin is limited and not controlled well enough to render it a strongly recommended therapy. Similarly, because very little evidence exists for the efficacy and safety of combination regimens, these are not
recommended for treating IA at this time. Nonetheless, this is an active area of exploration. Two recent single-center analyses have promoted plans for large multicenter studies. First, in an observational analysis of 48 patients with IPA failing AMB, many of whom had undergone HSCT, Marr and colleagues treated patients either with voriconazole alone or with voriconazole along with caspofungin. Cure rates and survival were greater in patients given combination therapy, and these differences persisted after controlling for multiple potential confounders. Second, Singh and colleagues prospectively treated 40 solid organ transplant recipients with IPA with voriconazole and caspofungin and compared outcomes with a historical control cohort given AMB (n = 47). Survival was higher in patients given combination therapy, but this difference only approached statistical significance. Beyond anti-infectives, surgery may be required in selected cases of IPA. Generally, surgical resection is used in instances where invasion of great vessels is threatened or in patients who have hemoptysis in association with a solitary lesion amenable to resection.

CANDIDAL BLOODSTREAM INFECTIONS

Epidemiology

Unlike Aspergillus, epidemiologic data regarding bloodstream infection (BSI) caused by Candida are more abundant. First, candidal BSIs occur 7 to 15 times more frequently than do cases of IPA. In fact, Candida represents the most common cause of invasive fungal disease. According to surveillance data from the US Centers for Disease Control and Prevention, Candida now accounts for 12% of all hospital-acquired BSIs. A major increase in candidal BSI initially was noted during the 1980s, with a more than quintupling in the rate of BSIs caused by this yeast. More recently, rates of BSI caused by Candida have stabilized or declined. For example, Fridkin and colleagues documented a fall in the incidence of candidal BSI among low birth weight neonates in the United States from 3.51 to 2.68 per 1000 patient days between 1995 and 2004. Similarly, a single-center pediatric study from Spain described that the incidence of candidemia had stabilized at a rate of 0.6 cases per 1000 hospitalizations between 1988 and 2000. Contrary to this rise, Trick and colleagues reviewed the National Nosocomial Surveillance System (NNIS) between 1989 and 1999 and noted that the rate of BSIs specifically caused by \textit{C albicans} in critically ill adults with central venous catheters (CVCs) fell from approximately 8.1 cases per 1000 CVC days in 1989 to about 2.2 cases per 1000 CVC days in 1999. Strikingly, rates of non-\textit{albicans} candidemia in aggregate remained stable during this period, although proportion of infections caused by \textit{C glabrata} BSI increased significantly. Other studies, both from the United States and abroad, however, have observed growth in the number of hospitalizations complicated by candidemia. Martin and colleagues, for instance, examined the epidemiology of sepsis in the United States between 1979 and 2000 and reported a tripling in the incidence of fungal sepsis. In an effort to gauge the burden of candidemia in patients presenting to the hospital as opposed to addressing a purely nosocomial process, Shorr and colleagues reviewed over 60,000 admissions where the patient presented with a BSI. Although candidemia was infrequent (1.2%) relative to BSI with either a gram-positive of gram-negative pathogen, the prevalence of candidal BSIs rose from approximately 7.5 cases per 1000 BSIs in 2000 to 12 cases per 1000 BSIs in 2005. Finally, a recent survey study reviewing United States hospital discharge data between 2000 and 2005 reported a 50% rise in the incidence of hospitalizations involving candidemia between 2000 and 2005. Studies from Iceland and Finland have reported similar growth in candidemia incidence. The differences in
candidemia temporal trends documented in the previously mentioned studies likely reflect differing study methodologies and differing populations (eg, neonates) and geographic areas (eg, Spain).

From an economic perspective, patients who have candidal BSIs consume substantial resources. Estimates of the costs of care associated with this syndrome vary based on the methodology used, but unlike the discordance regarding the frequency of candidal BSIs, all reports examining outcomes in this condition suggest that costs of care range from $15,000 to $40,000 per case.\textsuperscript{37,41,42} In one report, the excess costs of care for candidemia were more than $15,000 greater than for the costs related to treating other BSIs caused by bacterial pathogens.\textsuperscript{37} Driving these greater costs was an accompanying 5-day excess length of stay in the setting of \textit{Candida}.\textsuperscript{37}

One evident epidemiologic trend has been a shift in the distribution of candidal species responsible for BSI. Over the last decade, the proportion of infections caused by \textit{C albicans} has fallen. Presently, \textit{C albicans} appears to account for only half of all BSIs caused by yeast.\textsuperscript{43} More specifically, in 1990, 80\% of all fungal BSIs were caused by \textit{C albicans}.\textsuperscript{43} In a large 3.5-year multicenter prospective observational study of candidemia within the United States, Nguyen and colleagues\textsuperscript{44} demonstrated that nearly 50\% of all candidal isolates were of non-\textit{albicans} species, with \textit{C glabrata} (6.3\%) and \textit{C krusei} (4.3\%) representing over 10\% of all cultures. In a study from Italy looking at 182 episodes of candidemia between 1999 and 2003, the investigators found an even lower proportion of \textit{C albicans}, decreasing from 62\% of all candidal isolates in 1999 to only 24\% in 2003.\textsuperscript{45} The opposite trend was detected for \textit{C glabrata}, which went from 0\% in 1999 to 26\% in 2003.\textsuperscript{45} The authors noted a strong correlation of the rise in non-\textit{albicans} species with the use of fluconazole.\textsuperscript{45} The prevalence of these non-\textit{albicans} organisms is not restricted to the ICU. Shorr and colleagues\textsuperscript{46} examined candidal BSIs at two large United States hospitals. They specifically focused on the microbiology of these infections and observed no difference in the proportion of non-\textit{albicans} isolates recovered from ward patients and critically ill patients.\textsuperscript{46} Interestingly, no clinical factors separated patients with \textit{C albicans} from other forms of \textit{Candida}. Finally, a large multinational microbiologic study by Pfaller and colleagues\textsuperscript{47} detected a less dramatic shift in candidal species. In this study examining nearly 100,000 candidal isolates, the proportion represented by \textit{C albicans} went from 68\% between 1997 and 2000 to 63\% in 2005, while the proportion of \textit{C glabrata} remained stable between 10\% and 11\% during the same time frame. Interestingly, the prevalence of \textit{C tropicalis} increased from 5.2\% of all candidal isolates from 1997 to 2000 to 7.3\% in 2005.\textsuperscript{47} They also reported that in vitro resistance to fluconazole among \textit{C glabrata} decreased from 19\% to 15\%, while that among \textit{C albicans} increased from 0.9\% to 1.6\% and among \textit{C krusei} from 66\% to 79\%.\textsuperscript{47}

\textbf{Risk Factors}

Before considering treatment issues, clinicians must appreciate the risk factors for fungal BSIs. Through understanding the issues and variables that heighten the potential for candidemia, one can focus on efforts not only at prevention but also on prompt diagnosis and treatment. Common risk factors predisposing to candidemia include candidal colonization, prior exposure to antibiotics, renal failure, presence of a CVC, and need for total parenteral nutrition (TPN).\textsuperscript{48–51} In a case–control study, Wey and colleagues\textsuperscript{48} established that the number of antibiotics administered, candidal colonization, hemodialysis, and use of a Hickman catheter were strongly associated with the development of candidemia. A group of Swiss investigators led by Pittet in a study of 29 surgical ICU patients confirmed colonization to be a risk factor for candidal
infection. Additional risk factors consisted of length of previous antibiotic therapy and severity of illness. Fraser and colleagues, in a 104-patient single-center cohort study, determined that sustained fungemia is more likely than transient fungemia among patients who have neutropenia, CVCs, and a need for mechanical ventilation (MV). They further reported that exposure to TPN independently heightened the chance for candidal BSI. Blumberg and colleagues, in a large multicenter cohort study, confirmed the importance of the CVC and TPN as risk factors for developing candidemia in the ICU. This group defined acute renal failure to be an additional strong predictor of candidemia development (relative risk [RR] 7.3, 95% CI, 2.5 to 8.8). In the same cohort study, the incidence of candidemia was 9.8 cases per 1000 admissions; 55% of the cases were caused by non-albicans species, and over 10% of all isolates exhibited resistance to fluconazole. Blumberg and colleagues identified similar risk factors for albicans and non-albicans candidemia among ICU patients:

- Major operations, particularly gastrointestinal (GI) procedures
- Enteric source for bacteremia
- Hemodialysis days
- TPN duration and red blood cell transfusions

Specific to the ICU, several risk stratification schemes exist to facilitate identification of patients at high risk for candidemia. A multicenter, prospective cohort study from Spain including 1699 adult ICU patients identified surgery, multifocal colonization, TPN, and severe sepsis to be strong predictors of candidal infection. A key strength of this analysis was its multicenter nature and its systematic, prospective collection of information on colonization status. Assigning weighted points based on the β-coefficients for terms in a regression model, the investigators derived and validated a Candida score with good discriminative power. The authors suggested that patients who have a score above 2.5 might benefit from early antifungal treatment, although this assertion requires validation in future trials. Another large cohort study of nearly 3000 patients in United States and Brazilian ICUs determined that the presence of certain combinations of the following factors was highly predictive of subsequent development of invasive disease: antibiotics, CVC, TPN, dialysis, major surgery, pancreatitis, and steroids or other immunosuppressive agents. The same team attempted to apply this rule in their ICU to reduce the incidence of BSIs. In this study, the investigators stratified ICU patients using the previously developed rule, and, based on the presence of the required criteria, placed them on fluconazole prophylaxis. In the year of implementation (2005) 36 patients met criteria for and received prophylaxis, and in the same year, only two candidal BSI cases were diagnosed, compared with nine cases in the previous year and before the rule implementation, corresponding to a reduction from 3.4 cases per 1000 CVC days to 0.8 cases per 1000 CVC days. Because of the small sample size, no adjustment for confounding and other methodologic issues, it is difficult to draw conclusions about the effectiveness of this intervention, and the need for validating this approach remains.

Several substantial limitations remain associated with prior work regarding clinical prediction rules for risk of candidemia in the ICU. First, few of the risk stratification schemes have been validated prospectively. Second, although the presence of multiple risk factors may increase the chance for fungemia relatively, the absolute increase in risk may remain small. In other words, given the prevalence of MV, CVCs, broad-spectrum antibiotic use, and exposure to corticosteroids in critically ill patients, the currently available risk stratification schemes lack sufficient precision.
to allow for their broad application in identifying patients who might merit from either prophylaxis or presumptive therapy.

Because of frustration with risk stratification and diagnostic modalities, efforts recently have focused on developing surrogate markers to detect the presence of fungemia. Moreover, the sensitivity of blood cultures for this pathogen varies from 8% to 82%, depending on the population in question. Additionally, cultures may take several days to become positive. Similar to research addressing galctomannan for Aspergillus, the candidal cell wall has many components that can be detected with modern assays. The most promising target appears to be β-D-glucan. Unfortunately, diagnosis of candidemia remains a challenge. The β-D-glucan test has relatively high sensitivity, specificity, and positive and negative predictive values, although data in the ICU are lacking. The mostly small studies conducted to date mainly have enrolled severely immunosuppressed patients. Molecular testing to detect Candida DNA is in early development, and it is not clear how useful it will be among the critically ill. An additional challenge in the current environment is the proliferation of azole-resistant non-albicans species.

**Prophylaxis and Presumptive Therapy**

Because of the efficacy of prophylaxis in immunocompromised populations, some have advocated for a like strategy in high-risk critically ill patients. Garbino and colleagues evaluated the role for fluconazole prophylaxis among 204 high-risk critically ill medical and surgical patients already undergoing a selective digestive decontamination regimen. In this double-blind randomized placebo-controlled trial, colonization rates with Candida were similar in both groups at entry into the study, and only 4 of 103 patients in the fluconazole group, compared with 10 of the 101 in the placebo group, developed candidal infections. This study confirmed the results of an earlier randomized controlled trial by Eggimann and colleagues. In this randomized double-blind placebo-controlled trial, the efficacy of fluconazole prophylaxis against intra-abdominal candidiasis was tested in a cohort of surgical patients who had recurrent GI perforations or surgical anastomosis leakages. The rate of development of intra-abdominal Candida was 4% (1 of 23) in the fluconazole group and 35% (7 of 20) in the placebo group, corresponding to the relative risk of 0.12 (95% CI, 0.02 to 0.93). A meta-analysis of fluconazole prophylaxis in surgical patients confirmed the effectiveness of this approach in reducing the incidence of invasive candidiasis, but did not find a survival advantage. One concern with all of the trials of prophylaxis has been that they have defined candidal infection broadly, rather than specifically targeting BSI. In no study, has fluconazole prophylaxis been shown to reduce BSI with yeast. Admittedly, each study has been underpowered to address this question. Nonetheless, given that broader use of fluconazole could promote either the emergence of resistance or lead to an accelerated shift in microbiology toward organisms like C glabrata, this is not recommended routinely. Randomized prevention trials are ongoing with other nonfluconazole alternatives.

Beyond either prophylactic therapy or treatment when a candidal BSI is documented, the role for presumptive treatment is evolving. As with many bacterial infections, delay in initiation of treatment for fungemia independently increases the risk for mortality. An analysis by the Spanish group for fungal Infection in the ICU found that a delay in starting antifungal treatment increased the risk of hospital death by more than 60%, although this impact on death did not reach statistical significance because of the analysis’ small sample size. Others have provided more conclusive evidence of how a delay in treatment adversely affects outcomes. Morrell and colleagues performed a single-center retrospective cohort study investigating the impact of
treatment delay on mortality among 157 consecutive patients with *Candida* blood stream infection. In this study most of the isolates (53.5%) were *C. albicans*, and the cumulative proportion of *C. glabrata* and *C. krusei* was 14%. The investigators found that only 5 of the 157 patients received prompt, appropriate empiric therapy for candidemia. In a multivariate analysis, they reported that a delay of as little as 12 hours from when the eventually positive blood cultures were drawn more than doubled the risk for death (OR 2.09, 95% CI, 1.53 to 2.84). Readers should note that the delay was defined, not as time from when the laboratory contacted the provider and reported yeast in the cultures, but the time from which the initial evaluation for infection commenced. Garey and colleagues confirmed the Morrel group’s observation. In this multicenter cohort, investigators noted increasing mortality based on the delay, measured in days from when the culture was drawn to antifungal treatment. Similarly, a recent study by Labelle and colleagues expanded the definition of inappropriate therapy for fungemia to encompass more than just the time to treatment. In their analysis, they also defined the inadequate dosing of fluconazole as inappropriate. This, along with a delay in therapy independently raised the risk of death ninefold. All four of these studies underscore the importance of prompt appropriate treatment of candidemia to impact survival. They also reveal the need for an emphasis on prevention and an urgent need for rapid diagnostic strategies.

Embracing the need to be prompt in treatment of suspected candidemia should not lead intensivists to endorse presumptive therapy. In this case, presumptive therapy represents the administration of antifungals purely based on the presence of several risk factors for candidal infection and the development of a new fever. This approach represents a standard strategy for prolonged neutropenic fever. For critically ill subjects, however, a large multicenter, randomized trial demonstrated the futility of this paradigm. In this study, ICU patients who had persistent fever were assigned randomly to empiric fluconazole or placebo. To enrich the population as to their risk for fungemia, the protocol required patients to concurrently be receiving broad-spectrum antibiotics and have CVCs in place. Additionally, most subjects had been undergoing MV for several days. Overall, outcomes including mortality and fever resolution were similar. The main reason for these negative findings was that the rate of eventually documented fungemia was low; approximately 7% of subjects subsequently were diagnosed with a candidal BSI. This fact underscores the need for better risk stratification schemes. Also, the list of causes of fever in the ICU is extensive. Because the investigators did not require an effort to exclude other possible causes for fever, such as the presence of a new pneumonia, one limitation of the trial may have been that the entry criteria simply did not reflect the way clinical decision making makes takes place at the bedside in the ICU. In other words, the potential for fungemia is not simply a function of the number of risk factors present, but more properly reflects whether an alternative diagnosis for the nonspecific signs and symptoms that can be seen in with this condition is more or less likely.

**Treatment**

A key step in the approach to fungemia, irrespective of the antifungal used, remains management of the CVC. In many instances, the CVC represents the portal of entry for the fungus into the patient. Alternatively, the CVC may become seeded as a secondary point in the disease process. Current guidelines strongly advocate prompt CVC removal. This in part is based on the observation that the biofilm evolving on a CVC represents a relatively protected site for fungus. Older-generation antifungals (eg, fluconazole) penetrate biofilm very poorly. Moreover, older analyses have identified that CVC retention may be an independent predictor of mortality.
Some have criticized this approach of uniform CVC removal, because the initial reports addressing CVC removal failed to address confounding issues such as severity of illness and why the CVC was not removed. Patients in whom the CVC is not removed in fact may be described better as subjects for whom the CVC cannot be removed given comorbid issues, the need for continued central access, and risks associated with replacing the CVC. For example, Rodriguez and colleagues determined that severity of illness was the most important predictor of mortality in candidemic patients and that assessments of timing of removal were confounded by this overriding issue. They concluded that decisions regarding CVC removal must be individualized. Similarly, in a qualitative review of the topic, Pasqualotto and Severo observed that many analyses were too flawed to allow one to draw meaningful conclusions. They advocated for a randomized trial to determine appropriate practice. More careful and up-to-date analyses, however, clearly show the risks related to failing to remove the CVC in persons with fungemia. Raad and colleagues explored predictors of mortality in over 400 patients with cancer and candidemia. After adjusting for severity of illness, immune system status, and the source of the candidemia, failure to remove the CVC increased the probability of death more than fourfold. Labelle and colleagues reached similar conclusions. In addition to taking many variables into consideration that included severity of illness, comorbid illness, and most importantly the timing and appropriateness of antifungal treatment, they observed that catheter retention independently heightened the risk for death more than sixfold.

The past decade has witnessed a proliferation of commercially available antifungals. At present, the clinician must consider various forms of amphotericin, azoles, and echinocandins. For many years, amphotericin (AMB) represented the standard of care for candidemia. Although the utility of AMB is limited by its multiple toxicities, the newer liposomal AMB (L-AMB) formulations are tolerated better. In general, the L-AMB options lead to less nausea, vomiting, and fever. They clearly cause less nephrotoxicity. Unfortunately, L-AMB preparations still may result in substantial potassium wasting as is seen with AMB deoxycholate. Clinical trials document that L-AMB has similar but not better, efficacy relative to conventional AMB preparations.

Fluconazole represents a well-tolerated alternative for candidemia. In a randomized trial, fluconazole was shown to result in similar outcomes when compared with AMB. In this study, evaluating 206 non-neutropenic patients evenly divided between the two treatment regimens, mortality rates with fluconazole and AMB were 33% and 40%, respectively. This difference was not statistically different. Notably, the rates of blood culture clearance were also similar. The authors concluded that in patients without neutropenia, fluconazole and AMB had similar effectiveness. A similar trial from Canada confirmed these findings. One major limitation of studies employing fluconazole is that they were completed in an era when the prevalence of *C. glabrata* and *C. krusei* were much lower. For example, in the initial report by Rex and colleagues, these pathogens accounted for less than 15% of all isolates, while in modern settings, the proportion of candidal BSIs caused by these yeast species may be increasing. Furthermore, dosing of fluconazole can be confusing. Current guidelines recommend treatment with a greater dose of fluconazole. This theoretically allows one to potentially overcome the dose-dependent resistance seen in some candidal isolates. Unfortunately, observational analyses document that clinicians often underdose this agent.

Voriconazole, a triazole with excellent activity against *Aspergillus*, also has been examined as an alternative to AMB in non-neutropenic patients who have candidemia. In a randomized, noninferiority trial enrolling over 400 patients, voriconazole was found to be similar in effectiveness to AMB. Interestingly, despite more adverse
event-related treatment discontinuations in the voriconazole group, there were fewer reports of toxicities with voriconazole than with AMB.\(^7^6\) Again, the limitation of voriconazole for many critically ill patients arises because of the carrier molecule for the compound. One unique aspect of the trial reported by Kullberg and colleagues was the systematic analysis of transitioning to oral therapy. Those given voriconazole could step down to the oral form, while those treated with AMB could switch to oral fluconazole. Before this trial, patients infected with yeast who were not likely to respond to fluconazole had no oral alternative. Now those infected with \textit{C. glabrata} and \textit{C. krusei} can be switched to an oral agent, which may facilitate more rapid hospital discharge or help prevent the need of placement of a new CVC for continued antifungal treatment. Other azole compounds, itraconazole and posaconazole, exist. At present, these agents have not been well-evaluated as alternative treatments for invasive candidal infection.

A newer class of compounds, echinocandins, comprises three commercially available alternatives: caspofungin, micafungin, and anidulafungin. Echinocandins target the fungal cell wall. In general, these agents are tolerated well and come only as intravenous formulations.\(^7^7\)–\(^7^9\) As a class, they tend to have few drug–drug interactions. Two of the three (caspofungin and anidulafungin) require a loading dose.\(^7^7,7^8\) With respect to pharmacokinetics, anidulafungin has the longest half-life and greatest volume of distribution. Caspofungin must be dose-reduced in patients who have impaired liver function.\(^7^7\) This may have implications for use in the ICU, where occult liver disease caused by either hepatitis C infection or alcohol abuse can be an issue. Anidulafungin has been studied in patients with various ranges of liver impairment, and because the drug is not metabolized by the liver, dose reduction is not required.\(^7^8\) Similarly, micafungin does not appear to require dose reduction in people who have mild-to-moderate liver disease; this issue has not been worked out in patients who have severe hepatic impairment.\(^7^9\) Anidulafungin also does not interact with the cytochrome P450 system, which reduces the potential for many serious drug–drug interactions that can be encountered in patients in the ICU.\(^7^8\)

Four clinical trials have evaluated the various echinocandins. The first, by Mora-Duarte and colleagues,\(^8^0\) compared caspofungin with AMB as a treatment for candidemia in 224 patients who had invasive candidal infections, 80\% of which represented candidemia. In this noninferiority trial stratifying patients based on the presence of neutropenia, caspofungin performed as well as AMB in terms of the primary outcome of favorable response, regardless of the presence or absence of neutropenia.\(^8^0\) In an analysis of a predefined subpopulation of per-protocol subjects, caspofungin led to more favorable responses. This, however, was due to the fact that the number of patients having to discontinue therapy because of tolerability issues was higher in the AMB arm. Importantly, AMB deoxycholate was employed in this trial, so differences in tolerability are not surprising. Caspofungin has not been compared with either L-AMB or fluconazole in a randomized study.

Micafungin, in turn, has been compared with both L-AMB\(^8^1\) and caspofungin.\(^8^2\) Kuse and colleagues\(^8^1\) randomly assigned over 500 individuals who had disseminated candidiasis to treatment with either micafungin or liposomal AMB. Micafungin proved noninferior to L-AMB, regardless of neutropenia status, and once again its toxicity profile was favorable compared with L-AMB.\(^8^1\) In this trial, the starting dose of micafungin was 100 mg daily, but investigators could increase the dose to 150 mg daily. The study protocol did not prespecify criteria for dose escalation, raising concern that in some instances a 100 mg dose may be inadequate. A more recent study directly compared micafungin with caspofungin for candidemia.\(^8^2\) The study population (\(n = 600\)) was randomized to one of three arms: caspofungin, micafungin 100 mg
daily, or micafungin 150 mg daily. Outcomes were the same with all three strategies. In general, it therefore appears that the 100 mg dose of micafungin is adequate. Nonetheless, clinicians must note that among the patients given either dose of micafungin, the number of infections caused by *C. glabrata* and *C. krusei* was quite small.\(^\text{82}\)

Anidulafungin is the only echinocandin to be compared directly with fluconazole. Reboli and colleagues\(^\text{83}\) randomized 245 subjects to either anidulafungin or fluconazole. As with other studies, most patients suffered from candidemia, and few were neutropenic. Because of the innate resistance of *C. krusei* to fluconazole, patients found to be infected with this pathogen were dropped from the trial. Overall, 40% of infections were caused by non-\textit{albicans} species, including *C. glabrata*. Clinical success rates were significantly higher at end of therapy in patients treated with anidulafungin. This 15.4% difference in response rates did not arise because of fluconazole resistance, as few isolates displayed this. Anidulafungin, however, did not lead to higher survival rates.\(^\text{83}\) This report has been criticized, because one site in the study enrolled a disproportionate number of subjects. Additionally, concern has been expressed about a potential center effect. Statistical tests for an interaction between study site and outcome did not confirm this to be an issue.

**SUMMARY**

Mold and yeast infections remain diagnostic and therapeutic challenges. The prevalence of both of these types of infections is likely to grow over the next decade. Unfortunately, mortality rates with either process are exceedingly high. Coupled with the economic burden of these illnesses, physicians must remain vigilant when approaching patients at risk for these fungal diseases. Fortunately, newer diagnostic modalities are being developed and tested. Likely some combination of sero-diagnosis testing along with clinical risk stratification will evolve in the coming years. For both conditions, prompt diagnosis and treatment remain the keys to ensuring favorable outcomes. Newer agents for treatment are now commercially available. The literature on these therapies, as is the research into many aspects of fungal infection, is changing rapidly. Hence clinicians caring for the critically ill must strive to remain abreast of this information.

**REFERENCES**


