Invasive fungal infections (IFIs) remain an important cause of morbidity and mortality in patients with acute or chronic leukemia. Advances in the pharmacotherapy of fungal infections and a shift in the epidemiological characteristics of fungal pathogens toward fluconazole-resistant *Candida* species and saprophytic molds have placed a greater emphasis on selection of broader-spectrum agents for empirical therapy of IFIs in this high-risk population. Newer diagnostic modalities, such as the *Aspergillus* galactomannan test, the 1,3-β-D-glucan test, and polymerase chain reaction detection of fungal DNA, may facilitate the earlier diagnosis of IFIs, but their role in detecting breakthrough infection and their usefulness as a marker to withhold antifungal therapy in high-risk leukemia patients with IFI are less obvious, especially in patients who are receiving antifungal prophylaxis. Only 2 strategies have been shown in prospective studies to improve survival from mold infection in patients with acute myelogenous leukemia or myelodysplastic syndrome: (1) preemptive initiation of antifungal therapy at first sign of invasive aspergillosis on computed tomography (CT) scan and (2) antifungal prophylaxis with posaconazole. CT-guided treatment decisions are more complex in patients with advanced leukemia, however, because of concomitant infection or relapsing malignancy. Similarly, posaconazole is often not a viable prophylaxis or treatment option in patients with poor oral intake, gastrointestinal dysfunction, or possible drug interaction (eg, proton pump inhibitor prophylaxis in patients on high-dose glucocorticosteroids). As a result, the management of IFI in patients with leukemia demands an individualized treatment plan.

Recent advances in oncology and supportive care have extended the survival of severely immunocompromised patients with hematologic malignancies. With the improved control of bacterial infection that became possible with the availability of broad-spectrum antibiotics, invasive fungal infections (IFIs) have become a major cause of morbidity and mortality in these patients [1–4]. The complex scenarios in which these infections occur, especially late in the course of relapsing leukemia, create treatment challenges. For example, IFIs in patients with active leukemia are increasingly found in older patients with multiple comorbidities (eg, renal or hepatic dysfunction) that impair the therapeutic index of systemic antifungals. In this review, we summarize the challenges associated with IFI treatment in leukemia patients who had not undergone hematopoietic stem cell transplantation (SCT).

**EPIDEMIOLOGY OF IFIs: A MOVING TARGET**

The epidemiological characteristics of IFIs in leukemia patients continue to evolve (Figure 1). In the 1980s, candidiasis emerged as the prominent mycosis. However, since the widespread use of azole prophylaxis in the early 1990s in leukemia units, candidiasis has become less common [5]. *Candida* species that are fluconazole-resistant (*Candida krusei*) or susceptible–dose-dependent (*Candida glabrata*) currently account for most (>80%) candidiasis episodes in hematologic units [6, 7]. Whether fluconazole selection pressure is the sole cause of the changes in the relative distribution of *Candida* species in leukemia patients is controversial, because other host-related factors or antibacterial therapy may play a role [8]. Importantly, the recent introduction of echinocandins and newer azoles may have contributed to further shifts in the epidemiology of candidiasis. For example, the incidence of *Candida parapsilosis* and *Candida tropicalis* has increased in some treatment centers with the in-
Introduction and widespread use of echinocandins [9]. Notably, these infections were more likely to be catheter-associated infection rather than acute hematogenous candidiasis. Hepatosplenic candidiasis also appeared to be less common in leukemic patients, compared with its frequency in previous periods, on the basis of autopsy studies performed during the same period [4].

With improvements in the supportive care of patients with acute leukemia, including control of bacteria and *Candida* species, patients are surviving longer in a persistently neutropenic state. Prolonged neutropenia is a key risk factor for acquiring invasive mold infection, especially invasive aspergillosis (IA), which is typically caused by *Aspergillus fumigatus* [10]. Preceding the introduction of voriconazole, case-fatality rates of IA approached 70% in leukemia patients [11, 12]. An increased incidence of resistant non-*fumigatus* Aspergillus species, especially *Aspergillus terreus*, has been found in IA patients in some centers [13]. In addition, there has been an increased incidence of difficult-to-treat opportunistic molds such as zygomycetes, *Fusarium* species, and *Scedosporium* species, at least in some institutions [14, 15]. However, true epidemiologic assessments are complicated by the fact that >50% of hyaline molds that are identified in tissue cannot be microbiologically cultivated for definitive identification [14, 15]. The recent emergence of zygomycosis during a period of extensive use of Aspergillus-active agents such as voriconazole coincided with a decreased incidence of IA in the same population, emphasizing the dynamic nature of the epidemiology of opportunistic invasive mold infection (IMI) [15]. Reports of the declining contribution of IA as cause of death suggest that patterns of this disease are changing with improved antifungal therapy, earlier diagnosis, and new approaches to chemotherapy in the older patient that substitute novel “targeted” therapies for conventional high-dose cytoreductive chemotherapy that is associated with extensive organ toxicity [16–18]. However, these findings must be interpreted with caution; there is considerable uncertainty about the prevalence of IFIs, because autopsy rates have declined among leukemia patients and may be influenced by changes in the definition of IFI-attributed death and/or more extensive use of mold-active agents. In addition, >40% of IMIs are not diagnosed antemortem [4].

**CURRENT AND FUTURE APPROACHES TO DIAGNOSIS OF FUNGAL INFECTIONS**

Conventional diagnostic methods that are based on histologic evaluation and culture remain the cornerstones for establishing a definitive IFI diagnosis. In addition, cultures allow for speciation and susceptibility testing that could be useful in the selection of antifungals. However, obtaining appropriate specimens (eg, biopsy) from these patients may be difficult, because leukemia patients are frequently hemodynamically unstable, hypoxic, or coagulopathic [19, 20]. Even when invasive procedures are feasible, they may not provide a specific fungal diagnosis, because of prior antifungals, sampling error, or poor recovery of pathogens from infected tissues [21]. In situ hybridization directed against ribosomal 18S RNA sequences can distinguish between histopathologically proven, culture-nega-
tive hyalohyphomycoses (eg, IA, scedosporiosis, and fusariosis), but this approach remains investigational [22–24].

More recent diagnostic efforts have been focused on detecting non–culture-based serum markers (eg, circulating fungal antigens or DNA) that are associated with “early” IFIs. Among these new diagnostic tests, *Aspergillus* galactomannan (GM) has been the most intensively studied. A double-sandwich enzyme-linked immunosorbent assay (ELISA) GM assay capable of detecting GM at concentrations as low as 0.5 ng/mL has been approved by the United States Food and Drug Administration for use with serum samples [25]. False-positive results (eg, in patients receiving certain β-lactam antibiotics) and variables that reduce the fungal load and consequently reduce circulating GM levels, such as mold-active antifungal prophylaxis and corticosteroid-induced immunosuppression, decrease the assay performance [26–28].

1,3-β-d-glucan is an integral cell-wall component in pathogenic yeasts and filamentous fungi. Colorimetric detection assays that are sensitive to β-glucan (1 pg/mL) are now commercially available. When β-glucan was tested in patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS), it was highly specific and highly sensitive as a diagnostic adjunct [29]. The presence of β-glucan in serum signifies the presence of fungal invasion, but it is not specific for any fungi, and importantly the antigen is not extensively shed in patients with zygomycetes [30]. Therefore, it is unclear what the downstream diagnostic evaluation should be in a patient with a positive glucan test. False-positive β-glucan results are also possible, such as in dialysis patients when cellulose membranes are used and in patients treated with certain antimicrobials (eg, some cephalosporins, carbapenems, and ampicillin-sulbactam) [31]. Importantly, β-glucan has also been reported to cross-interact with *Pseudomonas aeruginosa*—a common copathogen in the leukemic population [32]. Polymerase chain reaction (PCR)—usually performed by amplifying ribosomal fungal DNA—is a promising method for detecting IFIs early, especially IA [33, 34]. One of the advantages of PCR is its ability to rapidly detect and molecularly identify opportunistic molds besides *Aspergillus* species. Unfortunately, these PCR diagnostic platforms have not been standardized and remain investigational, although coordinated efforts through the European Organization for Research and Treatment of Cancer/Mycoses Study Group to address the issue of standardization of nucleic acid–based testing are ongoing [33, 34].

Combinations of tests (eg, GM and β-glucan) could improve the specificity and sensitivity of IA diagnosis in high-risk hematologic malignancy patients [35]. In summary, non–culture-based biomarkers could expand our ability to establish early and specific diagnoses for IFIs or even to help with assessment of response to antifungal therapy [36]. However, it is unclear how these tests would perform outside the controlled environment of clinical studies, especially when performed as a “send out” test with several days of delay before results are reported. The high specificity of these antigen-based tests suggests that they may be more useful as an adjunctive diagnostic.

Radiologic imaging continues to play a pivotal role in the diagnosis of IFIs, especially IMIs. Computed tomography (CT) findings, especially the “halo sign,” are strongly suggestive of angioinvasive pulmonary fungal diseases in neutropenic patients with acute leukemia, and these findings are associated with improved outcome if antifungals are started at this early sign of infection [37–40]. However, the halo sign is transient—75% of initial halo signs disappear within a week, emphasizing the importance of systematic early use of CT [41]. The air crescent sign is highly specific for angioinvasive molds but is a late radiologic sign. The combination of radiologic and clinical data may help in the differential diagnosis of fungal disease. For example, prior voriconazole prophylaxis, sinustis, and multiple (>10) lung nodules or a “reverse halo sign” on CT suggest pulmonary zygomycosis [14, 42].

**IMPORTANCE OF EARLY TREATMENT**

In recent retrospective studies, conducted before the introduction of echinocandins, antifungal therapy within 12 hours after the first blood culture result positive for *Candida* species was important for a successful outcome in hospitalized candidemia patients [43, 44]. Such data do not exist specifically for patients with leukemia and candidemia, but given the propensity for neutropenic patients to develop metastatic and deep tissue infections, prompt initiation of antifungal therapy should be even more critical in these patients. For IMIs, retrospective data indicate that the prompt administration of empirical or preemptive therapy also leads to an improved outcome [40, 45]. A 7-day delay in treatment in a small series of patients with IA and zygomycosis resulted in a doubling of the mortality rate [45, 46]. Because of the difficulty in diagnosing IFIs early, institution-specific epidemiological characteristics are important for selecting an appropriate empirical or preemptive regimen.

The importance of timely diagnosis and early start of therapy has led to increased utilization of interventional diagnostics. In a recent study, high-risk patients who had CT findings suggestive of IFI were triaged by CT-guided percutaneous lung biopsy. Staining of the specimens with Calcofluor white allowed a rapid diagnosis and the differentiation between septate and unseptate hyphae, and it guided therapy toward *Aspergillus* versus zygomycetes [22].

**NEWER ANTIFUNGAL AGENTS**

Since the 1990s, there has been an acceleration in the introduction of new antifungal agents to the clinic. These agents have a broader spectrum of antifungal coverage (Table 1) and improved tolerability, compared with previous “gold standard”
The lipid formulations of AMB (LFAB), which are AMB lipid complex (ABLC), AMB colloidal dispersion, and liposomal AMB (L-AMB), are less nephrotoxic than conventional AMB-deoxycholate (AMB-D). Response rates with LFABs range 40%–60% in patients with IA that was refractory or intolerant to AMB-D because of side effects [47]. Whether the efficacy of AMB in IA treatment is improved by these formulations remains debatable. The increased length of stay and cost of renal toxicity associated with AMB-D may offset the higher acquisition costs of LFABs. This is especially true in high-risk hematologic malignancy patients [48]. Another controversial issue is whether there are clinically meaningful differences between the various LFABs, given their differences in volume of distribution and rate of tissue penetration [49]. Animal models and autopsy studies suggest that LFABs may differ with respect to the rate and extent of drug delivery at different sites, such as the lung or the brain. For example, ABLC results in substantially higher concentrations of total bound AMB in lung tissue in animal models than does L-AMB, which may enhance the rate of early fungal killing [50, 51]. Conversely, animal models have suggested that L-AMB may achieve higher tissue concentrations than ABLC in experimental models have suggested that L-AMB may achieve higher tissue concentrations than ABLC in experimental models have suggested that L-AMB may achieve higher tissue concentrations than ABLC in experimental 

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**NOTE.** +, in vitro activity; −, no in vitro activity; +/−, modest in vitro activity; AMB, amphotericin B; FLU, fluconazole; ITRA, itraconazole; ND, no data; POSA, posaconazole; VOR, voriconazole.

- Caspofungin, micafungin, and anidulafungin.
- Candida parapsilosis is less susceptible in vitro to the echinocandins.

amphotericin B (AMB)–based regimens. These agents are used prophylactically, empirically, and preemptively or for documented IFIs in leukemia patients.

The improved spectrum of these triazoles comes at the cost of higher toxicity and more drug interactions than fluconazole. Voriconazole, currently the preferred drug in the primary therapy of IA [20], can cause transient photopsia, liver toxicity, central nervous system adverse effects, and drug interactions because of cytochrome (CY) P450 enzyme inhibition [53]. Posaconazole, currently available only in oral formulation, must be administered in divided doses with a high-fat meal for optimal absorption [54]. Therefore, caution should be used in severely ill leukemia patients, such as those in intensive care units, those with mucositis or poor oral intake, and those with severe diarrhea, and in patients who are receiving potent acid-suppression therapy (ie, protein pump inhibitors) [55]. Posaconazole has a better drug interaction profile than voriconazole, because it inhibits only CYP3A4; however, severe drug interactions can still be problematic, especially with select immunosuppressive medications (eg, tacrolimus) and chemotherapy agents [56]. The main advantage of posaconazole is that it is the only agent besides AMB that is active against zygomycetes. The echinocandins (caspofungin, micafungin, and anidulafungin) inhibit 1,3-β-D-glucan synthase, which is the key enzyme for β-glucan biosynthesis, an important component of the cell wall of many medically important fungi. All echinocandins share the same relatively narrow spectrum; they are fungicidal against most Candida species [57] and fungistatic in vitro against Aspergillus species. They have no activity against non-Candida yeasts and non-Aspergillus molds. However, echi-
niconandins might have unconventional immune-enhancing properties [58–60]. Echinocandins are large lipopeptides with poor oral bioavailability; as such, they must be administered intravenously. They also have linear pharmacokinetic properties and a long half-life. Because they are not substrates or inhibitors for CYP450, their toxicity profile is characterized by minimal side effects and they have minimal drug interactions [61].

**CONSIDERATIONS FOR OPTIMAL PROPHYLAXIS STRATEGY**

Since the introduction of fluconazole prophylaxis, the incidence of candidemia has decreased in leukemia patients at the expense of the increased incidence of IA. Not all patients with leukemia are at the same risk for IA. Which leukemia patient subgroups would benefit from mold-active prophylaxis (eg, older patients with AML or MDS during induction chemotherapy) is often an institution-specific and sometimes a patient-specific question. To our knowledge, no formal comparative studies have been performed to calculate the number of patients to treat in order to prevent 1 IFI in each subgroup of patients with acute or chronic leukemia.

The use of LFAbs as prophylaxis has been explored, either on low-dose daily administration schedules or as infrequent (weekly or twice-weekly) infusions, in noncomparative studies [62]. Similarly, aerosolized AMB and LFAbs have been found to have protective effects in patients who are being treated with fluconazole [63]. Aerosolized delivery might be limited, because distribution to distal sites in lung parenchyma and long-term tolerability, most commonly cough and bronchospasm, are important concerns. Aerosolized delivery also would not be expected to provide sufficient protection outside the lung for endogenous pathogens such as *Candida*.

In one multi-institutional, prospective, nonblinded study of patients undergoing chemotherapy for AML or MDS, oral posaconazole (600 mg/day) prevented IFIs more effectively than did fluconazole and/or itraconazole and resulted in improved survival [64]. This was the first study to demonstrate that antifungal prophylaxis results in a survival benefit in high-risk leukemia patients. According to recent IDSA guidelines, antifungal prophylaxis with posaconazole can be recommended for neutropenic patients [20]. There has been little experience with the use of voriconazole prophylaxis in high-risk leukemia patients, although the results of recent studies suggest that it is useful as prophylaxis in hematopoietic SCT patients [65, 66].

The use of second-generation oral azoles as primary or secondary [67] prophylaxis in high-risk leukemia patients is becoming commonplace, even though these drugs are more expensive and more complicated to administer than fluconazole. From the pharmacoeconomic standpoint, these drugs are predicted to be a cost-effective prophylaxis when given to neutropenic AML or MDS patients after intensive chemotherapy [68]. Further study is required for issues such as the need for therapeutic drug monitoring (given that the intrapatient and interpatient pharmacokinetic variability of mold-active triazoles can lead to therapeutic failure or, in the case of voriconazole, toxicity) and the performance of serum diagnostic assays (eg, GM) in the setting of mold-active prophylaxis [27, 55].

Besides pharmacologic prophylaxis, other preventive measures have been proposed to reduce the burden of IFI in leukemia patients. Reports on nosocomial outbreaks of IMIs have linked cases to hospital construction, the absence of appropriate barriers between patients and the environment, and the presence of fungal spores in room air samples. A meta-analysis of 16 controlled trials that evaluated the effect of high-efficiency particulate air (HEPA) filtration on neutropenic patients with hematologic malignancies or SCT found that the placement of patients in protective environments appeared to be beneficial in preventing IFIs, but the data seemed insufficient to support specific conclusions [69]. The Centers for Disease Control and Prevention guidelines for preventing opportunistic IMIs in allogeneic SCT recipients recommend the use of HEPA filters in patient rooms [70]. Also, recent data suggest that not only hospital air but also hospital water is a potential source of transmission of filamentous fungi. A study that included molecular characterization of environmental and clinical isolates of *A. fumigatus* showed that patients can be infected by strains originating from water or from air [71]. In this study, aerosolized dispersion appeared to be the most logical route of infection, because all patients infected with a waterborne strain had a pulmonary infection. Thus, further research is needed into measures that can be adopted with regard to water quality and prevention of mold transmission through aerosolized water sources [71]. A neutropenic diet is often used to prevent infection in leukemia patients. Nevertheless, a recent randomized controlled trial in AML patients admitted to a HEPA-filtered room during periods of induction chemotherapy while on antifungal prophylaxis found no difference in infection rates between patients chosen by random selection to receive a diet containing neither raw fruits nor raw vegetables (cooked diet) and patients chosen to receive a diet containing fresh fruit and fresh vegetables (raw diet) [72].

**EMPIRICAL AND PREEMPTIVE ANTIFUNGAL THERAPY IN NEUTROPENIC HIGH-RISK HEMATOLOGIC MALIGNANCY PATIENTS**

Despite increasing focus on preemptive treatment approaches, empirical antifungal therapy is still an accepted practice, supported by the suboptimal early diagnosis of IFIs and the crucial role of early initiation of antifungal therapy [73]. In an era in which persistent fever in neutropenic patients has an increasingly complex differential diagnosis, it is important that antifungals are not prescribed without careful clinical evaluation.
Typically, antifungals are empirically administered after 3–7 days of persistent fever with neutropenia in patients who are receiving broad-spectrum antibiotics. The decision to start antifungal therapy should be based on risk stratification for the background rate of IFIs, the potential for toxicity and reactions with concomitant medications, prior antifungal exposure, and the cost of the proposed empirical therapy [73]. Therefore, there is no single drug of choice; decisions should be individualized. Among the current antifungal agents, especially those with a mold-expanded spectrum, LFAB, caspofungin, and voriconazole are the most attractive choices [74–77].

Whether preemptive antifungal therapy triggered by CT [78] and a serum marker (eg, GM [79] or PCR [80]) would be an effective substitute for empirical antifungal therapy is an important question and the subject of ongoing studies. A recent randomized trial that compared the 2 strategies showed that survival was similar in the 2 arms, except for patients receiving induction chemotherapy for AML, for whom empirical treatment may provide better survival rates [81].

**TREATMENT OF DOCUMENTED INVASIVE FUNGAL INFECTIONS IN LEUKEMIA PATIENTS**

**Candidiasis.** Prospective trials of candidemia in leukemia patients are limited, because these high-risk patients (eg, patients with neutropenia, high Acute Physiology and Chronic Health Evaluation [APACHE] scores, or organ dysfunction) are typically excluded in multicenter, randomized trials that are performed to support approval of new antifungals. Despite these limitations, recently updated treatment guidelines provide some specific recommendations for management of invasive candidiasis in the leukemic population [82].

The optimal therapy for neutropenic leukemia patients with candidemia depends on their clinical status and previous exposure to azoles. In patients previously exposed to azoles, an echinocandin or an LFAB is recommended as the initial therapy [82]. In this era of emerging fungal pathogens that cause blood culture results positive for yeast, clinicians must be aware that blood culture results positive for yeast may represent infection with *Cryptococcus* species, endemic fungal species, or rare yeasts such as *Trichosporon* species [83]. Therefore, before “ Committing” the high-risk leukemia patient to echinocandin-based therapy, the clinician should confirm that the patient indeed has candidiasis. When the patient is stabilized, transition to oral fluconazole or voriconazole is feasible, especially if the *Candida* isolate is azole susceptible and the patient’s neutropenia has resolved (Table 2). Antifungal therapy should be continued for \( \geq 2 \) weeks after the last positive blood culture result in the uncomplicated patient if neutropenia has resolved. Patients with prolonged neutropenia or evidence of metastatic infection should receive 4–6 weeks of therapy, continued until resolution of infectious signs and neutropenia.

**Aspergillosis.** Recommendations for IA treatment empha-
size the importance in this population of early diagnosis based on compatible radiologic findings on CT and possibly positive GM antigenemia [20]. Voriconazole has been established as the primary therapy in most patients, but L-AMB can be used as an alternative [20, 84]. Posaconazole, itraconazole, echinocandins, and other LFABs have been shown to be active in salvage trials, although these data are hard to interpret because of confounding factors. The choice of salvage therapy would depend on the prior antifungal regimens used, the site of infection, comorbidities, and dosing considerations that affect the agent’s tolerability and efficacy.

Given the relatively poor outcome of voriconazole monotherapy [85], considerable attention has been directed to the use of combination therapy for aspergillosis. Many combinations of antifungal drugs have been used, but the existing data are not sufficient to support the global acceptance of combination therapy as a first-line treatment approach. A prospective randomized trial of voriconazole versus posaconazole and anidulafungin is underway (ClinicalTrials.gov identifier, NCT00531479). The choice of combination therapy should be made on a case-by-case basis, taking into account both clinical and preclinical evidence [86].

The role of adjunct surgery in selected leukemia patients (eg, young patients with good performance status who are in remission, have a single residual fungal lesion, and are candidates for SCT) is promising [87]. The issues that arise are whether a delay in chemotherapy because of the recovery period would put patients at risk for relapse of leukemia and whether radical or “debulking” excision of a dominant fungal lesion is sufficient.

**Zygomycosis and other molds.** To our knowledge, no data exist on the primary treatment of zygomycosis. AMB-based therapy remains the standard of care. Posaconazole has been reported to have activity as second-line therapy (Table 2) [88]. The positive outcome in these patients is enhanced by surgical resection of affected tissue and stabilization or improvement of the underlying illness [89]. The combination of ABLC and caspofungin has been reported to result in improved response rates in nonneutropenic diabetic patients [90]. An open-label trial of the safety and tolerability of iron chelator deferasirox and L-AMB is currently underway. The utility of iron chelation has been extrapolated from preclinical studies and case reports that suggest a pivotal role of iron acquisition in the pathogenesis of zygomycosis [91, 92]. The clinical utility of hyperbaric oxygen is less certain, because of the absence of controlled randomized studies [93].

Because of the rarity of *Scedosporium* and *Fusarium* infections in leukemia patients, the optimal therapy of patients with these infections is undefined. However, therapy with triazoles such as voriconazole [94] and posaconazole [95] was beneficial in small salvage studies (Table 2). The role of combination therapy is unknown.

**ADJUVANT IMMUNE STRATEGIES IN THE MANAGEMENT OF INVASIVE FUNGAL INFECTIONS**

The response to antifungals has been inadequate in immunocompromised patients; therefore, there has been long-standing interest in the development of immune adjunct therapies. These approaches underline the importance of reducing the duration and severity of neutropenia, which are the principle driving factors influencing the outcome of IFI in leukemic patients. Granulocyte-macrophage–colony stimulating factor, granulocyte–colony stimulating factor, and recombiant interferon-α enhance the ability of neutrophils to phagocytose fungi and reverse steroid-induced dysfunctions of tissue and alveolar macrophages [96–99]. Donor granulocyte transfusions and recombiant interferon-α have been safely used in the context of immune enhancement in patients with hematologic malignancies [98]. Clinical and preclinical data indicate that these approaches may be an important bridge for controlling or even preventing infection until marrow recovery in selected patients [100].

**Table 3. Factors Influencing Decision Making of Antifungal Therapy in Leukemia Patients with Documented or Presumed Invasive Fungal Infection (IFI)**

| Risk of nephrotoxicity (eg, higher patient age, concomitant nephrotoxic drugs, or renal impairment) |
| Liver dysfunction |
| Ability for oral medication—gastrointestinal function (mucositis, nausea, and vomiting) |
| Active leukemia and plans for hemopoietic transplant |
| Type of chemotherapy (remission induction vs consolidation vs palliation) |
| Type of fungus |
| Site of infection (eg, central nervous system disease) |
| Certainty of diagnosis |
| Interactions of concomitant drugs with antifungals |
| Infected hardware or catheters |
| Prior antifungal exposure (risk of cross-resistance or tolerance with azoles) |
| Refractory IFI and number of previously failed regimens |
| Patient’s preference and ability to pay for oral antifungals |
| Immunosuppression and reconstitution (timimg and intensity of immunosuppression) |
| Concomitant infections (cytomegalovirus or bacteria) and their treatment |
| Patient’s compliance |
| Outpatient vs inpatient treatment |
**IMPORTANCE OF INDIVIDUALIZING THE TREATMENT APPROACH**

An algorithmic approach might be useful when treating a leukemia patient with IFI. However, clinical guidelines are supposed to be guides and not rules [101]. The complex clinical scenarios and the multiple comorbidities of leukemia patients are difficult to fully characterize in an algorithm for IFI treatment—it is certainly true that one size does not fit all patients. In everyday practice these patients are managed differently on the basis of a multitude of host and pharmacologic considerations (Table 3). The risk of death from an IFI is not constant over the course of leukemia treatment. Many patients will require alternating periods of intensifying and de-escalating therapy, depending on the natural history of their infection and malignancy status. Often patients may have incurable leukemia, which may justify treatment approaches that are more “suppressive” or “palliative” in nature rather than an aggressive pursuit of cures that may be associated with unacceptable adverse events and toxicity in the patient’s final stages of disease. In addition, the treatment plan for their underlying malignant disease necessitates flexibility and collaborative efforts to balance their overall health status. The individualization of treatment plans is of great importance in order to maximize the gains of therapy and best serve the needs of the patient.

In conclusion, tremendous progress has been made in the treatment of IFIs in leukemia patients over the past 2 decades. Treatments that are safer and better tolerated than AMB are available. The most urgent unmet need in IFI treatment is for improved early diagnosis and the introduction of new antifungal agents with a novel mechanism of action. More work is needed to determine the immunobiologic characteristics of IFIs and the risk stratification of leukemia patients on the basis of their immunologic [102], metabolic (eg, iron overload [103] or hyperglycemia [104]), and genetic profiles. We are entering an exciting era that could lead to individualized therapy, given the complex characteristics of IFIs in the leukemia patient population.

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