

How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach

Marcio Nucci¹ and Elias Anaissie²

¹University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; and ²Division of Hematology/Oncology, University of Cincinnati, Cincinnati, OH

Invasive fungal diseases (IFDs) represent an important cause of treatment failure in adults with acute leukemia. Because of leukemia's heterogeneity, the risk for IFDs is highly variable. We therefore apply a risk-adapted antifungal strategy with strong emphasis on pretreatment and day-15 posttreatment to allow earlier and more individualized interventions. We determine pretreatment risks for IFDs based on 4 factors: (1) host fitness for standard therapy (ie, fit, unfit, or frail); (2) leukemia

resistance (high vs low probability of achieving complete remission [CR]); (3) anticipated treatment-related toxicity such as neutropenia, mucositis, and steroid-induced immunosuppression; and (4) patient exposure to opportunistic fungi. Accordingly, we stratify patients as high, intermediate, or low risk for IFDs and apply risk-adapted antifungal strategies, including primary or secondary prophylaxis and diagnostic-based preemptive or empiric therapy. Prevention of IFDs also relies on optimizing organ function,

decreasing exposure to opportunistic fungi, and improving net state of immunosuppression with use of better-tolerated and investigational agents for unfit patients and those with adverse leukemia biology. Novel targeted and safe therapies that can achieve higher rates of sustained CR among patients with adverse genetics offer the best promise for reducing the burden of IFDs in these patients. (*Blood*. 2014;124(26): 3858-3869)

Introduction

The outcome of adults with acute leukemia (A-Leuk), including acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL), has improved over the last decade because of the availability of novel agents and improvements in supportive care such as effective antifungal prophylaxis.¹⁻³

Despite these advances,¹⁻³ treatment failure remains common and is driven by adverse leukemia genetics (translated into lower probability of achieving complete remission [CR])⁴⁻⁶ and by early treatment-related mortality (e-TRM,⁷ most commonly caused by infections, particularly invasive fungal diseases [IFDs]), which serve as markers of poor host fitness for therapy.⁸

We herein discuss novel risk-adapted and dynamic strategies for the prevention, diagnosis, and treatment of IFDs in patients with A-Leuk, with strong emphasis on pretreatment parameters that allow earlier interventions.

Fungal infections in children and recipients of hematopoietic cell transplantation and those caused by *Pneumocystis jiroveci* are not discussed. The following clinical course of a patient illustrates some pitfalls in managing IFDs in patients with A-Leuk.

A 45-year-old man was hospitalized for remission-induction of favorable cytogenetics AML using cytarabine and idarubicin (7 + 3). Prophylactic fluconazole was started along with thrice-weekly serum *Aspergillus* galactomannan index (s-GMI; positive if ≥ 0.5). On day +5, the patient developed blood culture-negative febrile neutropenia (FN) of 101.5°F with an absolute neutrophil count (ANC) of $<100 \mu\text{L}$. Piperacillin-tazobactam was started with rapid defervescence. On day +10, low-grade 99.5°F fevers were noted. Physical examination was normal, but s-GMI was elevated at 0.630, rising to 1.735 on day +12. Computed tomography of the chest (chest CT) revealed a 0.4-cm nodule and tree-in-bud pattern infiltrates in the right upper lobe, prompting IV voriconazole for invasive pulmonary aspergillosis (IPA). On day +15, s-GMI reached 2.134, then normalized

on day +19 when ANC reached 350/ μL . Day +16 bone marrow biopsy showed no blasts. The patient's clinical course and serial s-GMI remained unremarkable until day +23 when he complained of cough and dyspnea on exertion with hypoxemia. Chest CT revealed marked right upper lobe worsening with wedge-shaped infiltrates. A day +21 sputum yielded *Aspergillus versicolor*. Because clinical and radiologic worsening coincided with increasing ANC ($>4000/\mu\text{L}$), but with persistently normal s-GMIs and no other etiology for the infiltrates, a diagnosis of pulmonary inflammatory immune reconstitution syndrome (PIRIS)⁹ was made, and voriconazole continued. On day +24, he developed early respiratory failure, which rapidly responded to a 3-day course of 2 mg/kg of IV methylprednisolone per day. He was discharged in CR on oral voriconazole until resolution of IPA, with secondary voriconazole prophylaxis throughout consolidation. One year after diagnosis, he remained in sustained CR and free of IPA. This case illustrates several points relevant to IFDs in this patient population, including prevention (fluconazole prophylaxis), early diagnosis (serial s-GMI, cultures, chest CT findings, and confounding presentations such as PIRIS), and treatment (voriconazole), as well as the protective effects of remission status and secondary prophylaxis.

What has changed in the epidemiology of IFDs?

Much has changed in the epidemiology and management of IFDs since our 1995 review in *Blood*.¹⁰

Increasing mold infections

Invasive candidiasis (IC) was the most frequent IFD in patients with A-Leuk until the introduction of fluconazole,¹¹ which led to a decrease

in its incidence, a shift from susceptible (*Candida albicans* and *C tropicalis*) to more resistant species (*C glabrata* and *C krusei*),¹² and an increase in invasive mold infections (IMIs), particularly invasive aspergillosis (IA), followed by fusariosis, mucormycosis, and others.^{13,14} Prophylaxis with the newly available mold-active triazoles—voriconazole and posaconazole—reduced the incidence of IA but has been associated with breakthrough IMIs with non-*Aspergillus* molds, particularly mucormycosis.¹⁵ In vitro resistance of *Aspergillus* species to triazoles is reported,¹⁶ although its clinical relevance remains unclear.

Geographic and seasonal variations

The epidemiology of IMI is subject to geographic and seasonal variations. For example, scedosporiosis is most frequently observed in Spain and Australia,^{17,18} whereas the incidence of fusariosis is highest in Houston, Texas,¹⁹ and Brazil.¹⁴ Seasonal variations in the incidence of aspergillosis and fusariosis were reported in Seattle, Washington,²⁰ and Houston, Texas,¹⁹ respectively.

Waterborne IMIs

Patients with A-Leuk may acquire IMI from different sources, including air and water. *Aspergillus* species, *Fusarium* species, and the agents of mucormycosis were recovered from air, water, and water-related surfaces of hospitals,²¹ with demonstration of relatedness between patients' and waterborne strains.^{22,23}

What are the key risk factors for IFDs?

The risk for IFDs is higher among AML patients,¹³ except when ALL-intensified regimens are applied (Table 1). The highest rate is observed following salvage therapy for relapsed-refractory leukemia, although a significant proportion of newly diagnosed patients undergoing remission-induction develop IFDs, most commonly sinus, pulmonary aspergillosis (9% to 15%), or both.²⁴⁻²⁶ Despite long duration of severe neutropenia (DON; ANC <100/ μ L, \geq 10-14 days), the rate of IA is lower after consolidation therapy (5.7%),²⁷ reflecting the protective effect of CR status.^{25,26}

Similarly, patients with ALL develop IFDs during remission induction^{26,28,29} but may remain at risk after neutrophil recovery because of cumulative treatment-related immunosuppression²⁸ and corticosteroid-induced hyperglycemia.³⁰

Because of the heterogeneity of A-Leuk, the risk for IFDs is highly variable and results from interactions between net state of immunosuppression, organ dysfunction, and exposure to opportunistic fungi.³¹

Immunosuppression is highest among patients with AML and high-risk myelodysplasia (MDS) because of their older age^{4,5} and adverse cytogenetics (hence, lower CR probability),⁴⁻⁶ neutropenia at diagnosis,^{5,26} and prolonged treatment-related DON.³² Cumulative corticosteroid doses^{25,33} and phagocytic dysfunction with antecedent MDS contribute to immunosuppression.^{34,35}

Organ dysfunction increases IFD risk.⁴ For example, mucositis following mucotoxic regimens increases the risk for IC³⁶ because *Candida* species are normal colonizers of gut mucosa,³⁷ whereas preexisting lung pathology, including chronic obstructive pulmonary disease³⁸ and smoking,³⁹ predisposes patients to IA/IMIs following exposure to airborne conidia.²⁵

Exposure to opportunistic fungi raises the risk for IFDs; for example, multisite colonization by *Candida* species⁴⁰ and airway colonization by *Aspergillus* species⁴¹ predispose patients to IC and IPA, respectively.

Pretreatment risk assessment: leukemia genetics as markers for prolonged neutropenia and risk for IFDs

Because delayed diagnosis of IFDs is associated with higher morbidity and mortality, preventive measures should be taken as early as possible, preferably prior to antileukemic therapy.

Prolonged DON determines risk for IFD but because it is unknown prior to therapy, it is of limited value. Identifying pretreatment parameters that predict DON is therefore of paramount importance. Because the definition of CR requires an ANC >1000/ μ L, failure to enter remission is associated with longer DON and higher rates of severe infections, including IFDs³² and e-TRM.⁷ Hence, remission status that can be calculated prior to treatment predicts DON,^{42,43} with the caveat that unfit patients with favorable genetics may not survive long enough to achieve CR.⁴³⁻⁴⁵

Unfavorable prognostic factors for achieving CR and for e-TRM and toxic death include adverse cytogenetics and gene mutation profiles,⁴⁶ elevated WBC counts,⁴ older age (arbitrary cutoff point of 65-75 years),⁴⁴ and poor performance status.⁴⁴

We use an online AML model (www.AML-score.org),⁴² which predicts probability of CR and toxic deaths among newly diagnosed patients (\geq 60 years old) eligible for intensive therapy.

The importance of pretreatment variables for risk for and outcome of IFDs is illustrated in a study evaluating risk factors for IA among 258 patients with A-Leuk.²⁶ Median DON was 10 days longer among patients with IA than those without (31 vs 21 days, respectively), and DON was a risk factor for IA by univariate but not multivariate analysis. Only high-risk cytogenetics, neutropenia at diagnosis, and prior lung disease were independent predictors for IA. Strikingly, none of 33 patients with favorable cytogenetics developed IA vs 11 of 22 (50%) among those with adverse cytogenetics, and most patients who died of IA-related complications had refractory leukemia.²⁶

The dominant role of remission status as risk and prognostic factor for IA is further highlighted in a study in which failure to enter CR and older age, but not neutropenia, were independent risk factors for IA following remission-induction for AML,³² and in another study in which progressive leukemia was more predictive of IA-attributable mortality than neutrophil recovery.⁴⁷

Additional pretreatment risk factors (the most important shown in bold) are listed in Table 1.

Accordingly, a comprehensive assessment of pretreatment risk factors for infections in general, and IFDs in particular, should be part of routine evaluation in addition to leukemia diagnostics.

Day 15 posttreatment risk assessment

Another predictor of DON is day-15 blast count, as shown in a study of the impact of marrow evaluation for blast clearance: compared with patients with \geq 5% day-15 blast count, those with \leq 4% had shorter neutropenia (23 vs 33 days; $P < .0001$), lower rates of bloodstream infections (13.6% vs 23.2%; $P = .003$), and lower rates of aplastic death (1.8% vs 6.8%; $P = .001$).⁴⁸

How do we translate risk factors into a risk-adapted and dynamic strategy to prevent IFDs?

Pretreatment assessment of risk for IFDs

Based on factors related to host, leukemia, and fungal exposure, we stratify patients into 3 risk categories for IFDs—high, intermediate, or low—and apply risk-adapted antifungal strategies accordingly.

Table 1. Risk factors for and risk reduction of IFDs in patients with AML or ALL

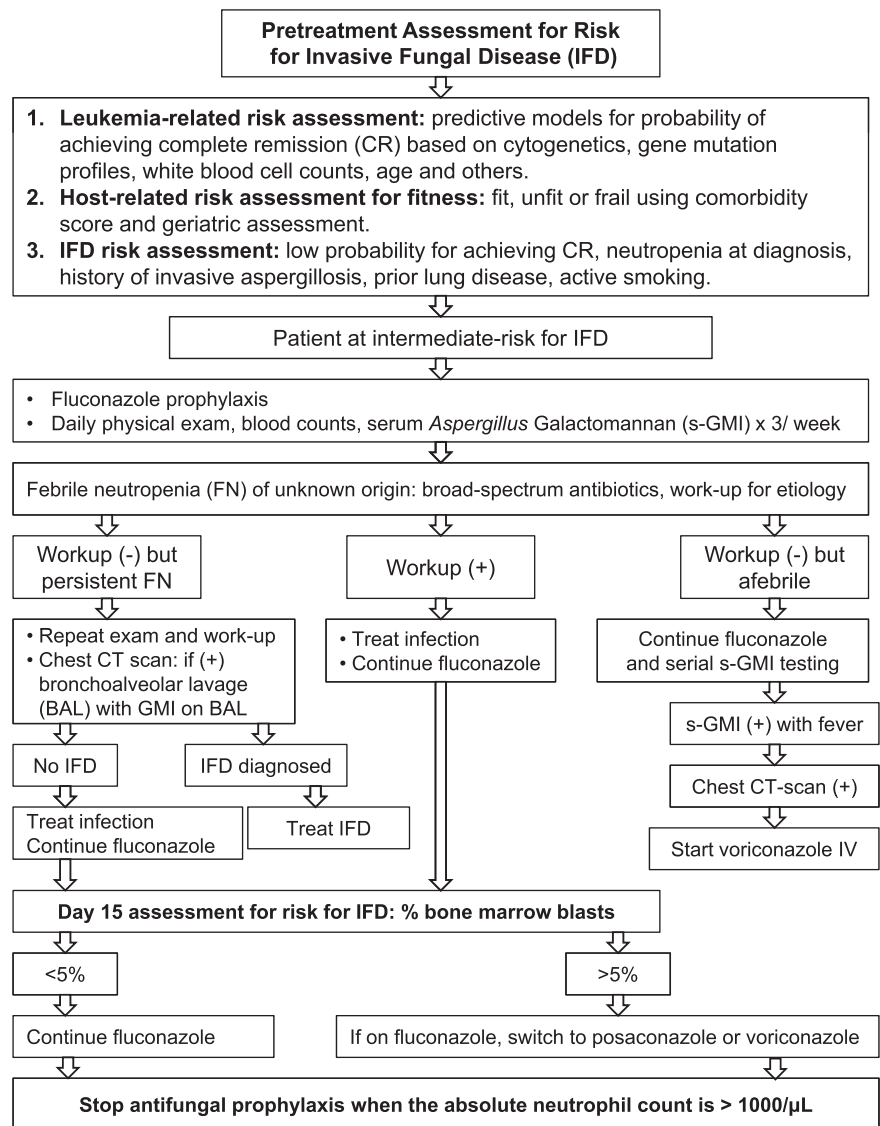
Risk factors	Risk reduction
Pretreatment	
Net state of immunosuppression	
Leukemia-related	
*Lower probability of CR ³² AML: adverse cytogenetic/gene mutation profiles, WBC \geq 50 000/ μ L, secondary leukemia, MDS or antecedent hematologic disorder $>$ 6 mo ^{4,5} ALL: adverse cytogenetic/gene mutation profiles, WBC \geq 30 000/ μ L, immunophenotype ⁶	Assess probability of CR and e-TRM ^{42,43} Determine risk for IFDs: high, intermediate, or low, and manage accordingly. Primary mold-active prophylaxis for high-risk patients. Serial s-GMI tests Lower cytarabine consolidation for patients with favorable cytogenetics ⁴³ Better-tolerated antileukemic regimens if high risk for e-TRM ⁶⁴⁻⁶⁸
*Baseline neutropenia ANC $<$ 500/ μ L for \geq 7 d, ²⁶ MDS-related phagocytic dysfunction	Manage as high risk for IFDs including mold-active prophylaxis G-CSF for patients with ALL, ¹¹⁴ and GM-CSF for those with AML ⁶⁹
*Leukemia status ³⁵ Relapse-refractory $>$ first induction $>$ consolidation	Manage as high risk for IFDs except for consolidation
Treatment-related	
*Corticosteroids (\geq 3 wk of $>$ 1 mg/kg per d of prednisone equivalent) ^{25,33}	Reduce corticosteroid dose, provide antifungal and <i>Pneumocystis</i> prophylaxis
*Highly mucotoxic regimen ³⁶ Cumulative myelotoxicity from rapidly cycling chemotherapy courses	Fluconazole prophylaxis ⁵⁹ even if low risk for IFDs Adjust dose density and intensity based on likelihood of CR42 ⁴³ and e-TRM ⁴³⁻⁴⁵
Host-related	
*Age $>$ 65 y (AML), ⁴⁴ $>$ 35 Y (ALL) ¹¹⁵ ; Down syndrome	Manage as high risk for IFDs, including mold-active prophylaxis Consider better-tolerated therapies ⁶⁴⁻⁶⁸
Immunity polymorphisms ³¹ ; pharmacogenomics of antineoplastic drugs ¹¹⁷	Avoid severe drug interactions and monitor clinical toxicity and drug levels ³¹
Organ dysfunction	
*High comorbidity scores ¹¹⁸ and e-TRM risk ⁴³⁻⁴⁵	Improve organ function and consider better-tolerated regimens ⁶⁴⁻⁶⁸
*Chronic obstructive pulmonary disease, ³⁸ smoking, ³⁹ respiratory viral infection ¹¹⁹	Manage as high risk for IFDs, including mold-active antifungal prophylaxis During influenza season: immunize patient and close contacts vs influenza viruses, prophylaxis with neuraminidase inhibitors, avoid sick visitors, ⁷² smoking cessation
*Poor physical functioning ECOG/WHO score, ¹²⁰ physiologic status, functional reserve, activities of daily living, gait speed, and others ¹²¹	Preemptive physical and occupational therapy
Hyperglycemia (blood glucose $>$ 200 mg/dL for $>$ 2 wk) ¹²²	Monitor and correct blood glucose
Exposure to pathogenic fungi	
*Prior aspergillosis \pm airway colonization by <i>Aspergillus</i> spp ^{41,49}	Manage as high risk for IFDs, including mold-active antifungal secondary prophylaxis ^{49,50}
Room without HEPA filtration ⁷³	Provide HEPA filtration ⁷³
Building constructions or renovation ⁷⁴	Ensure safe construction practices ⁷⁴
Room without water precautions ⁷⁵	Provide water precautions ^{21,75}
Posttreatment	
Net state of immunosuppression	
Neutropenia, severe and prolonged ⁸⁵ (ANC $<$ 100/ μ L for $>$ 10 d)	Manage as high risk for IFDs, including mold-active antifungal prophylaxis
*Expected severe and prolonged neutropenia AML: low CR score, ⁴⁻⁶ d 15 blasts $>$ 5%, ⁴⁸ no CR by end of induction ALL: no CR in 4 wk, persistent MRD ^{32,48}	Day-15 bone marrow biopsy for blast clearance and MRD ⁴⁸ G-CSF for patients with ALL ¹¹⁴ and G-CSF for those with AML ⁶⁹
Persistent lymphopenia (cells $<$ 300 μ L) with normal WBC/ANC	Reduce corticosteroid dose, antifungal and <i>Pneumocystis</i> prophylaxis
Organ dysfunction	
*Mucositis ³⁶ Severe, grade \geq 3 for \geq 7 d, especially if involving lower gut	Fluconazole prophylaxis
Exposure to pathogenic fungi	
Same as pretreatment	Same as pretreatment
*Multisite colonization by <i>Candida</i> species ⁴⁰	Fluconazole prophylaxis, unless a mold-active agent is indicated
Central venous catheter ¹²³	Optimal venous catheter care

Risk stratification is done prior to treatment and on day-15 bone marrow examination. Risk factors are shown according to type: immunosuppression, organ dysfunction, exposure to pathogenic fungi, and to timing (pretreatment or posttreatment). Yeast infections are typically caused by *Candida* species, whereas aspergillosis is the most common mold infection. ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; HEPA, high-efficiency particulate air; MRD, minimal residual disease; WBC, white blood cell; WHO, World Health Organization. *Most important risk factors.

A) High-risk group: patients with prior aspergillosis;^{49,50} those on salvage regimens for relapsed-refractory disease; and newly diagnosed patients undergoing remission-induction with any of

the following risk factors: neutropenia at baseline,^{5,26} low CR probability,⁴⁻⁶ age \geq 65 years,⁴⁴ significant pulmonary dysfunction,³⁸ and high e-TRM score^{4,44} (Table 1).

Figure 1. Risk-adapted antifungal strategy. Strategy based on pretreatment and day-15 posttreatment parameters for risk for IFDs in patients with AML undergoing remission-induction therapy. Example shown is for patients at intermediate risk for IFDs.



For these patients, we recommend a mold-active triazole (posaconazole or voriconazole) as primary or secondary prophylaxis, the latter in patients with prior IA or airway colonization with *Aspergillus* species.^{41,49}

Antifungal prophylaxis for AML patients undergoing remission-induction therapy was evaluated in randomized controlled trials (RCTs). In one study, posaconazole recipients had significantly lower rates of IFDs (including IA) and a survival benefit compared with those randomized to fluconazole (or itraconazole).⁵¹ As a result, posaconazole is increasingly used as prophylaxis.⁵² Although voriconazole prophylaxis was not tested in a large RCT in the same setting, it is widely used as prophylaxis because of its efficacy in IA.⁵³ Itraconazole is rarely considered for antifungal prophylaxis because of erratic bioavailability.

Problems associated with prophylaxis with mold-active triazoles include toxicity,⁵⁴ treatment adherence,⁵⁵ and variable bioavailability,⁵⁶ in addition to increasing breakthrough IFDs¹⁵ and a significant decrease in the sensitivity of the s-GMI, the cornerstone of managing IA.⁵⁷

Because of drug-drug interactions between antileukemic agents and mold-active triazoles, it is advisable to start the latter agents 24 hours after the last chemotherapy dose is infused.

In another RCT, prophylaxis with inhaled liposomal amphotericin B (L-AMB) reduced the rate of IPA, although 45% of patients discontinued prophylaxis for at least 1 week.⁵⁸

B) Low-risk group: newly diagnosed young patients (≤ 45 years old) undergoing first remission-induction or consolidation therapy and without risk factors for IFDs. These patients may benefit from fluconazole prophylaxis, particularly if mucotoxicity is expected.³⁶ Serial s-GMI testing is not recommended.

C) Intermediate-risk group: patients not meeting criteria for high- or low-risk groups. A diagnosis-driven preemptive antifungal therapy (DD-AFT) is best suited for these patients, using fluconazole prophylaxis⁵⁹ with a switch to a mold-active agent after s-GMI seroconversion and compatible clinical and radiologic findings.⁶⁰

The DD-AFT was evaluated in an RCT of 240 patients with A-Leuk and recipients of allogeneic hematopoietic cell transplantation randomized to DD-AFT ($n = 118$) or empiric therapy ($n = 122$).⁶¹ Blood samples for s-GMI and *Aspergillus* polymerase chain reaction were collected twice-weekly, and results only made available for DD-AFT recipients to allow mold-active therapy for seroconverters. Compared with empiric therapy, DD-AFT reduced the use of antifungal

agents (15% vs 32%; $P = .002$) and increased the rate of IA diagnosis (15% vs 1%; $P < .001$), with 10 additional cases of IA diagnosed after retrospective analysis of s-GMI and polymerase chain reaction of empirically treated patients.

Several other studies support the DD-AFT strategy.^{60,62,63}

We recommend DD-AFT because it provides earlier and more frequent diagnosis of IA and prompt therapy for fewer patients, thereby reducing drug cost, toxicity, and drug-drug interactions. Moreover, the diagnostic certainty inherent to an *Aspergillus*-specific assay is informative for the type and timing of chemotherapy and the need for secondary prophylaxis.⁵⁰ Figure 1 serves as an example of the DD-AFT management of patients at intermediate-risk for IFDs.

However, empiric therapy (ie, starting an antifungal agent after 4-7 days of antibiotic-refractory FN) is better suited at institutions at which s-GMIs are not resulted within 48 hours. The agent of choice depends on the antifungal prophylaxis received and may consist of an echinocandin, voriconazole, or L-AMB, the latter being the only option for recipients of mold-active prophylaxis because of infections with triazole-resistant molds, including mucormycosis.¹⁵

Dynamic day-15 posttreatment reassessment for risk for IFDs

Low- and intermediate-risk patients may be reclassified as high-risk for IFDs if their day-15 blast count is $\geq 5\%$.⁴⁸ Prophylactic fluconazole is then replaced by a mold-active agent.

Other measures to prevent IFDs

The following 3 measures can reduce the morbidity and mortality of IFDs (Table 1):

1) Improving net state of immunosuppression by corticosteroid-dose reduction,^{25,33} intermediate-dose cytarabine consolidation for patients with favorable cytogenetics,⁴³ and application of better-tolerated regimens; for example, arsenic trioxide with all-*trans*-retinoic acid for acute promyelocytic leukemia,⁶⁴ tyrosine-kinase inhibitors plus corticosteroids for Philadelphia chromosome–positive ALL,⁶⁵ first-line hypomethylating agents for elders with AML/MDS,⁶⁶ and other promising regimens.^{67,68}

A protective role for GM-CSF against infectious-related toxicities is strongly suggested in an RCT of older AML patients undergoing remission-induction therapy.⁶⁹

G-CSF-elicited granulocyte transfusions may serve as a bridge in severely neutropenic patients, in whom neutrophil recovery is not expected within 3 to 4 days.⁷⁰ Interferon γ , GM-CSF, or both may be useful in nonneutropenic patients, although solid evidence for these strategies is lacking.⁷¹

Lastly, unexpectedly prolonged DON requires evaluation to determine whether it is related to one or more concomitant viral infections, particularly cytomegalovirus, among patients treated for ALL.

2) Optimizing organ function, particularly pulmonary, by preventing respiratory viral infections, avoiding sick visitors,⁷² and smoking cessation, particularly among patients with chronic obstructive pulmonary disease³⁸ (Table 1).

3) Decreasing exposure to opportunistic fungi by reducing primarily airborne conidia with high-efficiency particulate air filters in patients' rooms⁷³ and by taking special precautions during any building construction or demolition.⁷⁴ Reducing secondarily airborne conidia from a water source⁷⁵ may also be beneficial.

How do we secure an early diagnosis of IFD?

Common manifestations of IFDs during aplasia

The clinical manifestations of IFDs depend on the site of infection, the severity and dynamic nature of immunosuppression, and the infecting pathogen. Hematogenous dissemination with or without metastatic skin lesions is the usual presentation of yeast infections (eg, *Candida* species), whereas angioinvasion with pneumonia and tissue infarction is the hallmark of mold infections (eg, *Aspergillus* species). A mixed presentation of hematogenous dissemination and angioinvasion occurs with infections caused by molds with adventitious sporulation; that is, those capable of hematogenous dissemination by yeast-like spores (eg, *Fusarium* species).³¹

During aplasia, unexplained fever is the most common presentation of IFDs, followed by pneumonia with or without sinusitis, and less commonly skin/soft tissue or disseminated infection.

Monitoring patients during aplasia includes history and physical examination, daily blood counts and serum C-reactive protein (CRP), and s-GMI thrice-weekly. Serial CRPs are obtained because of the high negative predictive value (NPV) of normal CRP for severe infections,⁷⁶ whereas elevated values can suggest an infectious etiology in patients with IFDs who may not develop fever.⁶⁰ For FN, an infectious disease workup is performed and IV broad-spectrum antibiotics are started. Additional workup is obtained for antibiotic-refractory FN, including chest CT even in the absence of pulmonary findings.⁷⁶ Patients with negative serum fungal biomarkers but with radiologic findings suggestive of IFD should undergo bronchoalveolar lavage (BAL), with testing of BAL fluids for fungal biomarkers. Table 2 shows additional clinical, laboratory, and imaging findings suggestive of IFDs.

Diagnostic tools

Blood cultures have moderate sensitivity for hematogenous infections with yeasts⁷⁷ and molds with adventitious sporulation⁷⁸ but have no sensitivity for IA.¹⁹ Cultures, stains, and histopathology with direct examination of involved sites can be diagnostic (eg, metastatic skin lesions of candidiasis, trichosporonosis,⁷⁹ and fusariosis).^{19,78}

Detecting s-GMI and BAL are particularly helpful in diagnosing IA.^{80,81} The test's performance in neutropenic patients with A-Leuk is excellent,⁸² allowing early diagnosis and treatment days before the overt manifestations of IA.⁶⁰ Early treatment is likely responsible for improved outcomes in IA.⁸³ The kinetics of s-GMI are critical for monitoring response because they correlate with outcome,^{62,84,85} with rapid and solid response predicted when s-GMI normalizes within 1 week after seroconversion,⁶³ and for distinguishing progressive aspergillosis from other infections or PIRIS.⁹ The test's sensitivity, however, is reduced with mold-active prophylaxis.⁵⁷ The occasional problem of false-positive values is minimized when testing is repeated before infusing broad-spectrum antibiotics. The test is also diagnostic in other IMIs such as fusariosis (sensitivity and specificity of 83% and 67%, respectively).⁷⁸ We do not consider this result a false positive but a true positive for an IMI, which can be differentiated from IA by its distinguishing clinical and laboratory findings.¹⁹

Detecting circulating serum 1,3- β -D glucan (s-BDG) may be useful in diagnosing various IFDs, including candidiasis, aspergillosis, fusariosis, and others^{86,87}; for example, s-BDG was positive in all

Table 2. Clinical, laboratory, and radiologic findings suggestive of specific fungal diseases in patients with A-Leuk, shown according to presence or absence of myelosuppression

Findings	During aplasia	After hematopoietic recovery
Hematogenous dissemination: yeasts, mostly <i>Candida</i> species		
Clinical	Hemodynamic instability may develop Skin lesions: painless subcutaneous nodules, maculopapular, pustular, purpura fulminans–like, rarely ecthyma gangrenosum (ulcerative, necrotic) Rarely myalgia, muscular tenderness	Abdominal pain and nausea with CDC ⁹⁵ Chorioretinal lesions, joint and bone pain infections Skin lesions and myalgia less conspicuous than during aplasia
Laboratory	Positive blood cultures, increased s-BDG ^{86,87}	Increased serum alkaline phosphatase in patients with CDC Increased s-BDG ^{86,87,90} with persistent infection
Imaging	Lower yield during aplasia	Multiple lesions in liver, spleen, kidneys on CT scan, ultrasound, or MRI in patients with CDC ⁹⁵
Angioinvasive molds, most commonly <i>Aspergillus</i> species		
Clinical	Pneumonia: dry cough, pleuritic chest pain, pleural rub Sinusitis: facial pain, nasal discharge, hard palate ulceration Skin lesions: maculopapular, pustular, or ecthyma gangrenosum ³¹	Pneumonia: respiratory findings may worsen with neutrophil recovery ⁹ Skin lesions: less conspicuous than during aplasia
Laboratory	Increased s-GMI ± s-BDG ^{82,90} Positive blood cultures represent contamination ³¹	Increased s-GMI ± s-BDG ^{86,87} in patients with persistent infection
Imaging	Chest CT: nodular or wedge-shaped infiltrates or halo sign ⁹³ Earlier nonspecific findings diagnostic if s-GMI is positive ⁸³	Larger nodules, air crescent sign, cavitation, other ⁹⁴ Worsening pulmonary infiltrates with rapid neutrophil recovery ⁹⁴
Angioinvasive molds capable of hematogenous dissemination,³¹ most commonly <i>Fusarium</i> species		
Clinical	Same as angioinvasive molds, but metastatic skin lesions more common, and target skin lesions may be present (<i>Fusarium</i> species) ¹⁹ Cellulitis at sites of skin breakdown: <i>Fusarium</i> species ¹⁹ Myalgia, muscular tenderness: <i>Fusarium</i> species ¹⁹	Same as angioinvasive molds, plus chorioretinal lesions, joint and bone pain infections, similar to features of hematogenous dissemination above
Laboratory	Same as angioinvasive molds, but blood cultures typically positive	Same as angioinvasive molds
Imaging	Same as angioinvasive molds	Same as angioinvasive molds

CDC, chronic disseminated candidiasis; MRI, magnetic resonance imaging.

10 patients with fusariosis and preceded manifestations by 7 days.⁸⁸ s-BDG may also be diagnostic for pneumocytosis, a concern in patients with ALL. However, false-positive s-BDG results are common due to several causes^{86,87} and limit the test's predictive value, although persistently negative results have a high NPV for IFD.⁸⁹ The combination of negative s-GMI⁸⁹ and s-BDG⁹⁰ practically excludes IFDs, except mucormycosis.^{82,90}

Chest CT can suggest a diagnosis of IFD,⁸² although findings vary according to host immunity and may occur with other IMIs⁹¹ and other infectious and noninfectious conditions.⁹² A halo sign⁹³ may suggest early IPA; however, earlier nonspecific findings indicate IPA when serial s-GMI values are elevated.^{60,83} Larger nodules (>1 cm) may develop with subsequent cavitation with or without air crescent sign after neutrophil recovery.⁹⁴ A reversed halo sign may suggest mucormycosis.⁹¹ Abdominal imaging can detect splenic and hepatic nodules suggestive of chronic disseminated candidiasis,⁹⁵ and positron emission tomography may be useful in staging extent and response of IFDs but is not recommended.⁹⁶

How do we treat IFDs?

The same principles outlined in “Other measures to prevent IFDs” are also applicable to treatment. Optimizing antifungal therapy is also critical and encompasses selecting the optimal agent, ensuring adequate drug exposure, managing drug-drug interactions, applying objective parameters for outcome assessment, and providing adequate duration of therapy (DOT). Except for hematogenous candidiasis, secondary prophylaxis is required if additional chemotherapy is planned (Table 3).

Selecting the optimal antifungal agent: an individualized approach

We consider several factors when selecting the antifungal agent, including host, pathogen, drug properties, and infection site or sites (Tables 3 and 4). The indications, dosage schedules of antifungal agents, and other treatment measures are shown in Table 3.

We start IV therapy and switch to an oral agent after improvement, provided treatment adherence is good and gut function is intact (Table 4). We select the oral agent based on recent patient exposure to the same antifungal class, and the agent's expected activity against IFDs. For fungi exhibiting variable susceptibilities (eg, *Fusarium* species⁹⁷ to voriconazole, and mucormycosis to posaconazole), we perform antifungal susceptibility testing and switch to these agents accordingly. For immune enhancement, we decrease corticosteroid doses and consider G-CSF and granulocyte transfusions if neutrophil recovery is not expected within 3 to 4 days, as discussed above.

Echinocandins are the drug of choice for hematogenous candidiasis, despite their limited activity against *C parapsilosis*.⁹⁸ An alternative is fluconazole, L-AMB, and possibly amphotericin B lipid complex. We discourage the use of deoxycholate amphotericin B because of unacceptable toxicity. We do not routinely remove central venous catheters unless the port or tunnel is infected or if candidemia persists after 5 days of adequate treatment, suggesting an endovascular source and therefore requiring central venous catheter removal and significantly longer DOT⁹⁹ (Table 3).

Chronic disseminated candidiasis is treated with the same agents used for hematogenous candidiasis. Oral corticosteroids can accelerate clinical improvement if symptoms persist despite antifungal therapy.¹⁰⁰ Radiologic persistence of lesions is not, by itself, indicative of active infection.

Table 3. Treatment of IFD in patients with A-Leuk

Disease	Drug of choice	Alternative	Comment
Candidemia	Echinocandin: anidulafungin, caspofungin, or micafungin	Fluconazole or L-AMB (3 mg/kg per day)	Anidulafungin (200-mg loading dose, then 100 mg/d) or caspofungin (70-mg loading dose, then 50 mg/d) or micafungin (100 mg/d). Switch to oral agent after a few days when conditions are met. Response criteria: clinical findings, blood cultures, CRP. DOT: 2 wk. If persistent candidemia, rule out endovascular infection (septic thrombophlebitis, endocarditis); remove central venous catheters; and consider switching to another drug class if no response after the above measures. Continue treatment of 2 wk after resolution of clinical findings and normal CRP.
Chronic disseminated candidiasis	L-AMB (3 mg/kg per day)	Echinocandin or fluconazole	Switch to oral agent after a few days when conditions are met. Immune modulation: consider oral corticosteroids (0.5 mg/kg of prednisone) if symptoms persist despite optimal antifungal therapy. ¹⁰⁰ Response criteria: clinical findings, CRP, and s-BDG (if elevated at baseline). Persistence of radiologic lesions is not, by itself, indicative of active infection. DOT: continuous throughout consolidation to prevent possible reactivation.
Aspergillosis	Voriconazole ⁵³ IV (loading 6 mg/kg every 12 h × 2, then 4 mg/kg every 12 h)	L-AMB (3 mg/kg per day)	Switch to oral voriconazole after a few days when conditions are met. Immune modulation: Decrease dose of immunosuppressive agents, particularly corticosteroids. Consider G-CSF and G-CSF-elicited granulocyte transfusions if neutrophil recovery is not expected within 3-4 d. Consider corticosteroids (prednisone 2 mg/kg per day for 2-3 d if early respiratory failure from PIRIS. ⁹ Response criteria: clinical findings, s-GMI ± s-BDG if elevated at baseline, CRP. Radiologic findings may be misleading (e., PIRIS ⁹) and lag behind response. DOT: until recovery from neutropenia, immunosuppression, resolution of clinical findings, and normalization of CRP and s-GMI ± s-BDG (if elevated at baseline).
Fusariosis	L-AMB (3 mg/kg per day) or voriconazole IV at same dose schedule as for aspergillosis	ABLCL (5 mg/kg per day)	Consider adding second agent (voriconazole) if no response after 3-4 d. Switch to oral voriconazole when conditions are met. The role of antifungal susceptibility tests in guiding therapy is not known. Immune modulation: same as for aspergillosis. Response criteria: blood cultures; otherwise, same as for aspergillosis. DOT: same as for aspergillosis.
Mucormycosis	L-AMB (5 mg/kg per day)	ABLCL (5 mg/kg per day) or posaconazole IV (loading 300 mg twice a day on day 1, then 300 mg/d)	Surgical debridement and control of acidosis if present. Switch to oral posaconazole when conditions are met, provided the organism is susceptible to the drug. Delayed-release tablets: loading dose 300 mg orally twice a day on day 1, then 300 mg/d. Oral suspension: 200 mg orally three times a day. Immune modulation: same as for fusariosis. Response criteria: clinical findings, CRP. DOT: until recovery from neutropenia, immunosuppression, resolution of clinical findings, and normalization of CRP.

The DOT should be individualized. Switching to oral therapy requires good treatment adherence and intact gut function. Except for hematogenous candidiasis, secondary prophylaxis is required if additional chemotherapy is planned. ABLCL, amphotericin B lipid complex.

Voriconazole is the drug of choice for aspergillosis,⁵³ with L-AMB¹⁰¹ as an alternative. A benefit from combination therapy is suggested by the findings of a RCT in which a nonsignificant trend ($P = .08$) for the primary end point (death at 6 weeks) favored voriconazole plus anidulafungin vs voriconazole plus placebo.¹⁰² This limited benefit is likely related to selecting a non-*Aspergillus*-specific end point.

Worsening pulmonary infiltrates⁹⁴ coinciding with neutrophil recovery likely represents PIRIS,⁹ which is distinguished from progressive aspergillosis by a normal s-GMI.⁶³

The outcome of invasive fusariosis remains largely dependent on persistent neutropenia, corticosteroid-induced immunosuppression,

or both.³³ Treatment options are shown in Table 3, with little data to support any of these choices. We start L-AMB or voriconazole (Table 3) and add the second drug in the absence of clinical response. After improvement, we switch to oral voriconazole if the organism is susceptible.⁹⁷

We treat mucormycosis with L-AMB, debridement of necrotic tissue, and correction of metabolic abnormalities.¹⁰³ Upon response, we add posaconazole if the organism is susceptible and continue both agents for 1 week to ensure steady-state plasma posaconazole concentrations (PPCs) and then discontinue L-AMB.

Table 4. Practical considerations for individualized selection of antifungal agents for patients with A-Leuk

Factors	Setting	Agent of choice, alternatives, and route
Host-related		
Hemodynamic instability	Hematogenous candidiasis	Echinocandin; fluconazole and L-AMB as alternatives
Organ dysfunction, severe		
Gastrointestinal tract	Mucositis, nausea, vomiting, diarrhea, poor adherence, drug-food interaction	IV route
Kidneys	Tumor lysis syndrome	Azoles, echinocandin; avoid amphotericin B products
Liver		Echinocandin, L-AMB, ABLC; avoid azoles
Drug-related		
Drug-drug interaction	Chemotherapy administration	Echinocandin, L-AMB, ABLC; avoid mold-active triazoles
Drug-food interaction	Food intake	Echinocandin, L-AMB, fluconazole IV; food intake may alter absorption of azoles
Breakthrough infection	Infection while on antifungal agent	Use different class of antifungal agents
Cost and convenience	Outpatient setting	Oral route always preferable to IV if gut function intact Select agent with longest dosing interval
Infection-related		
Site of infection	Urinary Ocular CNS	Fluconazole: only agent with urinary concentrations Triazoles, L-AMB; avoid echinocandins (poor distribution) Triazoles, L-AMB; avoid echinocandins (poor distribution)
Pathogen		
<i>Candida</i> species	Disseminated, acute and chronic	Echinocandin, fluconazole, L-AMB
<i>C krusei</i>	Disseminated, acute and chronic	Echinocandin, L-AMB; avoid fluconazole
<i>C glabrata</i>	Disseminated, acute and chronic	Echinocandin, L-AMB, voriconazole; avoid fluconazole
<i>C parapsilosis</i>	Disseminated, acute and chronic	L-AMB, voriconazole; avoid echinocandins
<i>Trichosporon</i> spp	Disseminated, acute and chronic	Fluconazole, other azoles; amphotericin B not effective
<i>Aspergillus</i> spp	Sinus, pulmonary, disseminated	Voriconazole, L-AMB, ABLC; no role for fluconazole
<i>Aspergillus flavus</i>	Sinus, pulmonary, disseminated	Voriconazole; posaconazole alternative
<i>Fusarium</i> spp	Sinus, pulmonary, cellulitis, disseminated	L-AMB, ABLC; voriconazole maintenance if susceptible
<i>Scedosporium apiospermum</i>	Sinus, pulmonary, ocular, CNS, bone and soft tissues, disseminated	Voriconazole; posaconazole alternative
Black molds	Various sites	Voriconazole; posaconazole alternative
Agents of mucormycosis	Sinus, pulmonary, disseminated	L-AMB, ABLC; posaconazole maintenance if susceptible

Antifungal agents include triazoles (fluconazole, voriconazole, posaconazole, and itraconazole), echinocandins (anidulafungin, caspofungin, and micafungin), and amphotericin B and its lipid formulations: L-AMB and ABLC. Severe organ dysfunction refers to grade ≥ 3 according to common toxicity criteria for adverse events (version 3.0). CNS, central nervous system.

Ensuring adequate drug exposure: any role for therapeutic drug monitoring?

The PPCs in patients with A-Leuk are significantly decreased in the presence of mucositis or diarrhea,^{56,104,105} poor food intake,¹⁰⁵ and concomitant receipt of proton pump inhibitors⁵⁶ or chemotherapeutic agents.¹⁰⁵ Lower PPCs have been associated with increased IFDs.¹⁰⁴ Compared with oral posaconazole solution, a once-daily tablet significantly improves bioavailability.¹⁰⁶ Posaconazole is now available intravenously. Voriconazole is available orally and intravenously and its plasma concentrations vary according to genotype and drug interactions; eg, voriconazole plasma concentrations are significantly decreased with coadministration of glucocorticoids.¹⁰⁷

The role of therapeutic drug monitoring for oral triazoles is unclear because the optimal concentrations remain to be defined and consistently correlated with clinical efficacy. We perform therapeutic drug monitoring when oral triazoles are given as prophylaxis for patients at high-risk for IFD and for the treatment of IFD, when concerns exist about gut function, triazole-related toxicity, or unexplained therapeutic failure.

Managing drug-drug interactions

Different interactions with triazoles must be considered,¹⁰⁴ and consultation with a pharmacist is recommended.

1) Interactions in which triazoles affect other drugs,¹⁰⁸ requiring monitoring for clinical toxicity and toxic-range blood levels

(eg, all-*trans*-retinoic acid, etoposide, vincristine,¹⁰⁹ ifosfamide, and cyclophosphamide).¹⁰⁸

2) Interactions in which other agents such as phenytoin, rifampin, and others decrease or increase triazole exposure (eg, protease inhibitors causing subtherapeutic or supratherapeutic levels of the antifungal agent).

Objective assessment of treatment response

Assessment of IFD response relies on clinical evaluation (fever, metastatic lesions, and others), quantitative laboratory tests (s-GMI, s-BDG, and CRP), and to a lesser extent imaging studies due to the presence of confounding variables and their lag-behind response⁹⁶ (Table 3).

How long do we treat an IFD?

The DOT is dictated by resolution of the IFD and recovery from neutropenia (ANC $> 1000/\mu\text{L}$), immunosuppression, or both. Evidence-based guidelines for DOT in immunosuppressed non-neutropenic patients are limited,¹¹⁰ and extrapolation from guidelines for HIV-positive patients is suggested.¹¹¹ When CD4 cells are not measured, we use the absolute lymphocyte count (ALC) to gauge severity of immunosuppression and consider it moderate if ALC is persistently $\leq 1000/\mu\text{L}$, and severe if ALC is persistently $\leq 300/\mu\text{L}$. Ideally, antifungal agents are stopped when the IFD resolves and ALC is consistently $\geq 1000/\mu\text{L}$,

absent other causes for lymphocytosis or lymphopenia, such as infections.

When is it safe to start/resume antileukemic therapy in patients diagnosed with an IFD?

A diagnosis of IFD delays chemotherapy and may compromise outcome.⁴⁹ Hence, careful evaluation of the activity of IFD prior to commencing chemotherapy is critical and relies on objective parameters including fever, s-GMI,⁶³ s-BDG, and CRP. Persistence of some imaging abnormalities does not imply active infection.⁹⁶ In patients with negative s-GMI, s-BDG, or both at diagnosis, we rely on clinical and radiologic findings and normal CRP values to exclude IFD.

If an IFD is diagnosed, antifungal treatment should be started immediately and chemotherapy delayed until the IFD is controlled, except in rare settings requiring urgent antileukemic intervention. Cytoreduction for elevated peripheral blast count can be achieved with oral hydroxyurea.

How do we manage refractory IFDs?

Failure to respond to antifungal therapy is not uncommon in patients with A-Leuk¹¹² and is related to persistent profound myelosuppression, immunosuppression, or both. Measures to enhance immunity in "Other measures to prevent IFDs" can be considered. However, every attempt should be made to exclude other causes, including wrong diagnosis (eg, PIRIS),⁹ mixed fungal and nonfungal infections, suboptimal dose schedule of antifungal agents, and residual effects of IFDs such as persistent neurologic deficits after cerebral infarcts caused by

angioinvasive molds. Although acquired drug resistance is rare, primary resistance of *Aspergillus* species to azoles is an emerging problem in some European countries.¹¹³

Conclusions and future directions

IFDs represent an important cause of treatment failure in adults with A-Leuk. Because of leukemia's heterogeneity, the risk for IFDs is highly variable. We therefore apply a risk-adapted antifungal strategy with strong emphasis on pretreatment and posttreatment variables to allow earlier and more individualized interventions.

Based on pretreatment factors related to host, leukemia, treatment regimen, and fungal exposure, we stratify patients as high, intermediate, or low risk for IFDs and apply measures to prevent and monitor IFDs accordingly. A day-15 blast evaluation allows further risk stratification. Patients at high risk for IFDs who have unfavorable biology or are unfit for therapy can benefit from less-toxic anti-leukemic regimens.⁶⁴⁻⁶⁸

Novel targeted therapies that can achieve higher rates of sustained CR among patients with adverse genetics offer the best promise for reducing the burden of IFDs in these patients.

Authorship

M.N. and E.A. wrote and edited the manuscript.

Conflict-of-interest disclosure: M.N. has received honoraria from Merck, Pfizer, Gilead, and Astellas. E.A. has received honoraria from Astellas, Onix, and Millenium.

Correspondence: Elias Anaissie, Hoxworth Center, 3130 Highland Ave, 3rd Floor, Cincinnati, OH, 45219-2316; e-mail: elias114@aol.com or anaissieeliasj@gmail.com.

References

- Lichtman MA. A historical perspective on the development of the cytarabine (7days) and daunorubicin (3days) treatment regimen for acute myelogenous leukemia: 2013 the 40th anniversary of 7+3. *Blood Cells Mol Dis*. 2013; 50(2):119-130.
- Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol*. 2013;50(3):185-196.
- Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol*. 2011;29(5):487-494.
- Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006; 106(5):1090-1098.
- Döhner H, Estey EH, Amadori S, et al; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-474.
- Chiaretti S, Vitale A, Cazzaniga G, et al. Clinicobiological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. *Haematologica*. 2013;98(11):1702-1710.
- Estey EH. Acute myeloid leukemia: 2013 update on risk-stratification and management. *Am J Hematol*. 2013;88(4):318-327.
- Walter RB, Estey EH. Management of older or unfit patients with acute myeloid leukemia. *Leukemia*. 2014;(Jul 9).
- Miceli MH, Maertens J, Buvé K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. *Cancer*. 2007;110(1):112-120.
- Uzun O, Anaissie EJ. Antifungal prophylaxis in patients with hematologic malignancies: a reappraisal. *Blood*. 1995;86(6):2063-2072.
- Bodey G, Buehlmann B, Duguid W, et al. Fungal infections in cancer patients: an international autopsy survey. *Eur J Clin Microbiol Infect Dis*. 1992;11(2):99-109.
- Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis*. 1997;24(6): 1122-1128.
- Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica*. 2006;91(8):1068-1075.
- Nucci M, Garnica M, Gloria AB, et al. Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. *Clin Microbiol Infect*. 2013;19(8):745-751.
- Auberger J, Lass-Flörl C, Aigner M, Clausen J, Gastl G, Nachbaur D. Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: real-life data from a single-centre institutional retrospective observational study. *J Antimicrob Chemother*. 2012;67(9):2268-2273.
- van der Linden JW, Camps SM, Kampinga GA, et al. Aspergillosis due to voriconazole highly resistant *Aspergillus fumigatus* and recovery of genetically related resistant isolates from domiciles. *Clin Infect Dis*. 2013;57(4):513-520.
- Alastruey-Izquierdo A, Mellado E, Peláez T, et al; FILPOP Study Group. Population-based survey of filamentous fungi and antifungal resistance in Spain (FILPOP Study). *Antimicrob Agents Chemother*. 2013;57(7):3380-3387.
- Heath CH, Slavin MA, Sorrell TC, et al; Australian Scedosporium Study Group. Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of *Scedosporium aurantiacum* infection. *Clin Microbiol Infect*. 2009;15(7):689-693.
- Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood*. 1997;90(3):999-1008.
- Panackal AA, Li H, Kontoyiannis DP, et al. Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2010;50(12):1588-1597.

21. Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic molds (including *Aspergillus* species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies. *Blood*. 2003;101(7):2542-2546.
22. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic fusarium species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. *Clin Infect Dis*. 2001;33(11):1871-1878.
23. Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic *Aspergillus* species recovered from a hospital water system: a 3-year prospective study. *Clin Infect Dis*. 2002;34(6):780-789.
24. Lortholary O, Gangneux JP, Sitbon K, et al; French Mycosis Study Group. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005-2007). *Clin Microbiol Infect*. 2011;17(12):1882-1889.
25. Walsh TJ, Anaissie EJ, Denning DW, et al; Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327-360.
26. Chabrol A, Cuzin L, Huguot F, et al. Prophylaxis of invasive aspergillosis with voriconazole or caspofungin during building work in patients with acute leukemia. *Haematologica*. 2010;95(6):996-1003.
27. Cannas G, Pautas C, Raffoux E, et al. Infectious complications in adult acute myeloid leukemia: analysis of the Acute Leukemia French Association-9802 prospective multicenter clinical trial. *Leuk Lymphoma*. 2012;53(6):1068-1076.
28. Henden A, Morris K, Truloff N, Nakagaki M, Kennedy GA. Incidence and outcomes of invasive fungal disease in adult patients with acute lymphoblastic leukemia treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone: implications for prophylaxis. *Leuk Lymphoma*. 2013;54(6):1329-1331.
29. O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer*. 2008;113(8):2097-2101.
30. Weiser MA, Cabanillas ME, Konopleva M, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate-cytarabine regimen. *Cancer*. 2004;100(6):1179-1185.
31. Anaissie E, Graziutti M, Nucci M. Invasive fungal infections in cancer patients. In: Anaissie EJ, McGinnis MR, Pfaller MA, eds. *Clinical Mycology*. 2nd ed. Philadelphia: Elsevier; 2009:431-471.
32. Michallet M, Sobh M, Morisset S, et al. Risk factors for invasive aspergillosis in acute myeloid leukemia patients prophylactically treated with posaconazole. *Med Mycol*. 2011;49(7):681-687.
33. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. *Cancer*. 2003;98(2):315-319.
34. Fianchi L, Leone G, Posteraro B, et al. Impaired bactericidal and fungicidal activities of neutrophils in patients with myelodysplastic syndrome. *Leuk Res*. 2012;36(3):331-333.
35. van de Peppel RJ, Dekkers OM, von dem Borne PA, de Boer MG. Relapsed and secondary disease drive the risk profile for invasive aspergillosis prior to stem cell transplantation in patients with acute myeloid leukemia or myelodysplastic syndrome. *Med Mycol*. 2014;52(7):699-705.
36. Bow EJ, Meddings JB. Intestinal mucosal dysfunction and infection during remission-induction therapy for acute myeloid leukaemia. *Leukemia*. 2006;20(12):2087-2092.
37. Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? *Clin Infect Dis*. 2001;33(12):1959-1967.
38. Guinea J, Torres-Narbona M, Gijón P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect*. 2010;16(7):870-877.
39. Verweij PE, Kerremans JJ, Voss A, Meis JF. Fungal contamination of tobacco and marijuana. *JAMA*. 2000;284(22):2875.
40. Martino P, Girmenia C, Micozzi A, De Bernardis F, Boccanera M, Cassone A. Prospective study of *Candida* colonization, use of empiric amphotericin B and development of invasive mycosis in neutropenic patients. *Eur J Clin Microbiol Infect Dis*. 1994;13(10):797-804.
41. Martino P, Raccan R, Gentile G, Venditti M, Girmenia C, Mandelli F. Aspergillus colonization of the nose and pulmonary aspergillosis in neutropenic patients: a retrospective study. *Haematologica*. 1989;74(3):263-265.
42. Krug U, Röhlig C, Koschmieder A, et al; German Acute Myeloid Leukaemia Cooperative Group; Study Alliance Leukemia Investigators. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet*. 2010;376(9757):2000-2008.
43. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013;381(9865):484-495.
44. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4423.
45. Garcia-Garcia FJ, Carcaillon L, Fernandez-Tresguerres J, et al. A new operational definition of frailty: the frailty trait scale. *J Am Med Dir Assoc*. 2014;15(5):371.e7-e371.e13.
46. Pastore F, Dufour A, Benthaus T, et al. Combined molecular and clinical prognostic index for relapse and survival in cytogenetically normal acute myeloid leukemia. *J Clin Oncol*. 2014;32(15):1586-1594.
47. Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis*. 2008;47(9):1176-1184.
48. Bertoli S, Bories P, Béné MC, et al; Groupe Ouest-Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang (GOELAMS). Prognostic impact of day 15 blast clearance in risk-adapted remission induction chemotherapy for younger patients with acute myeloid leukemia: long-term results of the multicenter prospective LAM-2001 trial by the GOELAMS study group. *Haematologica*. 2014;99(1):46-53.
49. Even C, Bastuji-Garin S, Hicheri Y, et al. Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study. *Haematologica*. 2011;96(2):337-341.
50. Cordonnier C, Maury S, Pautas C, et al. Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. *Bone Marrow Transplant*. 2004;33(9):943-948.
51. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348-359.
52. Vehreschild JJ, Rüpung MJ, Wisplinghoff H, et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. *J Antimicrob Chemother*. 2010;65(7):1466-1471.
53. Herbrecht R, Denning DW, Patterson TF, et al; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408-415.
54. Gerber B, Guggenberger R, Fasler D, et al. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. *Blood*. 2012;120(12):2390-2394.
55. Glasmacher A, Cornely O, Ullmann AJ, et al; Itraconazole Research Group of Germany. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. *J Antimicrob Chemother*. 2006;57(2):317-325.
56. Vehreschild JJ, Müller C, Farowski F, et al. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. *Eur J Clin Pharmacol*. 2012;68(6):987-995.
57. McCulloch E, Ramage G, Rajendran R, et al. Antifungal treatment affects the laboratory diagnosis of invasive aspergillosis. *J Clin Pathol*. 2012;65(1):83-86.
58. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2008;46(9):1401-1408.
59. Rex JH, Anaissie EJ, Boutati E, Estey E, Kantarjian H. Systemic antifungal prophylaxis reduces invasive fungal in acute myelogenous leukemia: a retrospective review of 833 episodes of neutropenia in 322 adults. *Leukemia*. 2002;16(6):1197-1199.
60. Nucci M, Nouér SA, Graziutti M, Kumar NS, Barlogie B, Anaissie E. Probable invasive aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. *Clin Infect Dis*. 2010;51(11):1273-1280.
61. Morrissey CO, Chen SC, Sorrell TC, et al; Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. *Lancet Infect Dis*. 2013;13(6):519-528.
62. Nouér SA, Nucci M, Kumar NS, Graziutti M, Barlogie B, Anaissie E. Earlier response assessment in invasive aspergillosis based on the kinetics of serum *Aspergillus* galactomannan: proposal for a new definition. *Clin Infect Dis*. 2011;53(7):671-676.
63. Nouér SA, Nucci M, Kumar NS, Graziutti M, Restrepo A, Anaissie E. Baseline platelet count and creatinine clearance rate predict the outcome of neutropenia-related invasive

- aspergillosis. *Clin Infect Dis*. 2012;54(12):e173-e183.
64. Lo-Coco F, Avvisati G, Vignetti M, et al; Gruppo Italiano Malattie Ematologiche dell'Adulto; German-Austrian Acute Myeloid Leukemia Study Group; Study Alliance Leukemia. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369(2):111-121.
 65. Foà R, Vitale A, Vignetti M, et al; GIMEMA Acute Leukemia Working Party. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2011;118(25):6521-6528.
 66. Falantes JF, Calderón C, Márquez-Malaver FJ, et al. Patterns of infection in patients with myelodysplastic syndromes and acute myeloid leukemia receiving azacitidine as salvage therapy. Implications for primary antifungal prophylaxis. *Clin Lymphoma Myeloma Leuk*. 2014;14(1):80-86.
 67. Kantarjian HM, O'Brien S, Cortes J. Homoharringtonine/omacetaxine mepesuccinate: the long and winding road to food and drug administration approval. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):530-533.
 68. Ghanem H, Kantarjian H, Ohanian M, Jabbour E. The role of clofarabine in acute myeloid leukemia. *Leuk Lymphoma*. 2013;54(4):688-698.
 69. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). *Blood*. 1995;86(2):457-462.
 70. Dignani MC, Anaissie EJ, Hester JP, et al. Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: a pilot study. *Leukemia*. 1997;11(10):1621-1630.
 71. Anaissie EJ. Diagnosis and therapy of fungal infection in patients with leukemia—new drugs and immunotherapy. *Best Pract Res Clin Haematol*. 2008;21(4):683-690.
 72. Engelhard D, Mohty B, de la Camara R, Cordonnier C, Ljungman P. European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN. *Transpl Infect Dis*. 2013;15(3):219-232.
 73. Abdul Salam ZH, Karlin RB, Ling ML, Yang KS. The impact of portable high-efficiency particulate air filters on the incidence of invasive aspergillosis in a large acute tertiary-care hospital. *Am J Infect Control*. 2010;38(4):e1-e7.
 74. Haiduvan D. Nosocomial aspergillosis and building construction. *Med Mycol*. 2009;47(Suppl 1):S210-S216.
 75. Anaissie EJ, Stratton SL, Dignani MC, et al. Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized *Aspergillus* species and other opportunistic molds. *Clin Infect Dis*. 2002;35(8):E86-E88.
 76. Prat C, Sancho JM, Dominguez J, et al. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. *Leuk Lymphoma*. 2008;49(9):1752-1761.
 77. Kami M, Machida U, Okuzumi K, et al. Effect of fluconazole prophylaxis on fungal blood cultures: an autopsy-based study involving 720 patients with haematological malignancy. *Br J Haematol*. 2002;117(1):40-46.
 78. Nucci M, Carlesse F, Cappellano P, et al. Earlier diagnosis of invasive fusariosis with *Aspergillus* serum galactomannan testing. *PLoS ONE*. 2014;9(1):e87784.
 79. Anaissie E, Gokaslan A, Hachem R, et al. Azole therapy for trichosporonosis: clinical evaluation of eight patients, experimental therapy for murine infection, and review. *Clin Infect Dis*. 1992;15(5):781-787.
 80. Maertens J, Verhaegen J, Demuyck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive *Aspergillus*. *J Clin Microbiol*. 1999;37(10):3223-3228.
 81. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. *Clin Infect Dis*. 2009;49(11):1688-1693.
 82. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis*. 2005;41(9):1242-1250.
 83. Nucci M, Nouér SA, Cappone D, Anaissie E. Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome. *Haematologica*. 2013;98(11):1657-1660.
 84. Miceli MH, Graziutti ML, Woods G, et al. Strong correlation between serum *Aspergillus* galactomannan index and outcome of aspergillosis in patients with hematological cancer: clinical and research implications. *Clin Infect Dis*. 2008;46(9):1412-1422.
 85. Woods G, Miceli MH, Graziutti ML, Zhao W, Barlogie B, Anaissie E. Serum *Aspergillus* galactomannan antigen values strongly correlate with outcome of invasive aspergillosis: a study of 56 patients with hematologic cancer. *Cancer*. 2007;110(4):830-834.
 86. Lamoth F, Cruciani M, Mengoli C, et al; Third European Conference on Infections in Leukemia (ECIL-3). β -Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). *Clin Infect Dis*. 2012;54(5):633-643.
 87. Sulahian A, Porcher R, Bergeron A, et al. Use and limits of (1-3)- β -D-glucan assay (Fungitell), compared to galactomannan determination (*Platelia Aspergillus*), for diagnosis of invasive aspergillosis. *J Clin Microbiol*. 2014;52(7):2328-2333.
 88. Nucci M, Garnica M, Reis H, et al. Performance of 1,3-beta-D-glucan (BDG) in the diagnosis and monitoring of invasive fusariosis [abstract]. Paper presented at the 23rd European Congress of Clinical Microbiology and Infectious Diseases. April 27-30, 2013. Berlin, Germany. Abstract O-166.
 89. Marchetti O, Lamoth F, Mikulska M, Viscoli C, Verweij P, Bretagne S; European Conference on Infections in Leukemia (ECIL) Laboratory Working Groups. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. *Bone Marrow Transplant*. 2012;47(6):846-854.
 90. Theel ES, Doern CD. β -D-glucan testing is important for diagnosis of invasive fungal infections. *J Clin Microbiol*. 2013;51(11):3478-3483.
 91. Legouge C, Caillot D, Chrétien ML, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? *Clin Infect Dis*. 2014;58(5):672-678.
 92. Escuissato DL, Gasparetto EL, Marchiori E, et al. Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. *AJR Am J Roentgenol*. 2005;185(3):608-615.
 93. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*. 1997;15(1):139-147.
 94. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol*. 2001;19(1):253-259.
 95. Anaissie E, Bodey GP, Kantarjian H, et al. Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. *Am J Med*. 1991;91(2):142-150.
 96. Mahfouz T, Miceli MH, Saghaifir F, et al. 18F-fluorodeoxyglucose positron emission tomography contributes to the diagnosis and management of infections in patients with multiple myeloma: a study of 165 infectious episodes. *J Clin Oncol*. 2005;23(31):7857-7863.
 97. Debourgogne A, de Hoog S, Lozniewski A, Machouart M. Amphotericin B and voriconazole susceptibility profiles for the *Fusarium solani* species complex: comparison between the E-test and CLSI M38-A2 microdilution methodology. *Eur J Clin Microbiol Infect Dis*. 2012;31(4):615-618.
 98. Ruhnke M, Paiva JA, Meersseman W, et al. Anidulafungin for the treatment of candidaemia/ invasive candidiasis in selected critically ill patients. *Clin Microbiol Infect*. 2012;18(7):680-687.
 99. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. *Clin Infect Dis*. 2010;51(3):295-303.
 100. Legrand F, Lecuit M, Dupont B, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. *Clin Infect Dis*. 2008;46(5):696-702.
 101. Cornely OA, Maertens J, Bresnik M, et al; AmBiLoad Trial Study Group. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis*. 2007;44(10):1289-1297.
 102. Marr KA, Schlamm H, Rottinghaus S, et al. A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis [abstract]. *Clin Microbiol Infect*. 2012;18:713.
 103. Skiada A, Lanternier F, Groll AH, et al; European Conference on Infections in Leukemia. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica*. 2013;98(4):492-504.
 104. Cojutti P, Candoni A, Simeone E, Franceschi L, Fanin R, Pea F. Antifungal prophylaxis with posaconazole in patients with acute myeloid leukemia: dose intensification coupled with avoidance of proton pump inhibitors is beneficial in shortening time to effective concentrations. *Antimicrob Agents Chemother*. 2013;57(12):6081-6084.

105. Vaes M, Hites M, Cotton F, et al. Therapeutic drug monitoring of posaconazole in patients with acute myeloid leukemia or myelodysplastic syndrome. *Antimicrob Agents Chemother.* 2012; 56(12):6298-6303.
106. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob Chemother.* 2012; 67(11):2725-2730.
107. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother.* 2012;56(9):4793-4799.
108. Gubbins P, Anaissie EJ. Antifungal therapy. In: Anaissie EJ, McGinnis MR, Pfaller MA, eds. *Clinical Mycology*. 2nd ed. Philadelphia: Churchill Livingstone; 2009:161-195.
109. Harnicar S, Adel N, Jurcic J. Modification of vincristine dosing during concomitant azole therapy in adult acute lymphoblastic leukemia patients. *J Oncol Pharm Pract.* 2009;15(3): 175-182.
110. Anaissie EJ, Kontoyiannis DP, O'Brien S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med.* 1998;129(7):559-566.
111. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA; Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;58(1): 1-10.
112. Nucci M, Perfect JR. When primary antifungal therapy fails. *Clin Infect Dis.* 2008;46(9): 1426-1433.
113. van der Linden JW, Snelders E, Kampinga GA, et al. Clinical implications of azole resistance in *Aspergillus fumigatus*, The Netherlands, 2007-2009. *Emerg Infect Dis.* 2011;17(10): 1846-1854.
114. Giebel S, Thomas X, Hallbook H, et al. The prophylactic use of granulocyte-colony stimulating factor during remission induction is associated with increased leukaemia-free survival of adults with acute lymphoblastic leukaemia: a joint analysis of five randomised trials on behalf of the EWALL. *Eur J Cancer.* 2012;48(3):360-367.
115. Ravandi F, Faderl S, Kebriaei P, Kantarjian H. Modern treatment programs for adults with acute lymphoblastic leukemia. *Curr Hematol Malign Rep.* 2007;2(3):169-175.
116. Patrick K, Wade R, Goulden N, et al. Outcome of Down syndrome associated acute lymphoblastic leukaemia treated on a contemporary protocol. *Br J Haematol.* 2014;165(4):552-555.
117. Emadi A, Karp JE. The clinically relevant pharmacogenomic changes in acute myelogenous leukemia. *Pharmacogenomics.* 2012;13(11):1257-1269.
118. Meyers J, Yu Y, Kaye JA, Davis KL. Medicare fee-for-service enrollees with primary acute myeloid leukemia: an analysis of treatment patterns, survival, and healthcare resource utilization and costs. *Appl Health Econ Health Policy.* 2013;11(3): 275-286.
119. Garcia-Vidal C, Barba P, Arnan M, et al. Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. *Clin Infect Dis.* 2011;53(6):e16-e19.
120. Sørensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer.* 1993;67(4):773-775.
121. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood.* 2013;121(21): 4287-4294.
122. Dare JM, Moppett JP, Shield JP, Hunt LP, Stevens MC. The impact of hyperglycemia on risk of infection and early death during induction therapy for acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer.* 2013; 60(12):E157-E159.
123. Gamaletsou MN, Walsh TJ, Zaoutis T, et al. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. *Clin Microbiol Infect.* 2014;20(1):O50-O57.



blood[®]

2014 124: 3858-3869
doi:10.1182/blood-2014-04-516211 originally published
online October 22, 2014

How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach

Marcio Nucci and Elias Anaissie

Updated information and services can be found at:

<http://www.bloodjournal.org/content/124/26/3858.full.html>

Articles on similar topics can be found in the following Blood collections

[Clinical Trials and Observations](#) (4711 articles)
[Free Research Articles](#) (4901 articles)
[How I Treat](#) (213 articles)
[Immunobiology and Immunotherapy](#) (5564 articles)
[Lymphoid Neoplasia](#) (2723 articles)
[Myeloid Neoplasia](#) (1793 articles)

Information about reproducing this article in parts or in its entirety may be found online at:

http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:

<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:

<http://www.bloodjournal.org/site/subscriptions/index.xhtml>