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

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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 μL. 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/μL), 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

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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 $<100/\mu L$, $\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 immunosuppression[28] 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 IC[36] because *Candida* species are normal colonizers of gut mucosa,[37] whereas preexisting lung pathology, including chronic obstructive pulmonary disease[38] 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* species[40] and airway colonization by *Aspergillus* species[41] 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 $>1000/\mu L$, failure to enter remission is associated with longer DON and higher rates of severe infections, including IFDs[32] 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 immunosupression	
Leukemia-related	
*Lower probability of CR[32]	
AML: adverse cytogenetic/gene mutation profiles, WBC ≥50 000/μL, secondary leukemia, MDS or antecedent hematologic disorder >6 mo[4,5]	Assess probability of CR and e-TRM[42,43] Determine risk for IFDs: high, intermediate, or low, and manage accordingly.
ALL: adverse cytogenetic/gene mutation profiles, WBC ≥30 000/μL, immunophenotype[6]	Primary mold-active prophylaxis for high-risk patients. Serial s-GMI tests Lower cytarabine consolidation for patients with favorable cytogenetics[43] Better-tolerated antileukemic regiments if high risk for e-TRM[64-68]
*Baseline neutropenia	
ANC <500/μL for ≥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 (≥3 wk of >1 mg/kg per d of prednisone equivalent)[25,33]	Reduce corticosteroid dose, provide antifungal and *Pneumocystis* 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 ± airway colonization by *Aspergillus* 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 immunosupression	
Neutropenia, severe and prolonged[35] (ANC <100/μL 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	Day-15 bone marrow biopsy for blast clearance and MRD[48]
ALL: no CR in 4 wk, persistent MRD[32,48]	G-CSF for patients with ALL[114] and G-CSF for those with AML[69]
Persistent lymphopenia (cells <300 μL) with normal WBC/ANC	Reduce corticosteroid dose, antifungal and *Pneumocystis* prophylaxis
Organ dysfunction	
*Mucositis[36]	
Severe, grade ≥3 for ≥7 d, especially if involving lower gut	Fluconazole prophylaxis
Exposure to pathogenic fungi	
Same as pretreatment	Same as pretreatment
*Multisite colonization by *Candida* 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 ≥65 years,[44] significant pulmonary dysfunction,[38] and high e-TRM score[4,44] (Table 1).

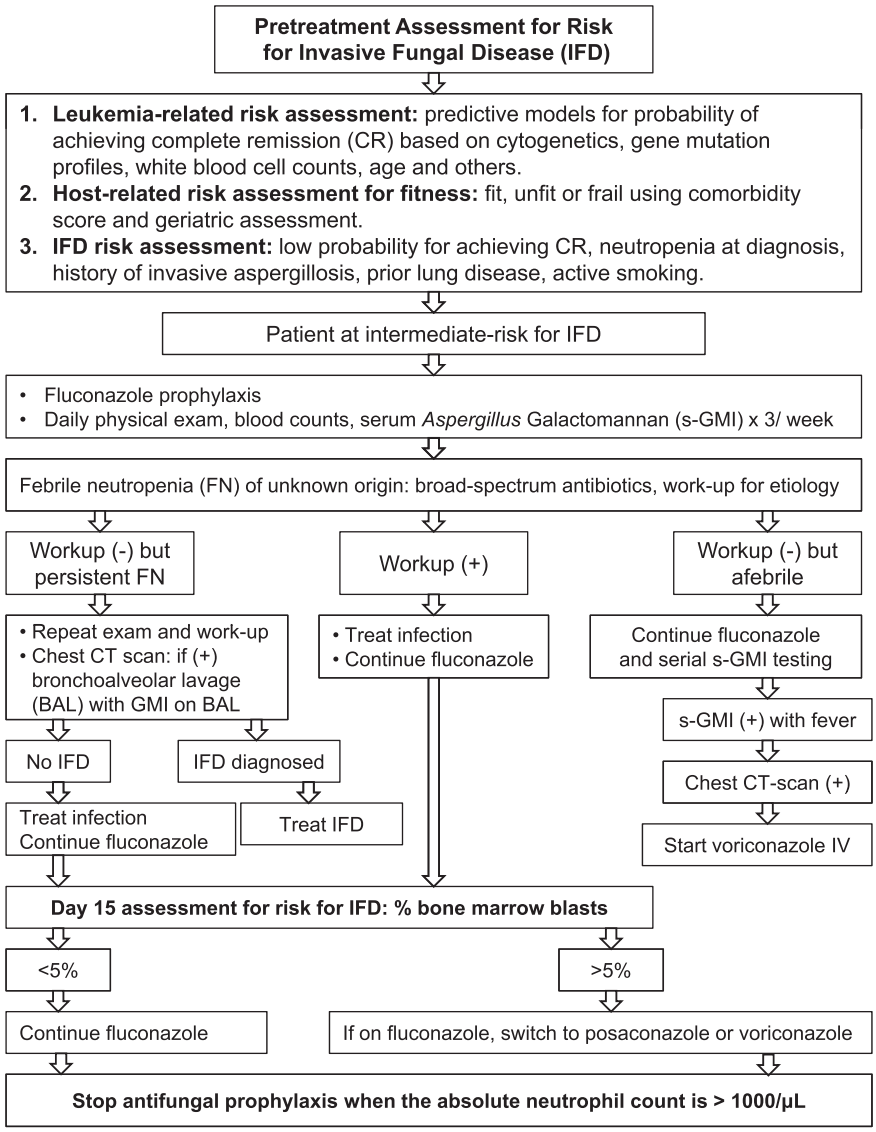

Figure 1. Risk-adapted antifungal strategy. Strategy based on pretreatment and day-15 posttreatment parameters for risk for IFDs in patients with AML undergoing remission-induction therapy. Example shown is for patients at intermediate risk for IFDs.

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 IFDs[15] 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 prophylaxis[59] 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 ≥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 disease[38] (Table 1).

3) Decreasing exposure to opportunistic fungi by reducing primarily airborne conidia with high-efficiency particulate air filters in patients' rooms[73] and by taking special precautions during any building construction or demolition.[74] Reducing secondarily airborne conidia from a water source[75] 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 yeasts[77] and molds with adventitious sporulation[78] 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 *Candida* species		
Clinical	Hemodynamic instability may develop	Abdominal pain and nausea with CDC[95]
	Skin lesions: painless subcutaneous nodules, maculopapular, pustular, purpura fulminans–like, rarely ecthyma gangrenosum (ulcerative, necrotic)	Chorioretinal lesions, joint and bone pain infections
		Skin lesions and myalgia less conspicuous than during aplasia
	Rarely myalgia, muscular tenderness	
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 *Aspergillus* species		
Clinical	Pneumonia: dry cough, pleuritic chest pain, pleural rub	Pneumonia: respiratory findings may worsen with neutrophil recovery[9]
	Sinusitis: facial pain, nasal discharge, hard palate ulceration	Skin lesions: less conspicuous than during aplasia
	Skin lesions: maculopapular, pustular, or ecthyma gangrenosum[31]	
Laboratory	Increased s-GMI ± s-BDG[82,90]	Increased s-GMI ± s-BDG[86,87] in patients with persistent infection
	Positive blood cultures represent contamination[31]	
Imaging	Chest CT: nodular or wedge-shaped infiltrates or halo sign[93]	Larger nodules, air crescent sign, cavitation, other[94]
	Earlier nonspecific findings diagnostic if s-GMI is positive[83]	Worsening pulmonary infiltrates with rapid neutrophil recovery[94]
Angioinvasive molds capable of hematogenous dissemination,[31] most commonly *Fusarium* species		
Clinical	Same as angioinvasive molds, but metastatic skin lesions more common, and target skin lesions may be present (*Fusarium* species)[19]	Same as angioinvasive molds, plus chorioretinal lesions, joint and bone pain infections, similar to features of hematogenous dissemination above
	Cellulitis at sites of skin breakdown: *Fusarium* species[19]	
	Myalgia, muscular tenderness: *Fusarium* species[19]	
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-GMI[89] and s-BDG[90] 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 IMIs[91] and other infectious and noninfectious conditions.[92] A halo sign[93] 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* species[97] 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 DOT[99] (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	ABLC (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)	ABLC (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. ABLC, amphotericin B lipid complex.

Voriconazole is the drug of choice for aspergillosis,[53] with L-AMB[101] 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 infiltrates[94] 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	Fluconazole: only agent with urinary concentrations
	Ocular	Triazoles, L-AMB; avoid echinocandins (poor distribution)
	CNS	Triazoles, L-AMB; avoid echinocandins (poor distribution)
Pathogen		
Candida species	Disseminated, acute and chronic	Echinocandin, fluconazole, L-AMB
C krusei	Disseminated, acute and chronic	Echinocandin, L-AMB; avoid fluconazole
C glabrata	Disseminated, acute and chronic	Echinocandin, L-AMB, voriconazole; avoid fluconazole
C parapsilosis	Disseminated, acute and chronic	L-AMB, voriconazole; avoid echinocandins
Trichosporon spp	Disseminated, acute and chronic	Fluconazole, other azoles; amphotericin B not effective
Aspergillus spp	Sinus, pulmonary, disseminated	Voriconazole, L-AMB, ABLC; no role for fluconazole
Aspergillus flavus	Sinus, pulmonary, disseminated	Voriconazole; posaconazole alternative
Fusarium spp	Sinus, pulmonary, cellulitis, disseminated	L-AMB, ABLC; voriconazole maintenance if susceptible
Scedosporium apiospermum	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 inhibitors[56] 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 response[96] (Table 3).

How long do we treat an IFD?

The DOT is dictated by resolution of the IFD and recovery from neutropenia (ANC >1000/μL), 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 ≤1000/μL, and severe if ALC is persistently ≤300/μL. Ideally, antifungal agents are stopped when the IFD resolves and ALC is consistently ≥1000/μL,

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-Leuk[112] 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 honoaria from Astellas, Onix, and Millenium.

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