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Prevention of Invasive Aspergillosis in High-Risk Patients: Universal Versus Preemptive, Targeted Treatment

John W. Baddley, MD and Senu Apewokin, MD

Abstract

Invasive aspergillosis (IA) is associated with increased morbidity and mortality, and there is a need for better preventative and therapeutic approaches. Successful treatment of documented IA remains difficult, often because of the inability to detect disease at an early stage. An important, recent advance in the management of aspergillosis is the availability of the newer broad-spectrum azoles, voriconazole and posaconazole, which have good activity against *Aspergillus* spp. In addition, newer diagnostic modalities including *Aspergillus* galactomannan, β -glucan, and polymerase chain reaction are more readily available. These diagnostic and treatment options have made new strategies possible for the management of IA. Prophylaxis and empirical therapy for high-risk patients have been popular for decades, and now a preemptive, targeted approach to IA management has become more attractive. This article reviews strategies for the prevention and management of IA and compares and contrasts universal prophylaxis to the preemptive, targeted approach for IA in high-risk patients.

Introduction

Invasive aspergillosis (IA) is associated with increased morbidity and mortality and occurs most frequently in immunocompromised patients, such as stem cell and solid organ transplant recipients and patients with hematologic malignancies. Over the past two decades, the incidence of IA has been increasing, probably due to an overall increase in the immunocompromised patient population [1•,2]. The incidence of IA may approach 25% in patients with acute leukemia, up to 30% in solid organ transplant patients, and up to 15% among allogeneic stem cell transplant patients [1•]. Despite changes in transplantation practices and growth of the antifungal armamentarium, improving outcomes in patients with IA has been particularly challenging for several reasons: 1) a timely diagnosis of IA is difficult given the currently available tests; 2) treatment of IA, although improving, is still plagued by intolerance to medications, adverse reactions, and drug interactions; and 3) patient populations may have prolonged at-risk periods for IA, making prophylaxis strategies difficult. An important recent advance is the availability of the newer broad-

Corresponding author: John W. Baddley, MD, Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, 1900 University Boulevard, 229 Tinsley Harrison Tower, Birmingham, AL 35294, USA. jbaddley@uab.edu.

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spectrum azoles, voriconazole and posaconazole, which have good activity against *Aspergillus* species [3,4]. In addition, there have been recent advances in fungal diagnostics with the development and US Food and Drug Administration approval of *Aspergillus* galactomannan and β -glucan [5–7]. There is certainly a need for better preventative and therapeutic approaches for the treatment of IA because of increased associated mortality. With these recent advances and management strategies, there is potential for earlier diagnosis, more effective therapy, and improved outcomes.

Definitions

There are several important strategies employed in the prevention and management of IA: prophylaxis, empirical therapy, preemptive, targeted therapy, and antifungal treatment for documented infection (Table 1). These management strategies have important limitations, including drug toxicities, drug costs, difficulties in diagnosis resulting in lack of recognition of invasive fungal infection (IFI), breakthrough infection, and potential for selection of resistance. Moreover, identification of the ideal patient in whom prophylaxis, empirical therapy, or preemptive, targeted therapy is necessary is not easily accomplished.

Prophylaxis is defined as administration of an antifungal agent in order to prevent fungal infection in a patient who is at risk for the infection but shows no signs or symptoms of active disease. Important issues regarding the decision to use prophylaxis include ability to successfully treat the infection, seriousness of disease, safety of the prophylactic regimen, and the effectiveness of the prophylaxis (number needed to treat) [8,9]. With the high mortality associated with IA and difficulty of diagnosis, prophylaxis seems like a logical strategy in high-risk patients.

Ideally, prophylaxis is given for the period of risk, although the “at-risk” period for aspergillosis is not always easy to define. For stem cell transplant patients, two main periods exist: the early neutropenic period and a period 2 to 4 months after transplantation (a result of graft-versus-host disease and its treatment). For solid organ transplant patients, the at-risk period is less clear, as lifelong immunosuppressive medications are often required. For other malignancies, the prolonged (usually > 10 days) neutropenic period after intensive chemotherapy, with or without fever, is considered an at-risk period for invasive mold infections. With the availability and widespread use of fluconazole as a prophylactic agent, invasive *Candida* infections have decreased in frequency among patients with leukemia and hematopoietic stem cell transplants (HSCTs) [10,11]. Consequently, fluconazole prophylaxis may be associated with increased colonization of patients with non-*albicans* *Candida* species and potential azole resistance [12]. However, because an important limitation of fluconazole prophylaxis is its lack of activity against molds, infections due to aspergillosis and zygomycosis have become an important concern over the past decade. The availability of the oral azoles itraconazole, voriconazole, and posaconazole and the echinocandin class (micafungin, caspofungin, anidulafungin) of antifungal agents has expanded the options for prophylaxis because they possess antimold activity. What remains to be fully discovered is the relative effectiveness of these agents for preventing IA [13,14–16]. Important consequences of prophylaxis include toxicities, drug interactions, breakthrough infections,

selection or development of resistant organisms, and potential limitations in future antifungal therapy if a fungal infection is documented.

Empirical antifungal therapy has been used for several decades in the hematologic malignancy population who have a possible fungal infection [17•]. This approach has been widely adopted for the febrile, neutropenic patient with underlying malignancy or recipients of stem cell transplantation. The strategy is employed in the high-risk neutropenic population with persistent unexplained or relapsing fever despite the receipt of broad-spectrum antibiotics (for 4 days or more) and no other obvious signs of IFI [17•,18–20]. Administration of antifungal agents usually begins after at least 96 hours of unresponsive fever. Early trials using this approach, despite important design limitations, demonstrated a reduction in mortality and IFI [19,20]. The insensitive and nonspecific nature of persistent fever despite antibiotics is a major limitation of this strategy, particularly with regard to overtreatment with antifungal agents. In several large clinical trials, only a small percentage of patients had proven baseline fungal infections, leading to potentially unnecessary treatment in more than 75% of patients [17•,21–23]. For these reasons, other strategies such as preemptive, targeted therapy are enticing. This review will not discuss further controversies related to empirical antifungal therapy.

Given the limitations of universal prophylaxis and empirical therapy, an alternative management strategy is the use of *preemptive*, targeted therapy. Such an approach has been effective for preventing cytomegalovirus disease in stem cell and solid organ transplant recipients, in which antivirals are initiated only when a serially performed blood test for cytomegalovirus replication shows evidence of significant replication. Successful employment of preemptive therapy to impact outcomes depends on correctly identifying patients with early or probable IA on the basis of host characteristics, radiographic signs of infection, and laboratory markers of disease. Preemptive, targeted therapy for IA is an approach that has been recently explored, primarily due to improvements in diagnostic modalities such as high-resolution CT and fungal serology [5–7,24••]. The widespread availability of these modalities has made this approach more applicable to multicenter clinical trials. Several recent studies have explored this strategy among stem cell transplant patients and patients with hematologic malignancy [25•,26–28].

The last stage of management is *treatment* for documented disease. Because of diagnostic limitations, late-stage disease at presentation is common, resulting in suboptimal treatment outcomes [1••,2,29]. Voriconazole has become the standard of care for primary IA and was proven to be superior to conventional amphotericin B therapy in both clinical efficacy and survival [3]. However, drug interactions and toxicities must be thoroughly considered. Combination antifungal therapy is enticing but remains unproven. Moreover, choice of the appropriate combination of antifungal agents is difficult and complicated by a large number of patients with IA receiving prophylaxis. Despite more efficacious drugs and new strategies, outcomes of late-stage IA remain unacceptable (> 50% mortality), and thus prophylaxis, and identification and treatment at the early stages of disease with preemptive, targeted therapy remain important management strategies.

Universal Prophylaxis

Many antifungal drugs have been evaluated for the prevention of IFI in high-risk patients, and several meta-analyses were recently performed summarizing the important issues [13•, 14–16,30–33,34•,35–38]. Early studies with fluconazole demonstrated a decrease in invasive *Candida* infections in patients with leukemia and HSCT recipients [10,11]. However, with the widespread use of fluconazole, there has been an emergence of non-*albicans Candida* and increased azole-resistance [12]. In part, because of the effectiveness of fluconazole prophylaxis for *Candida* prevention, more focus has been placed on prevention of IA in the past decade. The availability of oral azoles and echinocandins has resulted in newer options for prevention and more available clinical trial data. Studying the prevention of IA has been somewhat difficult because of the larger sample sizes needed to compare antifungal drugs. A summary of selected antifungal prophylaxis trials for IA are described below and listed in Table 2.

Amphotericin B formulations

Amphotericin B preparations have been used at a range of doses and dose frequencies in hopes of avoiding toxicities [35–37]. An important limitation of amphotericin B formulations, besides nephrotoxicity and infusion-related adverse events, is the lack of an oral formulation. Several studies with amphotericin B preparations demonstrated a reduction in fungal colonization but no effect on aspergillosis compared with placebo [35,36]; however, these studies were powered for prevention of all fungal infections, not aspergillosis specifically. From the available studies, there is no convincing evidence to support use of intravenous preparations of amphotericin B for the prevention of IA in the patient with hematologic malignancy or stem cell transplants. Inhaled amphotericin B preparations have proven safe when studied for IA prevention in patients with stem cell and lung transplants, but additional studies are needed to determine efficacy in the prevention of IA [37].

Echinocandins

Echinocandins (caspofungin, micafungin, anidulafungin) have activity against *Candida* and *Aspergillus* spp and have shown efficacy and safety in the treatment of IA in patients who are refractory to or intolerant of other anti-fungal therapy [38,39]. Micafungin has been studied in a randomized, double-blind, comparative trial as prophylaxis during neutropenia in patients undergoing HSCT [15]. When compared with fluconazole, the overall efficacy of micafungin in the prevention of IFI was superior (80% vs 73.5%; $P = 0.03$). Proven and probable aspergillosis was less common in the micafungin group compared with the fluconazole group (0.2% vs 1.5%; $P = 0.071$). There was no significant difference in overall adverse events in the two groups.

Caspofungin was compared with intravenous itraconazole in an open-label study for the prevention of IFI in patients undergoing induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome [31]. Of 192 patients evaluable for efficacy, 12 (6.3%) developed an IFI (5 in the itraconazole group and 7 in the caspofungin group). Aspergillosis was uncommon, with one case in the itraconazole group and two in the caspofungin group. Both drugs were well tolerated. Although the above studies provide

some evidence of the efficacy of echinocandins as prophylaxis for IFI, lack of an oral agent, cost, and paucity of *Aspergillus* cases in the studies remain important limitations.

Newer azoles

Itraconazole—Itraconazole has been studied extensively as prophylaxis for fungal infections largely do to its oral formulation and antimold activity. Most studies have evaluated primary prophylaxis for IFI in stem cell and organ transplants and patients with hematologic malignancy, but many have been underpowered to evaluate for IA prophylaxis (Table 2). In a study by Winston et al. [40], itraconazole was more effective at reducing proven IFI when compared with fluconazole as prophylaxis in allogeneic HSCT patients (9% vs 25%; $P < 0.05$); however, a mortality benefit was not appreciated. In a more recent trial comparing itraconazole with fluconazole in HSCT patients, itraconazole patients had a lower mold infection rate when compared with the fluconazole group (5% vs 12%; $P = 0.03$) [32]. Adverse events and tolerability issues in the itraconazole group were more common and were cited in the study as factors that may limit the use of itraconazole prophylaxis. Finally, a recent large, randomized, open-label trial compared itraconazole with fluconazole in patients with hematologic malignancy and neutropenia (no stem cell transplant patients) [30]. The incidence of IFI was low in the study population, and no significant differences in proven IFIs were present in the treatment groups. Two recent meta-analyses have conflicting results on the efficacy of itraconazole as prophylaxis for IFI, one suggesting no difference in reduction of IFI when compared with fluconazole [33,34]. By contrast, a review by Glasmacher et al. [16] suggested a reduction in IFI and mortality attributable to IFIs with the use of itraconazole compared with fluconazole. Important limitations of itraconazole for prophylaxis remain erratic absorption and tolerability issues that have led to the study and use of other azole alternatives.

Voriconazole—Because of its efficacy against IA and the availability of an oral and intravenous formulation, voriconazole is attractive as an agent for prophylaxis [3]. However, reports of breakthrough infections with zygomycetes in patients on voriconazole prophylaxis and treatment have been concerning [41,42]. Voriconazole is currently being studied for prophylaxis in several populations, including stem cell transplant patients and organ transplant recipients (<http://www.clinicaltrials.gov>; identifiers NCT001177827, NCT00177788, NCT00289991, NCT00075803, NCT00079222), but few studies have been published. Preliminary results of a randomized, double-blind trial of fluconazole versus voriconazole for the prevention of IFI in allogeneic blood and marrow transplant patients were reported recently in abstract form [14]. The primary endpoint was fungal-free survival at 6 months, and there was no significant difference in the two groups (78% for voriconazole; 76% for fluconazole). However, there were fewer cases of microbiologically documented IFI caused by *Aspergillus* in patients who received voriconazole when compared with those who received fluconazole (7 vs 16 cases; $P = 0.05$), which would be expected. Additional results of efficacy, safety, and breakthrough infection are needed to better define the role of voriconazole in prophylaxis for IA in high-risk patients.

Posaconazole—Posaconazole is a potent oral azole with good activity against *Aspergillus* spp [4]. Several recent studies evaluating posaconazole prophylaxis in patients with

hematologic malignancy or recipients of stem cell transplants with graft-versus-host disease have been reported [13•,43]. The first was a multicenter, randomized trial of the safety and efficacy of posaconazole compared with fluconazole or itraconazole in 304 patients with neutropenia resulting from chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome [13•]. The dosages used were posaconazole 200 mg orally three times daily versus fluconazole orally 400 mg daily or itraconazole solution orally 200 mg twice daily. Proven or probable IFIs were significantly fewer in the posaconazole group compared with the fluconazole or itraconazole group (2% vs 8%; $P < 0.001$). In addition, fewer cases of aspergillosis were present in the posaconazole group (2 [1%] vs 20 [7%]; $P < 0.001$), and patients who received posaconazole had prolonged survival ($P = 0.04$). It is important to note that many patients in the fluconazole or itraconazole group had probable aspergillosis based on a positive galactomannan, not necessarily a positive culture or histopathologic findings. However, it is not uncommon to have probable diagnoses in everyday clinical practice, especially given the proportion of false-positive galactomannan tests and abnormal chest imaging studies. Additional data on these probable cases would better define the relative effectiveness of posaconazole. Serious adverse events possibly related to treatment were more common in posaconazole-treated patients (6% vs 2%).

The second study compared posaconazole with fluconazole as prophylaxis for patients with graft-versus-host disease who were receiving immunosuppressive therapy [43]. The primary endpoint was the incidence of proven or probable IFI from randomization up to 16 weeks in to the fixed treatment period of the study. Posaconazole was as effective as fluconazole in preventing IFI (incidence 5.3% and 9.0%, respectively; $P = 0.7$). As would be expected, posaconazole was superior to fluconazole in preventing aspergillosis (2.3% vs 7.0%; $P = 0.006$). Interestingly, 23 (8.5%) of 600 patients had a positive *Aspergillus* galactomannan antigen index at baseline, indicating that posaconazole or fluconazole was used unexpectedly as a “preemptive, targeted” strategy in some cases. The number of deaths from IFIs was lower in the posaconazole group compared with the fluconazole group (1% vs 4%; $P = 0.046$). No significant difference in number of adverse events was seen in the two groups.

Limitations of Prophylaxis and Future Challenges

As discussed previously, several antifungal drugs are effective for IFI prophylaxis, but demonstrating effective IA prophylaxis has been more difficult in clinical trials because of lack of power in some studies. Clearly, oral, mold-active agents have a theoretical advantage assuming safety, tolerability, and adequate drug levels are achieved. Breakthrough fungal infections, especially those caused by azole-resistant yeasts and zygomycetes, remain a concern, and continued careful monitoring for breakthrough infections will be required. Finally, our ability to predict the incidence of IA in certain patient populations at the institutional level will be important in determining the effectiveness of prophylaxis and may be the major determinant in the use of prophylaxis versus a preemptive strategy. Better tools for risk assessment are needed, and improved methods to reliably diagnose IA in these patients are welcomed.

Preemptive, Targeted Therapy

Preemptive, targeted therapy is becoming more attractive and feasible in the past decade with the availability of better diagnostic studies and imaging techniques and the belief that earlier detection of infection will lead to improved outcomes [24•,25•,26,44,45]. In contrast to starting antifungal therapy for persistent or recrudescing fever in the high-risk neutropenic patient (empirical therapy), preemptive, targeted antifungal therapy would be instituted for a radiologic sign of IA (pulmonary nodule or “halo,” for example), positive lab marker of disease (galactomannan, β -glucan, or fungal polymerase chain reaction [PCR]), or other modalities that would identify IA. Fever alone would not lead to the institution of antifungals. Ideally, the negative predictive value of diagnostic tests, if sufficient, would persuade the clinician to withhold antifungal therapy pending further investigation. Conversely, a positive test would trigger an aggressive search of IA, and treatment would be instituted at an early stage of disease [22,26]. It is imperative to better identify the patient at high risk for IA and the periods of high risk, which would improve the predictive value of diagnostic testing and potentially limit overtreatment with antifungal therapy. Although this preemptive, targeted strategy is appealing, additional clinical trial data employing this strategy are needed to determine effectiveness.

A non-comparative observational study evaluated the strategy of a nested PCR panfungal assay in pediatric cancer patients who did not receive antifungal prophylaxis [28]. Patients who were febrile and neutropenic were screened for IFI with blood cultures and PCR assay every 2 to 3 days until fever resolved; patients with a positive PCR assay had a repeat sample obtained. For patients with persistent fever on broad-spectrum antibiotics, amphotericin B was instituted only if there were positive blood cultures for fungi or two consecutive positive PCR assays. A total of 83 episodes from 42 patients with febrile neutropenia were evaluated. Among 52 PCR-negative episodes, no IFI was diagnosed and no antifungal therapy given. Among 29 PCR-positive assays, 22 were confirmed by blood culture. PCR testing preceded positive blood cultures by 1 to 8 days, resulting in earlier institution of therapy. The study demonstrated that this preemptive approach led to a reduction in antifungal use for patients with persistent, febrile neutropenia and to the earlier institution of therapy with use of PCR testing. An important limitation is that patients did not receive antifungal prophylaxis, so most fungal infections were candidemia. Only one case of aspergillosis was detected by PCR, probably a false-positive; therefore, additional studies are needed to determine the effectiveness of this strategy for patients with IA.

Maertens et al. [25•], in a pilot study, used an algorithm that combined galactomannan testing and high-resolution CT scanning to identify patients most likely to benefit from antifungal therapy. Liposomal amphotericin B was instituted for two or more consecutive positive galactomannan tests (index = 0.5), or CT findings suggestive of IFI supported by a culture or microscopic evaluation positive for mold. One-hundred thirty-six treatment episodes for persons at risk were screened with these methods. Neutropenic fever developed in 117 episodes, of which 41 (35%) satisfied criteria for empirical antifungal therapy. The preemptive protocol approach reduced the rate of antifungal therapy for these episodes from 35% to 7.7% and led to early initiation of antifungal therapy in 10 (7.3%) episodes that were not clinically suspected of being IFI. No undetected cases of IA were identified, and

importantly, only one case of mold infection (zygomycosis) was missed. Among the patients studied, fluconazole was given routinely for prophylaxis, thereby reducing the risk of *Candida* infections. No patients received mold-active antifungal prophylaxis, perhaps improving the sensitivity of galactomannan testing and allowing the preemptive strategy to be more effective.

A retrospective study recently reported evaluated a “presumptive” treatment strategy in HSCT patients in whom antifungal therapy was administered to those who developed positive serum tests (galactomannan, β -glucan) or pulmonary abnormalities on chest radiography or CT scan and had persistent febrile neutropenia [27]. Routine screening of all patients with serum tests and radiography was not performed. All patients received fluconazole (200 mg/d) prophylaxis. Among 60 patients who followed the presumptive strategy, only four (6.7%) received antifungal therapy. Thirteen patients received standard empirical antifungal therapy. Two patients in the presumptive strategy developed early IA but were successfully treated. The authors noted that, with this presumptive strategy, there was a decrease in the use of antifungal agents. However, because of the retrospective nature there may have been selection bias involved, with the high-risk patients perhaps receiving empirical therapy at the discretion of the treating physicians.

Limitations of the Preemptive, Targeted Strategy and Future Challenges

Although these studies have demonstrated interesting results, especially reduction of inappropriate antifungal use, earlier detection of disease, and identification of IFI that would not have been suspected due to lack of fever, these trials were preliminary and do not allow for comparative outcome data [25,27,28]. Additional comparative, randomized trials are needed. Another important limitation is the predictive value of diagnostic modalities. For the preemptive, targeted strategy to be most effective, the positive and negative predictive values must be reasonably high. This raises two important questions: in whom should these strategies be implemented and are our diagnostic modalities good enough? We must continue to better define the “high-risk” patient but allogeneic stem cell transplant patients seem the logical group to study further. As for the diagnostic modalities, there are important concerns, such as false-positives due to antimicrobials, reduced sensitivity because of antimold antifungal prophylaxis or treatment, long turnaround time for results, and lack of data using these tests in a preemptive trial setting. Moreover, these tests are expensive and may not be available in resource-limited settings. We must proceed with an understanding of these limitations and await development of more sensitive or specific diagnostic tests.

Conclusions

Over the past several decades we have witnessed the development of new strategies for the management of IA: prophylaxis, empirical therapy, and preemptive, targeted therapy. Successful treatment of documented IA remains problematic and is associated with unacceptable mortality, often because of inability to detect disease at an early stage. Until the outcomes of patients treated for documented IA improve, many prevention and treatment strategies may be required. Each strategy has benefits and limitations, but important considerations include incidence of IA in the population, drug toxicities and costs,

overtreatment of patients, and selection of drug resistance. Recent technology (serologic testing, improved imaging) and drug development (oral, mold-active drugs) have afforded us multiple management opportunities, but we can only hope that diagnostics and antifungal agents continue to improve and clinical trials involving management strategies are reported. By continuing to refine the approach to management of IA, we hope that patients will be able to achieve better outcomes.

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Table 1

Management strategies for invasive aspergillosis

Strategy	Definition
Prophylaxis	Antifungal agent is initiated before or during a period of high risk to prevent invasive fungal infection
Empirical therapy	Antifungal agent is initiated in high-risk patients who manifest clinical signs or symptoms (usually fever) of invasive fungal infection but have no other obvious signs of invasive fungal infection
Preemptive, targeted therapy	Antifungal agent is administered to patients with suspected early or probable aspergillosis on the basis of host characteristics, radiographic signs of infection, or laboratory markers of disease
Treatment	Administration of an antifungal agent for proven or probable invasive fungal infection

Table 2

Summary of selected prophylaxis trials in high-risk patients

Study [ref]	N	Drug (dosage)	Comparator (dosage)	Invasive fungal infection		Invasive aspergillosis	
				Drug	Comparator	Drug	Comparator
Polyene studies							
Perfect et al. [36]	182	cAmB (0.1 mg/kg/d)	Placebo	8.8%	14.3%	1%	1%
Kelsey et al. [35]	163	LAmB (2mg/kg three times weekly)	Placebo	0%	3.4%	0%	0%
Echinocandin studies							
Van Burik et al. [15]	882	Micafungin (50 mg/d)	Fluconazole (400 mg/d)	1.6%	2.4%	0.2%	1.5%
MattiuZZi et al. [31]	200	Caspofungin (50 mg/d)	Itraconazole (200 mg/d)	6%	6%	1.2%	2.8%
Mold-active azole studies							
Winston et al. [40]	140	Itraconazole (200 mg every 12 h)	Fluconazole (400 mg/d)	9%	25%	4%	12%
Marr et al. [32]	299	Itraconazole (2.5 mg/kg three times daily)	Fluconazole (400 mg/d)	7%	15% [*]	6.8%	11.6% [*]
Glasmacher et al. [30]	494	Itraconazole (2.5 mg/kg twice daily)	Fluconazole (400 mg/d)	1.6%	2%	0.8%	1.2% [‡]
Wingard et al. [14]	600	Voriconazole (200 mg twice daily)	Fluconazole (400 mg/d)	6.6%	10.6% [‡]	2.3%	5.4% [§]
Cornely et al. [13•]	602	Posaconazole (200 mg three times daily)	Fluconazole (400 mg/d)	2%	8%	1%	7%
Ullmann et al. [43]	600	Posaconazole (200 mg three times daily)	Fluconazole (400 mg/d)	5.3%	9%	2.3%	7%

^{*} On-treatment population results.[‡] Proven invasive aspergillosis.[‡] Proven, probable, and presumptive invasive fungal infection at 6 months.[§] Microbiologically documented invasive aspergillosis.

cAmB—conventional amphotericin B; LAmB—liposomal amphotericin B.