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MINIREVIEW

Strategies in Prevention of Invasive Pulmonary Aspergillosis in Immunosuppressed or Neutropenic Patients

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Aspergillus species are increasingly recognized as major fungal pathogens in severely immunosuppressed or neutropenic patients (8, 9, 20, 22, 51, 62, 71, 81, 82, 103, 107, 112). As organ transplantations and aggressive antineoplastic chemotherapy regimens are becoming more frequent, increasing numbers of patients will be susceptible to an *Aspergillus* infection. Moreover, patients with AIDS probably have a higher incidence of *Aspergillus* infections than immunocompetent individuals (21). In the immunosuppressed or neutropenic host, invasive pulmonary aspergillosis (IPA), characterized by hyphal invasion and destruction of pulmonary tissue, is the most common manifestation of an *Aspergillus* infection, although local infections also occur in the sinuses, the skin, or intravenous catheters (1, 8, 9, 20, 82, 89, 101). Dissemination from these initial ports of entry to other organs can be a secondary event in about 20% or more of the cases (1, 8, 9, 20, 22, 82, 101). *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus* strains were the most frequently observed strains in cases of documented infection (105).

Aspergilli are respiratory pathogens, and pulmonary infections are usually acquired through the inhalation of *Aspergillus* conidia, which are universally present in unfiltered air (9, 73, 81, 103). With a diameter of about 2.5 to 3.5 μm, these conidia are able to reach small airways and the alveolar space, where the impaired host defense mechanisms allow hyphal germination of the aspergilli and subsequent tissue invasion (9, 44, 83, 103, 105). Some patients, however, may have *Aspergillus* colonization of the nasal sinuses and endogenous spread to the lungs, causing IPA (9, 89, 101). In these latter cases, the exact pathomechanisms of IPA manifestation and the way in which it disseminates from the sinuses to the lungs are less clear.

The true incidence of IPA in susceptible patients is not known. In two relatively recent autopsy series, IPA was documented in about 10% of patients with hematological malignancies (8, 20). In many cases the condition was not suspected clinically (20). Clinical reports show that the incidence of IPA differs greatly worldwide, at different treatment centers and even within the same institution, ranging from as low as 0% to 25% or more (8, 9, 28, 62, 82, 88, 103). Several factors are responsible for this variability. One crucial factor influencing the incidence of IPA is the degree of environmental exposure. The usual spore numbers per m^3 of unfiltered outdoor air range between 0.2 and 3.5 in the North American and European climates, with seasonal variation, i.e., higher counts in the late fall and lower counts in the winter. However, much higher counts of 15 spores or more per m^3 can occur when spores are released near organic debris (9, 62, 73, 88). Spore counts in the hospital environment depend on the location and type of building and the type of air filtration used at the time the samples were taken. Without air filtration, spore counts of 5.0/m^3 probably do not differ from outdoor samples, whereas by using high-efficiency particulate air (HEPA) filtration, concentrations of spores as low as 0.009/m^3 can be achieved (73, 88). *Aspergillus* infections occur more frequently when the spore counts are high. Numerous reports describe microepidemics of IPA coinciding with construction activity or with defective ventilation systems, and variable counts of 2.3 to 5.9 spores per m^3 have been measured at these locations (9, 72, 73, 81, 88, 103). A patient's susceptibility to an *Aspergillus* infection is determined by the "net state of immunosuppression" that is present (80). Patients at risk of acquiring IPA are patients on chronic glucocorticoid or immunosuppressive treatment (34, 61), patients with impaired neutrophil/macrophage function such as in chronic granulomatous disease (16), patients with AIDS (21), and neutropenic patients with aplastic anemia (107) or chemotherapy-induced neutropenia (9, 27, 103, 108). The risk of acquiring IPA correlates with the duration and degree of immunosuppression or neutropenia (27, 108) and is the highest in patients with prolonged neutropenia of more than 20 days and in those with multiple risk factors, e.g., following allogeneic bone marrow transplantation (BMT) or other organ transplantations (9, 22, 51, 62, 71, 82, 112).

The still unsatisfactory diagnosis and treatment of IPA result in an overall mortality of more than 50% (9, 22, 27, 28). The mortality of patients after BMT can even be as high as 95% (22, 55, 56, 62). Delays in the diagnosis of IPA are frequent and are associated with a higher mortality rate (20, 24, 42, 81). Despite the development of new azole drugs, amphotericin B (amB) is still the antifungal agent of choice for individuals with a suspected or documented *Aspergillus* infection (2, 7, 22, 32, 50, 66, 81, 103). It has been shown that early empiric treatment with this drug decreases the overall mortality from IPA (12, 24, 42, 68, 81, 104). However, those patients with manifest disease and persistent neutropenia or immunosuppression will almost inevitably die from disease progression or dissemination (32, 81, 107). Furthermore, even in adequately treated patients there is a high rate of relapse of invasive disease if the immunosuppression or neutropenia is reintroduced (41, 76, 101). In leukemic patients the occurrence of IPA during induction chemotherapy will delay or impair potentially curative treatment (20, 41, 76, 81). In one group of patients after

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BMT, the elimination of IPA would have reduced the overall mortality from nosocomial pneumonia by 40% (62). For these reasons, several strategies for the prevention of IPA have been investigated and are the subject of this review: the reduction of environmental exposure, systemic or topical prophylaxis with amB or other antifungal agents, and the use of hematopoetic growth factors.

REDUCTION OF ENVIRONMENTAL EXPOSURE

Aspergillus species have a major reservoir in organic debris, bird droppings, dust, and building material (72, 73, 103). Therefore, the first steps in the prophylaxis of IPA consist of general measures to eliminate obvious sources of aspergilli, such as removing plants from the adjacent environment of a patient (47, 52, 72, 73, 103). In some instances surface disinfection with copper-8-quinolinolate has been reported to be effective (60, 73, 103). Susceptible patients should not be treated in areas with construction activity, and if such activities are under way, measures should be undertaken to seal these sites to prevent air exchange with the patients' environment (2, 60, 72, 73, 88, 103). Certain foodstuffs, such as cereals, nuts, and spices, have been found to be contaminated with aspergilli and should not be offered to patients at risk of developing IPA (52, 72, 73, 103).

It has been shown that air filtration reduces or even eliminates *Aspergillus* spores from the air, and HEPA filtration must be considered the current standard in IPA prevention (9, 47, 72, 73, 81, 88, 103). Several authors have reported the control of epidemic outbreaks of IPA during periods of construction work with the use of HEPA filters (60, 88, 103). Furthermore, patients rarely develop IPA when they are treated in laminar airflow facilities with HEPA filtration throughout the period of immunosuppression or neutropenia, so long as some technical requirements are met. High air exchange rates, the use of positive air pressure in the patient's immediate environment, point-of-use air filtration, regular filter changes, and surveillance air sampling for monitoring filter efficacy have been considered necessary for effective prophylaxis, although no numerical data on the contribution of each measure to the overall efficacy of HEPA filtration are available (60, 72, 73, 88, 103). The obvious disadvantage of this strategy is the high cost of construction and maintenance of HEPA-filtered facilities. These environments are expensive and will only be available to a minority of patients with the highest risk of developing IPA. In addition, the protective effect is lost if the patient is moved outside the HEPA-filtered facility even for short periods of time (4, 51, 66, 72, 73, 88, 103). Moreover, rare cases of IPA may still occur despite HEPA filtration in patients with *Aspergillus* colonization of the nasal sinuses prior to the onset of neutropenia (47, 50, 51, 66, 89, 101).

SYSTEMIC PROPHYLAXIS WITH amB

Intravenous amB desoxycholate remains the most effective drug against aspergilli in humans but is associated with a number of toxicities, such as fever, chills, electrolyte disturbances, and renal impairment, that preclude its prophylactic use in the majority of patients at risk of developing IPA (24, 26, 50, 66, 68). However, prophylactic intravenous amB desoxycholate given in a dose of 1 mg/kg/day in combination with 5-fluorocytosine was used during reinduction chemotherapy in nine leukemic patients with documented or suspected IPA during previous treatment cycles. The IPA did not recur or progress in any of these patients, and all survived beyond neutrophil recovery. A single patient who did not receive this prophylaxis progressed and died of IPA (41). More recently, one report on a small series of patients after BMT suggests that a lower dose of 0.75 to 1.0 mg of prophylactic intravenous amB desoxycholate per kg per day without additional 5-fluorocytosine might also be sufficient to prevent recurrence of IPA (74).

In an attempt to avoid the toxicities of prophylactic amB desoxycholate administration, reduced doses of 0.1 to 0.25 mg/kg/day were investigated for IPA prophylaxis (59, 65, 78). In a retrospective analysis of 186 neutropenic patients after BMT, prophylactic "low-dose" administration of 0.15 to 0.25 mg of amB per kg per day was considered effective in reducing the incidence of IPA to 9% in 110 patients, compared with 76 historical controls from the same treatment center in whom no prophylaxis or only HEPA filtration was used (78). There was an unusually high IPA incidence of 23% in 48 of the 76 control patients despite the use of HEPA filtration. This did not differ from the 24% IPA incidence in 28 of the 76 control patients who had no prophylaxis at all. Apart from the incidence of graft versus host disease, no information concerning the degree and duration of neutropenia was given (78). Furthermore, the results of this trial have to be challenged in view of the questionable value of historical controls in studying the effects of a prophylactic strategy for IPA and the large variations in the incidence of *Aspergillus* infections. Despite another preliminary report that seems to confirm the effectiveness of prophylactic amB desoxycholate (59), this strategy was not found to have a prophylactic effect at doses of 0.1 mg/kg/day in a prospective, randomized, placebo-controlled trial in 182 neutropenic patients after autologous BMT (65). In that trial, the placebo and the prophylactic amB arms showed no difference in either the incidence of suspected or proven IPA or the frequency of clinical settings that required subsequent empiric treatment with amB desoxycholate at doses of 0.6 mg/kg/day. This higher dose of amB had to be used in 77 of 91 patients (85%) in the placebo arm after a median of 7.9 days postrandomization, compared with 72 of 91 (79%) in the prophylactic amB arm after 8.8 days. The use of prophylactic low-dose amB resulted in more fever, chills, and renal toxicity and higher treatment costs in the prophylactic amB arm. However, the 12% overall incidence of suspected or proven systemic fungal infections, as well as the 1% incidence of possible IPA, in that study was low, and the authors concluded that in patients with a higher risk for developing fungal infections, there might still be a role for prophylactic low-dose amB (65). Other reports also show a lack of prophylactic efficacy of low-dose amB desoxycholate as well as the progression of IPA despite early empiric treatment with amB even at higher doses of 0.5 mg/kg/day (2, 12, 22, 42, 104, 107, 109). After the intravenous administration of amB desoxycholate, most of the drug can be recovered from the liver and spleen at postmortem examinations, and only about 1.2 to 6% of the entire dose delivered can be recovered from pulmonary tissue (15, 17). Moreover, not all of the amB measurable in pulmonary tissue has antifungal activity. Therefore, the pulmonary concentrations of amB after prophylactic low-dose intravenous administration might not be sufficient to prevent the manifestation of IPA.

More recently, the availability of new delivery systems for amB has made this drug more attractive for systemic prophylaxis of IPA (11). Traditionally, in order to disperse and intravenously administer amB, desoxycholate was added as a solvent. Most of the toxicities of intravenous amB were attributed to this desoxycholate component of the formulation. The toxicities of intravenous amB are markedly reduced when the drug is incorporated into liposomes without the use of desoxycholate. Liposomal amB can be used in higher doses and with

much less toxicity even in patients with IPA progression and/or in those who suffer from adverse events during pretreatment with amB desoxycholate. Its high cost, however, limits its use on a more general basis (48, 49, 75). A much cheaper approach of mixing amB desoxycholate with intravenous lipids has also been reported to decrease the systemic side effects of this drug (13, 53). Whereas both lipid preparations have been used with encouraging results in the treatment of IPA, no randomized trials comparing their therapeutic efficacies with that of standard amB desoxycholate treatment have yet been performed. Data are not yet available on the efficacies of prophylactic administration of these lipid preparations in immunosuppressed or neutropenic patients, but such investigations are in progress.

SYSTEMIC PROPHYLAXIS WITH AZOLE ANTIFUNGAL AGENTS

In the past 20 years a great number of azole antifungal agents with in vitro activity against *Candida* and *Aspergillus* species have been developed (3, 7, 32, 86). Of these, miconazole, ketoconazole, fluconazole, and, most recently, itraconazole have been used in immunosuppressed or neutropenic patients for the prophylaxis of fungal infections. Although most of the clinical trials focused on the prevention of *Candida* infections, some data on the incidence of *Aspergillus* infections, and especially of IPA, are available.

Miconazole was the first azole antifungal agent that was available for prophylactic intravenous administration. It has little in vitro activity against aspergilli (7, 36). The prophylactic use of miconazole was reported to reduce the incidence of fungal sepsis and to delay the initiation of empiric amB administration for unexplained fever in 97 patients after BMT in a prospective, randomized trial, as well as in an additional 121 patients during a subsequent open trial with unblinded prophylactic use of this drug (110). However, 2 of these 218 patients developed IPA despite prophylactic miconazole administration and at an incidence equal to that among the 111 placebo group patients who did not receive the miconazole prophylaxis. Hematological toxicity, nausea, fever, and chills as well as the high cost of intravenous miconazole precluded its use on a more general basis.

Ketoconazole also shows only marginal in vitro activity against *Aspergillus* species (7, 86). The drug is available for oral administration only, and several randomized trials showed a reduction of *Candida* colonization in neutropenic patients with the prophylactic or therapeutic use of this agent. No effect on the incidence of suspected or documented IPA was observed (7, 25, 87, 92, 106). The side effects of this drug were mainly gastrointestinal toxicity and hepatotoxicity. The variable bioavailability of this oral agent, the interactions with various drugs that are metabolized through the cytochrome P-450 system, and the only moderate effect on invasive fungal infections led to the discontinuation of this agent for antifungal prophylaxis (5, 7, 25, 106).

Fluconazole has been investigated more recently. In contrast to other azoles, it is hydrophilic and has a high oral bioavailability and little toxicity after oral or parenteral administration. Although there is good in vitro activity against most *Candida* strains, the in vitro data on its activity against *Aspergillus* species are equivocal (7, 63, 64, 93). For humans, there are anecdotal data on the successful treatment of IPA with fluconazole, but these preliminary reports have to be challenged. One case report describes the successful treatment of IPA in an individual who was not neutropenic. In addition, the IPA was suspected only after growth of *A. fumigatus* in bronchoalveolar lavage fluid and a positive *Aspergillus* antibody titer (70). Another report describes a 44.2% efficacy rate in 43 patients with IPA or pulmonary aspergillomas, but no information is given on the underlying clinical diagnoses in these patients, on the diagnostic criteria for IPA, on neutrophil counts at the time of diagnosis, or on the coincidence of neutrophil recovery and response to treatment with fluconazole (38). The results of three large prospective, randomized studies which investigate the use of prophylactic administration of fluconazole in immunosuppressed and/or neutropenic patients after allogeneic BMT or antileukemic chemotherapy are available. Daily doses of 400 mg of oral or intravenous fluconazole reduced the incidence of *Candida* colonization and infections with only minimal side effects but did not prevent the occurrence of IPA (30, 79, 111). In all three studies there was no difference between the fluconazole and the placebo arms in the incidence of IPA. Although the 1% overall incidence of documented IPA was low, in one study all three patients with *Aspergillus* tissue invasion died (30). However, there is the possibility that a higher dose of fluconazole could have been used for antifungal prophylaxis. In one report, daily doses of up to 2,000 mg of fluconazole were tolerated (2), but it remains to be shown whether this increased dose will result in an improved efficacy against *Aspergillus* species.

Itraconazole shows a better in vitro activity against *Aspergillus* species than fluconazole and is comparable to amB in vitro (14, 31, 95, 96, 98). It is available for oral administration only. An oral solution and an intravenous preparation have been studied in animals but have not been released for clinical use (31, 95). Itraconazole capsules are tolerated with acceptable toxicity, and there have been several reports on the successful treatment of IPA in neutropenic patients with this preparation (14, 22, 23, 31, 94, 100). In a small randomized trial, 400 mg of itraconazole (capsules) per day was compared with intravenous amB desoxycholate at a dose of 0.6 mg/kg/day in 32 patients with suspected or proven fungal infections (99). IPA was suspected or documented in 13 of 32 (41%) of the patients. The overall response rate was similar, with 63% in the itraconazole arm and 56% in the amB arm, but all three fatalities with documented IPA were treated with amB. Patients with *Candida* infections responded better to amB, whereas patients with *Aspergillus* infections had a better response to itraconazole, but this difference was not statistically significant. The median treatment duration of 20 days with itraconazole and 13 days with amB was short, and the responses to amB and to itraconazole were associated with neutrophil recovery in most patients (99). Itraconazole has also been successfully used in the treatment of IPA in patients who do not respond to amB desoxycholate (23). For the prevention of fungal infections, itraconazole has been compared with ketoconazole and nystatin in neutropenic patients in retrospective analyses and was found to be superior (91, 92). In one study, there were no deaths due to fungal infections among 92 neutropenic episodes with itraconazole prophylaxis, compared with six deaths among eight episodes with prophylactic nystatin. In all patients who died, IPA was demonstrated (91). In the other study, the incidence of suspected or proven IPA was 19 of 52 (36.5%) in patients with ketoconazole prophylaxis of 200 mg twice daily and 5 of 45 (11.5%) in patients with itraconazole (capsules) prophylaxis of 200 mg twice daily (92). One placebo-controlled, randomized trial on antifungal prophylaxis with itraconazole has been completed thus far (102). In 92 neutropenic patients, itraconazole capsules of 400 mg/day reduced the overall incidence of proven fungal infections to 9 of 83 neutropenic episodes (11%), compared with 15 of 84 episodes (18%) in the placebo arm; however, this effect was mainly due

to a reduction of systemic *Candida* infections and was not statistically significant. The incidence of suspected or proven cases of IPA was similar in the prophylactic itraconazole (5 of 83 [6%]) and the placebo (4 of 84 [5%]) arms. Unfortunately, serum itraconazole levels were not measured in that study. The absorption of itraconazole from the gastrointestinal tract varies within a wide range and is largely unpredictable, so itraconazole doses higher than 400 mg or therapeutic drug monitoring might be necessary for effective antifungal prophylaxis with this drug (10, 67, 90). There are a number of drugs that interfere with the absorption of itraconazole, among which are agents such as antacids that are also commonly used in neutropenic patients (32, 90). In one study on prophylactic itraconazole in 72 neutropenic patients, suspected or proven fungal infections, including IPA, occurred significantly more often in patients with inadequate serum itraconazole levels (<250 ng/ml) (10). Further trials including larger numbers of patients are needed to make a definite statement on the effectiveness of itraconazole for the prophylaxis of IPA. To facilitate the prophylactic use of this agent, the availability of an itraconazole formulation with improved and more predictable bioavailability would clearly be beneficial.

Apart from itraconazole, several other azole antifungal agents with excellent in vitro activity against aspergilli have been investigated. Of these, saperconazole, Bay R 3783, and SCH 39304 have documented activity in animal models. However, saperconazole is probably too toxic for administration in humans, and the others have not yet been clinically evaluated (7, 35, 86, 97).

TOPICAL PROPHYLAXIS

In an attempt to avoid the systemic side effects of intravenous amB administration and because of the unsatisfactory results with azole antifungal agents for the prophylaxis of IPA, several groups investigated the use of topically administered amB. The idea was to deliver high concentrations of amB to all sites within the respiratory tract where *Aspergillus* infections occur by using aerosols with particles about the same size as *Aspergillus* conidia.

The first attempts were made with intranasal instillations of amB. Although this way of application was attractive because of few or no side effects, there are equivocal data on the effectiveness of this approach (39, 40, 48). Data from studies with animals are not available. In a preliminary report on a small prospective, randomized trial, one documented case and no suspected cases of IPA were observed among 40 leukemic patients who received intranasal amB instillations, compared with 7 suspected or documented cases of IPA among 43 patients in the group without intranasal instillations (48). In a more recent retrospective analysis on 159 neutropenic episodes in 109 patients with leukemia or lymphoma and 21 patients after allogeneic BMT treated over a period of 12 years, administration of intranasal amB spray at 5 mg/day throughout the hospital stay was reported to be effective in preventing IPA (39). Among 52 neutropenic episodes in patients given intranasal amB, no proven *Aspergillus* infection occurred, compared with 22 proven infections among 107 episodes in the historical control group. During the study period, confounding factors such as construction activity, the use of empiric intravenous amB, and other prophylactic measures changed in addition to the introduction of intranasal amB administrations, and these variations could also have been responsible for the reported decrease in the incidence of IPA in this series. On the other hand, there is at least one report on 5 of 15 patients developing IPA despite prophylactic administration of intranasal amB instillations of 5 mg/day in patients treated for leukemia (40).

Another approach to the topical prophylaxis of IPA is the aerosol application of amB desoxycholate. Delivery of a single 1.6-mg/kg aerosol amB dose 2 days prior to *Aspergillus* exposure significantly delayed the mortality from IPA in immunocompromised rats (85). In these animals, pulmonary amB levels of 9.88 μg/g were achieved after four aerosol amB applications of 1.6 mg/kg each, compared with levels of 4.34 μg/g after seven intraperitoneal administrations of 4 mg/kg each (58). In these studies no systemic absorption of aerosol amB occurred. However, in the same animal model a single 1.6-mg/kg aerosol amB dose was not effective for secondary prophylaxis once the infection was established and immunosuppression was reintroduced (57). Liposomal amB can also be administered as an aerosol and has been investigated in mice for prophylaxis and treatment of *Cryptococcus* infections (29). No data are available on aerosolized liposomal amB for prophylaxis of IPA. In another study, the combination of a single dose of 1.6 mg of aerosol amB per kg followed by oral administration of itraconazole or SCH 39304 7 days later was more effective for prophylaxis of IPA than aerosol amB alone (84). Aerosol amB was investigated for the treatment of pulmonary fungal infections in humans as early as 1959 (43). More recently, five groups have reported on aerosol administration of amB for the prevention of IPA (6, 18, 33, 37, 54). In these series, no cases of documented IPA were observed in patients who received the prophylaxis throughout their neutropenic period, but four cases of suspected or documented IPA were observed in cases in which prophylaxis was discontinued (6). Aerosol amB can be delivered with little toxicity despite daily doses of up to 25 mg and without the known systemic side effects of intravenous amB administration (6, 18, 33, 54). Only minimal systemic absorption of amB occurred despite documented pulmonary deposition of the drug (6, 54). However, at present nothing is known about the optimal dose, frequency, or duration of the prophylactic aerosol amB administration necessary to be effective for the prophylaxis of IPA, and the results of these pilot studies have not yet been confirmed in larger prospective trials.

OTHER APPROACHES

With the use of recombinant growth factors such as granulocyte colony-stimulating factor (G-CSF), macrophage CSF (M-CSF), GM-CSF, interleukin-3, or stem cell factor, a new strategy to decrease the incidence of IPA has become available (19, 45, 46). The administration of these cytokines either alone or in combination has been shown to accelerate neutrophil recovery after conventional chemotherapy or BMT, thus eliminating one of the major risk factors for the development of IPA (19). The administration of these agents is safe for the majority of patients treated for solid tumors and probably also for patients with hematologic malignancies or after BMT (19, 45, 55, 56). Preliminary data from studies with animals indicate that there might be a protective effect of human G-CSF against the development of IPA in neutropenic mice (69, 77). The use of M-CSF in humans has been studied in a phase I trial with patients with invasive fungal infections after BMT and was tolerated to a maximal dose of 2,000 $\mu g/m^2$ before dose-limiting thrombocytopenia occurred (55). However, with longer follow-up, 15 of 46 patients with a suspected or proven *Aspergillus* infection still had a poor prognosis despite the use of M-CSF. Thirteen of 15 patients (87%) with a suspected or proven *Aspergillus* infection died, and 10 patients still had evidence of an *Aspergillus* infection at the time of their death

(56). There are no data available yet on the effect of the prophylactic use of G-CSF, M-CSF, or any of the other cytokines on the incidence of IPA in immunosuppressed or neutropenic patients.

CONCLUSION

Presently, the reduction of environmental exposure to aspergilli and early empiric antifungal treatment with amB in those patients with known risk factors or when IPA is suspected still remain the standard procedures to reduce the incidence of and the mortality from this condition. However, several novel approaches for the systemic and the topical prophylaxis of IPA are currently under investigation. Of those, the most promising seem to be the prophylactic systemic use of new amB formulations or high doses of one of the newer azol agents, the topical prophylaxis with amB aerosols, and the shortening of neutropenia through the administration of recombinant growth factors. Investigations into the effectiveness of each of these approaches will have to consider the specific epidemiology of IPA, the variable host susceptibilities, and the difficulties in diagnosing the condition. At present, the absence of prospective multicenter trials with adequate patient numbers to investigate strategies of preventing IPA is striking. Cooperative efforts will be necessary in order to achieve the goal of evaluating the contribution of each of these new approaches or their combinations in the prevention of IPA.

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