As it tackles the control of life-threatening diseases, the medical community continues to be faced with severely immunosuppressed individuals and the complicating features of managing invasive fungal infections. Fortunately, through the efforts of the pharmaceutical industry and clinical investigators during the past decade, 3 classes of antifungal agents (polyenes, azoles, and echinocandins) have been improved, expanded, and created, respectively. We are truly fortunate to have these excellent drugs available to treat our seriously ill patients. Although it will be extremely helpful to have new and/or improved antifungals in the future, a present focus of our clinical investigations needs to be the evaluation of strategies to optimally use the antifungal drugs we currently possess. For example, how do we use risk factors or fungal biomarkers to rapidly and consistently deliver prophylactic, empirical, preemptive, or therapeutic drugs? In this respect, the article by Rijnders et al. [1], published in this issue of Clinical Infectious Diseases, is right on target. The study by Rijnders and colleagues applies the use of available antifungal agents to a high-risk population of patients with prolonged neutropenia in a controlled, randomized, and placebo-driven manner to determine a new strategy to prevent invasive aspergillosis. This study was built on the backbone of successful antifungal prophylaxis with fluconazole in high-risk patients and the concerns that certain patient populations with invasive mold infections, such as invasive aspergillosis, escape detection. This study represents the third recent investigation that explores successful strategies to reduce the number of aspergillosis cases with antimold drugs. The other 2 studies used posaconazole in patients with high-risk hematologic malignancies and graft-versus-host disease [2, 3].

Credit should be given to the investigators in this study for their careful evaluation of aerosolized polyenes because this therapeutic area has always been murky; in fact, 1 previous placebo-controlled study did not show efficacy [4]. However, the findings of the animal studies were supportive of continuing with these studies, and with new lipid formulations of amphotericin B the efficacy might be different. The hypothesis that local drug administration into the lung would be protective needed to be retested. The article by Rijnders et al. convincingly indicates that this strategy is safe and reduced the number of invasive aspergillosis cases in this patient population at the medical center for this study. What does this study really mean for clinical practice? Approximately 15 years ago, during the beginning of the systemic azole prophylaxis era, I suggested that all clinicians consider at least 6 criteria before justifying the use of antifungal prophylaxis: (1) safety, (2) efficacy, (3) cost, (4) consequence, (5) prevalence, and (6) resistance [5]. I believe it is time to review this study in the context of these criteria.

Safety is an important issue in prophylaxis, because many of the patients who are given a drug may never need it, so clinicians must be sure to do no harm. In this aerosolized liposomal study, there was an increased risk of cough in patients receiving prophylaxis compared with those receiving placebo but no other identifiable adverse events. In our studies with aerosolized amphotericin B lipid complex [5, 6], we observed that it was better tolerated than aerosolized amphotericin B deoxycylolate [7], and so these lipid preparations or even others with amphotericin B not using the detergent deoxycholate may produce fewer adverse effects. Even when we examined lung tissue histologic findings with the use of aerosolized lipid amphotericin B, we did not find serious attributable lung abnormalities [6]. The accumulated human experience with aerosolized lipid products of amphotericin B might not yet reach toxicologic support for safety by the US Food and Drug Administration standards, but thus far, these products appear to be safe in their present use. In fact, there is a substantial therapeutic advantage in a drug that is admin-
istered to a single site and does not affect other organs or interact with other drugs. In the polypharmacologic use of our immunocompromised patients, this advantage should not be overlooked.

Efficacy is an important issue. This study has advanced the use of aerosolized drugs in its rigor of design and results. Of course, critics can point out the lack of a survival benefit, and others might focus on the use of less validated biomarkers, such as bronchoalveolar lavage galactomannan monitoring results, for end point diagnosis. Regarding survival benefit, it is likely that, in this group of patients, the study was underpowered for such an observation, and recently, in very high-risk neutropenic patients, it has been shown that prevention of invasive aspergillosis showed survival benefit with the use of posaconazole [2]. In this aerosol study, the biomarkers were also supported by radiographic findings, validating the hypothesis that aerosolized liposomal amphotericin B reduces invasive aspergillosis. In the clinical milieu today, it is likely that biomarkers will become an important end point in the evaluation of therapeutic strategies. From an efficacy standpoint, this is the most robust clinical study to date to support the value of aerosolized drug prophylaxis to prevent invasive aspergillosis. It is an excellent model for further strategies. Of course, it does not answer the question of whether it is the best or even comparable to other mold-active agents, such as systemic posaconazole, voriconazole, or even the polyenes/candins. Those comparisons will require further studies.

Costs of using antifungal agents for long periods in patients who may not need them can be substantial. Prophylactic strategies should always undergo a pharmacoeconomic analysis. However, the aerosolized drug is given in small amounts and intermittently, so drug acquisition costs are minimized. Furthermore, recent studies show that costs attributable to the management of an invasive aspergillosis will add more than $20,000 to hospital costs [8], and this does not factor in the productivity loss of any patient deaths.

The consequence of an invasive aspergillosis case is substantial, with mortality rates in some populations of >80% [9]. In this study, short-term survival did not have an impact, but with more patients and a longer observation period, the impact of invasive aspergillosis might be better appreciated. No clinician wants to treat a patient with invasive aspergillosis along with the underlying disease.

The prevalence of the infection is absolutely critical to decisions about antifungal prophylaxis. For most institutions, it is likely that the frequency of fungal infections would need to be >10% of the at-risk population to detect a local reduction in the number of fungal infections observed with prophylaxis [5]. For instance, in this study in the “on-treatment” analysis, ~13% of subjects in the placebo arm had invasive aspergillosis, compared with 2% in the aerosolized liposomal amphotericin B arm. However, in the posaconazole study of hematologic malignancies, the use of an extended-spectrum azole performed well enough to show that the number needed to treat to prevent invasive aspergillosis was 16 patients, even when the incidence rate in the other azole arm was slightly less than 10% [2]. The message to all clinicians is that there are now regimens that can reduce but not eliminate the incidence of invasive aspergillosis, and it is critical that clinicians carefully examine their patient population and general prevalence of invasive aspergillosis in their institution before selecting a specific mold prophylactic strategy.

Resistance must always be considered when antimicrobials are administered to large numbers of immunocompromised patients. It is likely that despite the lack of drug-resistant transposons or plasmids, fungi can develop resistance mechanisms and superinfections [10]. This possibility is always lurking with widespread azole use and will need to be carefully monitored. However, the rate of polyene resistance in fungi is very low, and high concentrations in airways have yet to demonstrate selection of drug-resistant strains.

In summary, this study has strengths and limitations. It is the culmination of animal studies and open human trials that support the use of aerosolized polyenes for prophylaxis in high-risk patients, and it is a viable strategy with many positive marks when the 6 criteria are examined. The field of clinical mycology continues to evolve and improve with this type of study, and it represents an alternate strategy for prophylaxis for these high-risk patients with neutropenia. On the other hand, there remain questions and limitations. First, the study only supports prophylaxis and not the use of an aerosolized lipid product for treatment of established aspergillosis infections. Would aerosolized drug penetrate necrotic infected tissue and could it synergize with systemic antifungals? Second, with the number of different nebulizers and preparations of amphotericin B and only a few dosages studied, it is not clear that we have optimized aerosolization strategies. Third, no comparative studies have been performed between aerosolized polyenes and the broader-spectrum azoles administered systemically for mold prophylaxis. Fourth, we have no understanding of long-term or repeated-use efficacy in other high-risk populations (e.g., lung transplant recipients) or whether other antifungal agents (e.g., the echinocandins) could be aerosolized. These limitations will require further studies, but there is no question that this study has put aerosolized liposomal amphotericin B on the map of strategies to prevent invasive aspergillosis in high-risk patients. “An ounce of prevention is worth a pound of cure” or is it “take a whiff for a protective gift”?

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References