Clinical Issues Regarding Relapsing Aspergillosis and the Efficacy of Secondary Antifungal Prophylaxis in Patients with Hematological Malignancies

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Advancements in early diagnosis and the introduction of effective agents have improved the rates of response of aspergillosis to primary antifungal therapy. These changes allow the subsequent continuation of cytotoxic chemotherapy and/or performance of hematopoietic stem cell transplantation in an increasing number of patients with hematological malignancies. These developments have increased interest in secondary prophylaxis of aspergillosis, because the resumption of myelotoxic chemotherapy in these patients is associated with high rates of relapse of this opportunistic mycosis in the absence of prophylaxis. However, the risk factors for relapsing invasive aspergillosis and the strategies for reducing risk are not well defined. Furthermore, differentiating aspergillosis relapse from reinfection with a new Aspergillus isolate is problematic when using the available laboratory tools. We summarize the existing knowledge regarding the pathogenesis of, risk factors for, and natural history of relapsing invasive aspergillosis and review the limited data regarding the role of secondary antifungal prophylaxis.

Invasive aspergillosis (IA) is the most common invasive mold infection in patients with hematological malignancies who have protracted severe neutropenia and immunosuppression because of chemotherapy and/or hematopoietic stem cell transplantation (HSCT). Pneumonia, with or without sinusitis, is the most common form of aspergillosis in this population [1]. Historically, the IA mortality rate has been high in such patients [2]. Use of new effective, less toxic antifungals, such as voriconazole, and routine early implementation of high-resolution chest CT, leading to prompt intensive antifungal therapy, have improved responses and survival [3, 4]. Such strategies frequently allow continued treatment of hematological disease with subsequent consecutive cycles of myelotoxic chemotherapy and/or peripheral blood stem cell transplantation or bone marrow transplantation (BMT). These developments have increased the interest in secondary antifungal prophylaxis (SAP), because prior IA without prophylaxis carries an unacceptable risk of relapse and death in patients with subsequent immunosuppression [5, 6]. Herein, we summarize the existing knowledge regarding the pathogenesis of, risk factors for, and natural history of relapsing aspergillosis and the role of different SAP strategies.

DEFINITIONS

We defined relapsing IA as a new episode of infection caused by the same Aspergillus isolate in a patient with prior IA treated successfully with an antifungal. However, distinguishing relapsing IA from reinfection due to another isolate of the same Aspergillus species during subsequent immunosuppression is not feasible on the sole basis of clinical grounds and conventional laboratory methods.

We defined successful treatment as resolution or near
resolution of attributable signs and symptoms of IA plus resolution or marked improvement and stabilization of radiographic abnormalities and sterilization of cultures (if the results were positive for IA). Because the aim of SAP is prevention of relapsing IA, we defined SAP as (1) antifungal administration (typically orally) as “step-down” therapy for IA that responded to systemic antifungals or (2) resumption of antifungal administration, with or without other interventions (e.g., granulocyte transfusions), in patients with prior IA that apparently resolved during subsequent intensification of immunosuppression.

**SEARCH METHODS**

We searched the Medline database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and relevant English-language articles, book chapters, and conference proceedings. We used the search terms “Aspergillus,” “antifungal therapy,” “relapsing or invasive aspergillosis,” “fungal infections,” and “antifungal secondary prophylaxis.”

**RESULTS**

We identified 25 studies that contained adequate information [5–29]. All 239 patients described therein had hematological malignancies, except for 10 patients [6, 29] who underwent HSCT for nonmalignant hematological disease (mainly aplastic anemia). Four studies [7, 17, 22, 23] were pediatric and reported data for only 16 patients; this did not allow us to reach conclusions for this age category.

All studies assessing the risk of relapsing IA and value of SAP were limited by small, heterogeneous patient populations; uncontrolled, retrospective designs; and different definitions of relapsing IA and SAP. Importantly, no studies differentiated IA relapse from reinfection. Typically, those describing primary IA responses to treatment did not include prolonged follow-up to assess relapse rate. Additionally, many studies did not document IA according to published consensus criteria [30]; however, these criteria do not capture many patients with histopathologically proven aspergillosis [31, 32]. Finally, frequent use of cointerventions (e.g., concomitant surgery and SAP) made separate assessment of each intervention difficult. Therefore, one should interpret these data cautiously because of potential publication biases, such as reporting only successfully treated cases, and miscategorization biases.

**PATHOGENESIS OF RELAPSING IA**

Although the pathogenesis of relapsing IA remains unclear, the most plausible mechanism is reactivation of a latent, subclinical infection that had not been fully eradicated by previous antifungal therapy. Unfortunately, the apparent resolution of attributable signs and radiological abnormalities of IA by antifungals after recovery from immunosuppression does not always imply a cure, because deep-seated microfoci of infection (i.e., less than the detection threshold with high-resolution CT [>1 mm]) remain, and reactivation could occur during subsequent immunosuppression.

Why aspergilli survive in infected tissue despite adequate antifungal treatment and eventual neutrophil recovery is not fully understood. Antifungal resistance and tolerance apparently are not major factors for such persistence, because resistant Aspergillus fumigatus strains are not frequently selected, even after prolonged antifungal therapy [33, 34]. In contrast, IA persistence may result from poor tissue penetration of antifungals in affected areas [34]. Aspergillus is an angioinvasive mold that causes tissue microinfarcts and poorly perfused necrotic areas.

Other factors may also impact the pathogenesis of IA relapses. For example, reactivation of herpesviruses or a respiratory virus or a concomitant bacterial infection may exert local or systemic immunosuppressive effects, allowing IA recurrence [35]. Even Aspergillus per se can suppress the host’s cellular immune responses [36].

Another potential factor predisposing patients to relapsing IA is propagation of IA at sites where sterilization with antifungals is difficult. These include foreign bodies (i.e., central venous catheters) [37], vegetations with Aspergillus endocarditis [38], and necrotic bone and lung lesions (sequestra) [39]. Finally, no data suggest a difference in the propensity for relapse among various Aspergillus species.

**CLINICAL FACTORS THAT AFFECT RELAPSING IA**

Immunosuppression, although difficult to quantify, is important to both risk and relapse of primary IA. Thus, during intensifying immunosuppression, factors like chemotherapy-induced, severe, and protracted neutropenia [40]; prior adrenal corticosteroid use [41]; reactivation of cytomegalovirus infection; and relapsed underlying leukemia reduce effector immune cells’ ability to control residual Aspergillus infection in areas of prior tissue damage, increasing the risk of relapsing IA. Table 1 lists factors that predispose individuals to relapsing IA.

Regarding patients with leukemia who do not undergo HSCT, a prospective, multicenter European registry collected data on 204 such patients with a previous treated, proven, or probable invasive fungal infection [42]. Among 72 patients with a proven invasive fungal infection, 51 (71%) had IA. Logistic regression analysis showed that predictors of relapsing invasive fungal infection during subsequent immunosuppression were steroid use, failure to induce complete remission of the underlying disease, high-dose cytokine arabinoside use, administration of >3 antibiotics, antibiotic use for >30 days, and neutropenia for >28 days.
Table 1. Factors predisposing patients to relapsing invasive aspergillosis (IA) according to the literature.

| Prior documented (versus probable/possible) IA [6, 19, 29] | Site of the initial Aspergillus infection (sinuses versus other) [6, 18] |
| Site of the initial Aspergillus infection (sinuses versus other) [6, 18] | Partial clinical response of prior IA and incomplete resolution of imaging findings before additional chemotherapy [6, 9, 14, 29] |
| Use of systemic corticosteroids [42] | Lack of remission of the underlying hematological malignancy [42] |
| Lack of remission of the underlying hematological malignancy [42] | Use of high doses of cytosine arabinoside [42] |
| Use of high doses of cytosine arabinoside [42] | Administration of >3 antibiotics [42] |
| Administration of >3 antibiotics [42] | Duration of neutropenia of >28 days [42] |
| Duration of neutropenia of >28 days [42] | HSCT with stem cells obtained from unrelated donors and/or mismatched family donors [6] |
| HSCT with stem cells obtained from unrelated donors and/or mismatched family donors [6] | Duration of primary antifungal therapy <1 month [29] |
| Duration of primary antifungal therapy <1 month [29] | Hematopoietic stem cell source (the highest risk for cord blood, followed by bone marrow and peripheral blood) [29] |

NOTE. HSCT, hematopoietic stem cell transplantation.

The literature on risk factors for relapsing IA with HSCT is scant. Whether well-known IA risk factors, such as use of corticosteroids, prolonged neutropenia, graft-versus-host disease (GVHD) [43, 44], advanced age, cytomegalovirus infection, receipt of antiviral prophylaxis with myelosuppressive agents like gancyclovir, and respiratory viral infections [45–48], also apply for relapsing IA in BMT is unknown. The published retrospective studies had small patient populations and, therefore, lack the statistical power to detect risk factors for relapsing IA. In the largest such study, which included 48 patients with prior IA and who subsequently underwent BMT, Offner et al. [6] examined the effect of variables like donor type (autologous, matched allogeneic sibling; mismatched sibling; or unrelated matched or mismatched donor), conditioning regimen, total body irradiation, T cell depletion, cyclosporine and growth factor use, neutropenia duration, and GVHD on the risk of relapsing IA. None of these factors affected the relapse or IA-related mortality rate except for use of a conditioning regimen with busulfan and cyclophosphamide, which was associated with a reduced IA-related mortality rate. However, even this finding should be interpreted cautiously, because those not receiving this regimen included 4 patients with aplastic anemia who underwent BMT despite having persistent active IA; all 4 had a poor outcome. In another retrospective study of 45 patients with known IA before HSCT [29], 13 patients (29%) had relapsing IA. In univariate statistical analysis, factors associated with increased risk of relapsing IA were a shorter primary antifungal therapy duration (≤30 vs. >30 days), hematopoietic stem cell source (cord blood vs. bone marrow vs. peripheral blood, 2 of 2 vs. 6 of 28 vs. 2 of 15; P = .001), and proven or probable diagnosis of prior IA versus possible diagnosis [29]. In multivariate analysis, only the pretransplantation antifungal therapy duration remained statistically significant. More recently, 43 patients with previous proven, probable, or possible invasive fungal infection underwent HSCT while receiving prophylaxis with systemic amphotericin B; only 11 patients (26%) had proven IA [19]. Advanced age, antithymocyte globulin use, neutropenia duration, and GvHD were not associated with an increased incidence of posttransplantation relapsing invasive fungal infection or with the invasive fungal infection–related mortality rate.

Because graft-manipulation procedures and conditioning therapy are changing, reexamination of the risk of relapse in contemporary series of HSCT recipients is important. For example, according to the limited literature, whether procedures that reduce neutropenia durations, such as reduced-intensity conditioning regimens and use of peripheral blood as a stem cell source, reduce the risk of relapsing fungal infections is unclear [10, 13, 27–29, 49].

The clinical activity of IA and type and intensity of antifungal treatment of primary IA may also affect the risk of relapse after further immunosuppression. In some studies, almost all patients with active IA before undergoing further chemotherapy or BMT died of rapidly progressive IA despite receiving antifungal therapy [6, 9, 14, 29]. In most published series and cases of relapsing IA, the patients received amphotericin B (deoxycholate or liposomal) alone or in combination with other antifungals (e.g., itraconazole or fluconazole). The existing data do not enable comparisons of amphotericin B with newer, more effective antifungals (e.g., voriconazole or caspofungin) or studies of combination antifungal therapy concerning the risk of relapse.

Finally, the initial Aspergillus infection site seems to influence the relapse risk, because Aspergillus sinusitis tends to relapse and disseminate more frequently. Specifically, Viollier et al. [18] showed that 11 (61%) of 18 leukemic patients with prior Aspergillus sinusitis had infection relapse and dissemination during subsequent chemotherapy. In the study by Offner et al. [6], all 4 patients with persistent Aspergillus sinusitis died of disseminated IA after subsequent BMT.

**CLINICAL FEATURES OF RELAPSING IA**

The IA relapse site is usually the primary IA site, although dissemination can occur. Offner et al. [6] reported relapse in the original location in all 16 patients with relapsed IA after BMT and in a different location in 3 patients. In a study of 13 patients with relapsing IA after HSCT, Fukuda et al. [29] found IA in the original location in all but 2 patients.

Relapsing IA has a higher mortality rate than primary IA does, ranging from 88% to 100% in the 2 studies described above [6, 29]. IA-related and overall mortality rates are higher among patients with prior documented IA, compared with patients with prior possible aspergillosis [6, 19, 29], probably reflecting the former patients’ higher fungal burden. Furthermore, the timing of IA relapse varies greatly. Offner et al. [6]
found that relapse occurred a median of 15 days (range, 0–120 days) after BMT, whereas Fukuda et al. [29] observed that the median time was 26 days (range, 1–242 days) after HSCT. Because the latter study was performed 6 years after the former, factors including use of newer antifungals, newer conditioning regimens, and better diagnostic modalities may have affected the timing of relapse.

**STRATEGIES FOR THE PREVENTION OF RELAPSING IA**

**SAP.** No prospective studies have examined SAP or its role in preventing relapsing IA. The existing experience with SAP is based on case reports and small retrospective studies (table 2). These studies included a total of 197 patients with previous proven or possible IA who received additional cytotoxic chemotherapy or HSCT while receiving SAP with amphotericin B, itraconazole, or flucytosine or combinations of these agents. SAP appeared to be successful, because only 31 patients (16%) had a documented IA relapse. However, whether this partially reflects publication bias is unknown. Furthermore, the overall mortality rate was significant (79 [40%] of 197 patients died) and was largely attributed to other causes. However, autopsy was performed in only a minority of cases. Therefore, one should interpret these data cautiously.

However, not initiating SAP in patients with previous IA clearly increases the risk of relapse unacceptably: 26 (62%) of 42 reported patients who did not receive SAP had relapsing IA after chemotherapy and/or HSCT (table 2). This risk is significantly higher than that in patients receiving SAP (26 of 42 vs. 31 of 197 patients; \( P < .0001 \)). Although the risk of IA relapse should be higher in patients receiving SAP with fluconazole than in patients receiving SAP with a mold-active agent, no studies have specifically addressed this issue.

The introduction of antifungals strongly active against *Aspergillus* species, such as voriconazole [50], itraconazole, the echinocandins [51], and posaconazole [52], has offered new options for secondary prophylaxis in patients with prior IA undergoing additional immunosuppression. For example, 2 retrospective studies [8, 26] that involved 2 and 10 leukemic patients with prior IA who received SAP with oral or intravenous voriconazole, respectively, for 44–245 days during HSCT (11 patients) or consolidation chemotherapy (1 patient) found that no patients had an IA relapse. Also, in a recent multicenter retrospective European study, 31 patients with a prior invasive fungal infection (6 with proven IA) received additional chemotherapy and SAP with caspofungin [53]. The overall incidence of relapsing invasive fungal infection was 19%, and the overall mortality rate was 16%, with only 1 death attributed to relapsing invasive fungal infection.

**Surgery.** Resection of residual *Aspergillus* lesions after the primary infection might also prevent relapsing IA after additional immunosuppression. There have been numerous reports of patients with IA (pneumonia, abscess, or sinusitis) treated with resection of lesions plus administration of antifungals before further chemotherapy or HSCT [6, 9, 12, 14, 15, 20–23, 28, 29]. The timing and magnitude of these interventions varied greatly. The vast majority of patients had no IA relapse even without receiving SAP. This agrees with the findings of most [4, 29, 54] but not all [13, 20] studies reporting lower mortality rates in patients with IA receiving antifungals and surgery than in those receiving antifungals only. However, 4 studies [5, 6, 18, 29] showed that surgery did not significantly affect the risk of relapsing IA after BMT. In addition, although there have not been frequent reports of relapsing IA because of infected foreign bodies, removal of such foci of infection before further immunosuppression seems reasonable.

Although the role of surgery in preventing relapse of IA remains undefined, young patients in hematological remission with good performance statuses and solitary *Aspergillus* lesions appear to benefit the most. In comparison, postoperative recovery may delay chemotherapy or HSCT and thus the durability of hematological remission.

**Immune enhancement and other strategies.** The role of hematopoietic colony-stimulating factors, such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and granulocyte-IFN colony-stimulating factor, in preventing relapsing IA has not been established by existing data [6, 29]. In the study by Offner et al. [6], only 11 patients received growth factors during BMT. The administration of these factors did not reduce the risk of relapsing IA; yet there was a trend toward reduced relapse, overall mortality, and IA-related mortality rates.

For some time, granulocyte transfusion remained a logistically difficult, expensive, experimental intervention with questionable efficacy [29, 55]. Use of granulocyte colony-stimulating factor to stimulate donor leukocytes has increased the numbers of collected granulocytes and renewed interest in this method. In 2 recent studies [28, 56], investigators used granulocyte colony-stimulating factors–elicited granulocyte transfusions as SAP during HSCT in 2 and 12 patients with prior IA, respectively. No patients had an infection relapse, but during the long-term follow-up period, only 5 patients (2 and 3 patients, respectively) survived. Although the investigators in the second study [56] performed no autopsies, they did not list relapsing IA as a contributor to death in the remaining 9 patients.

Regarding adjunct immune augmentation strategies in heavily immunosuppressed nonneutropenic patients with prior IA, no studies have focused specifically on secondary prophylaxis. Recent exciting work on the feasibility of adoptive immunotherapy with *Aspergillus*-specific T cells in haploidentical transplant recipients with IA may open doors for novel immune
Table 2. Clinical data from reports of patients with hematological malignancies and a history of invasive aspergillosis (IA) who underwent further chemotherapy (CHT) and/or hematopoietic stem cell transplantation (HSCT).

<table>
<thead>
<tr>
<th>Reference Year</th>
<th>No. of patients with proven or probable IA</th>
<th>Therapy for primary IA (no. of patients)</th>
<th>Subsequent CHT/HSCT (no. of patients)</th>
<th>Status of IA before CHT/HSCT (no. of patients)</th>
<th>Type of SAP (no. of patients)</th>
<th>Proportion of patients with IA relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18] 1986</td>
<td>18</td>
<td>AmB</td>
<td>CHT</td>
<td>CR</td>
<td>None</td>
<td>11/18 (61)</td>
</tr>
<tr>
<td>[21] 1988</td>
<td>1</td>
<td>AmB, 5-FC, and surgery</td>
<td>HSCT</td>
<td>CR</td>
<td>AmB and Itr</td>
<td>0/1</td>
</tr>
<tr>
<td>[14] 1988</td>
<td>10</td>
<td>AmB and 5-FC</td>
<td>CHT</td>
<td>CR (5); PR (5)</td>
<td>AmB and 5-FC (9)</td>
<td>AmB and 5-FC group, 0/9; no SAP, 1/1</td>
</tr>
<tr>
<td>[22] 1992</td>
<td>1a</td>
<td>AmB and surgery</td>
<td>HSCT</td>
<td>NM</td>
<td>None</td>
<td>0/2</td>
</tr>
<tr>
<td>[15] 1993</td>
<td>7</td>
<td>AmB (4); AmB and Itr (1); and AmB and surgery (3)</td>
<td>CHT</td>
<td>CR</td>
<td>AmB</td>
<td>0/8</td>
</tr>
<tr>
<td>[12] 1993</td>
<td>7</td>
<td>AmB (1); AmB and surgery (6)</td>
<td>HSCT</td>
<td>CR</td>
<td>AmB</td>
<td>0/7</td>
</tr>
<tr>
<td>[23] 1994</td>
<td>3a</td>
<td>AmB and Itr (2); AmB and surgery (1)</td>
<td>HSCT (2); CHT (1)</td>
<td>CR</td>
<td>Itr</td>
<td>0/3</td>
</tr>
<tr>
<td>[11] 1994</td>
<td>4</td>
<td>AmB and Itr (3); Itr (1)</td>
<td>HSCT</td>
<td>CR</td>
<td>Itr</td>
<td>0/4</td>
</tr>
<tr>
<td>[20] 1996</td>
<td>7</td>
<td>AmB (3); AmB and Itr (4)</td>
<td>HSCT</td>
<td>CR</td>
<td>Itr</td>
<td>0/7</td>
</tr>
<tr>
<td>[16] 1994</td>
<td>2</td>
<td>AmB (1); AmB and surgery (1)</td>
<td>HSCT</td>
<td>CR</td>
<td>Itr</td>
<td>0/2</td>
</tr>
<tr>
<td>[17] 1997</td>
<td>4a</td>
<td>AmB (2); AmB and surgery (2a)</td>
<td>HSCT</td>
<td>CR</td>
<td>Itr</td>
<td>0/4</td>
</tr>
<tr>
<td>[9] 1997</td>
<td>8</td>
<td>AmB (4); Itr (1); AmB and Itr (2); AmB and surgery (1)</td>
<td>HSCT (6); CHT (2)</td>
<td>CR</td>
<td>Itr</td>
<td>Prior CR IA, 0/4; prior active IA, 3/4</td>
</tr>
<tr>
<td>[6] 1998</td>
<td>48</td>
<td>Itr (4); AmB and Itr (4); AmB (38); AmB and 5-FC (2); antifungals and surgery (20)</td>
<td>HSCT</td>
<td>CR (30); PR (12); active (6)</td>
<td>AmB (23); Itr (6); AmB and Itr (12); none (7)</td>
<td>With SAP, 12/41; without SAP, 1/4</td>
</tr>
<tr>
<td>[27] 1999</td>
<td>1</td>
<td>AmB</td>
<td>HSCT</td>
<td>Active</td>
<td>AmB followed by Vor</td>
<td>0/1</td>
</tr>
<tr>
<td>[10] 2000</td>
<td>1</td>
<td>AmB and Itr</td>
<td>HSCT</td>
<td>Active</td>
<td>AmB</td>
<td>0/1</td>
</tr>
<tr>
<td>[13] 2001</td>
<td>9</td>
<td>AmB and Itr (8); AmB and Vor (1)</td>
<td>HSCT</td>
<td>CR</td>
<td>PR</td>
<td>AmB (7); none (2)</td>
</tr>
<tr>
<td>[24] 2001</td>
<td>9</td>
<td>AmB (2); AmB and Itr (4); AmB and surgery (2); Itr (1)</td>
<td>HSCT</td>
<td>CR</td>
<td>PR</td>
<td>AmB (5); Itr (4)</td>
</tr>
<tr>
<td>[28] 2001</td>
<td>2</td>
<td>AmB and surgery</td>
<td>HSCT</td>
<td>PR</td>
<td>AmB (1); AmB and Vor (1)</td>
<td>0/2</td>
</tr>
<tr>
<td>[26] 2002</td>
<td>2</td>
<td>Vor</td>
<td>HSCT</td>
<td>CR</td>
<td>Vor</td>
<td>0/2</td>
</tr>
<tr>
<td>[7] 2003</td>
<td>8a</td>
<td>AmB (2); AmB and surgery (6)</td>
<td>HSCT (3); CHT (5)</td>
<td>CR</td>
<td>AmB and Itr (3); Itr (5)</td>
<td>1/8</td>
</tr>
<tr>
<td>[8] 2004</td>
<td>10</td>
<td>AmB plus Vor and/or Itr (9); Itr and Vor (1)</td>
<td>HSCT (6); CHT (5)</td>
<td>CR</td>
<td>PR (4)</td>
<td>Vor</td>
</tr>
<tr>
<td>[29] 2004</td>
<td>45</td>
<td>AmB (38); AmB plus Vor or Casp (7); antifungals and surgery (13)</td>
<td>HSCT</td>
<td>CR</td>
<td>PR (19)</td>
<td>AmB (40); Flu or Itr (5)</td>
</tr>
<tr>
<td>[19] 2005</td>
<td>11</td>
<td>NM</td>
<td>HSCT</td>
<td>CR</td>
<td>AmB (with or without Flu-Itr)</td>
<td>2/11</td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B (deoxycholate and liposomal); Casp, caspofungin; CR, complete remission; Flu, fluconazole; 5-FC, 5-flucytosine; IFI, invasive fungal infection (i.e., infections due to any fungus, including *Aspergillus* or *Candida* species); Itr, itraconazole; NM, not mentioned; PR, partial remission; SAP, secondary antifungal prophylaxis; Vor, voriconazole.

a Pediatric patients.
b All 4 patients also received Itr, 5-FC, or Flu.
c Data from 34 patients with pulmonary aspergillosis.
interventions for both primary and secondary prophylaxis for IA [57].

Finally, because reactivation of an endogenous focus of a preexisting *Aspergillus* lesion is the mechanism of relapsing IA, isolation of patients with prior IA in a room equipped with a laminar airflow system and high-efficiency particulate air filtration may prevent reinfection but not a relapse.

### EARLY DIAGNOSIS AND TREATMENT OF RELAPSING IA

Because diagnosing relapsing IA in a reliable, timely manner is difficult, a high index of suspicion and careful clinical assessment are required. Extensive staging evaluation should precede resumption of chemotherapy and initiation of HSCT in patients with prior IA. Also, physicians should perform biopsies of suspicious lesions; CT imaging of the chest, sinuses, abdomen, and brain; and appropriate mycology cultures. There is not much experience with performing newer non–culture-based diagnostic methods, such as *Aspergillus* galactomannan ELISA [58] and PCR [59], to detect early relapsing IA and thus promptly initiate pathogen-specific therapy. Only anecdotal reports have suggested the potential of galactomannan ELISA in monitoring progression and/or relapse [60, 61].

Furthermore, organized experience and published data regarding the best treatment of relapsing IA are lacking. Almost all reported patients with relapsing IA received amphotericin B alone or combined with itraconazole, with poor results. The number of patients who survived relapsing IA was too small to draw conclusions from their antifungal regimens [6, 24]. However, the high mortality rate in patients with relapsing IA shows that aggressive approaches (such as use of rapid tapering of immunosuppression, a low threshold for switching to investigational antifungals, and antifungal therapy plus immune restoration strategies) are needed.

### PERSPECTIVES/OBJECTIVES FOR FUTURE RESEARCH

The poor natural history of IA in highly immunosuppressed hosts with hematological malignancies has made clinicians reluctant to perform otherwise life-saving chemotherapy or HSCT with myeloablative conditioning regimens in patients with prior IA [62]. Although the transplantation risk-benefit ratio in patients with IA is not clear, studies suggest that the BMT benefits outweigh the IA relapse risk [6, 15–17]. Well-designed prospective studies assessing old and new antifungals in SAP and cointerventions, such as granulocyte colony-stimulating factor–elicited granulocyte transfusions plus antifungal administration, are urgently needed. Additionally, future research should include using innovative imaging techniques (e.g., positron emission tomography) [63] to monitor the metabolic activity and viability of *Aspergillus* in pulmonary nodules after primary antifungal therapy and before further immuno-suppression; further development and standardization of non–culture-based techniques to diagnose relapse reliably and early; use of molecular typing to differentiate between IA relapse and reinfection; identification of risk factors and development of risk-stratification models to further identify patients at increased risk for relapse (e.g., patients who have unique polymorphisms); and development of effective strategies for preventing and treating relapsing IA.

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