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Aspergillosis: Spectrum of Disease, Diagnosis, and Treatment

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Aspergillus species are ubiquitous environmental molds that grow on organic matter and aerosolize conidia [1]. Humans inhale hundreds of conidia per day without adverse consequences except for a small minority of people for whom infection with *Aspergillus* spp causes significant morbidity. The clinical manifestations of aspergillosis are determined by the host immune response to *Aspergillus* spp with the spectrum ranging from a local inappropriate inflammatory response, causing allergy, to local saprophytic lung disease with mycelial balls, to catastrophic failure of the immune response to contain pulmonary disease and resultant systemic *Aspergillus* spp dissemination. For the clinician, *Aspergillus* spp infection presents a diagnostic and management challenge. Only by understanding the immune status of the host and the resultant risk of allergic versus local versus potentially invasive disease can the clinician attempt to make an appropriate diagnosis and management plan.

Mycology and pathogenesis of disease

In the environment *Aspergillus* spp are present as the mold form with formation of aerial hyphal stalks [1]. The conidia formed by asexual reproduction are small (2–10 μm in diameter) and hydrophobic, which aids aerosolization

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[2]. After inhalation by the host, uncontrolled germination of conidia into hyphae in the lung results in the potentially angioinvasive form of the mold [2].

The *Aspergillus* genus comprises approximately 180 species, of which 34 have been associated with human disease. Historically, *A fumigatus* caused 90% of aspergillosis syndromes. Increasingly, disease is caused by non-fumigatus species, however [3–5]. In a recent study the *Aspergillus* spp associated with infections occurring after hematopoietic stem cell transplantation (HSCT) included *A fumigatus* (56% of cases), *A flavus* (18.7%), *A terreus* (16%), *A niger* (8%), and *A versicolor* (1.3%) [3]. Of particular concern is *A terreus*; the prognosis of invasive disease is especially poor, and the organism is resistant to amphotericin in vitro [4]. In addition, other species with variable susceptibilities to antifungal agents are being described [5,6].

Although *A fumigatus* is recognized as the most common cause of invasive infection, few virulence genes have been identified, probably, in part, because of difficulties in disruption of gene candidates and redundancies in cellular functions [2]. Recently, however, the expressed transcriptional regulator; LaeA, which coordinates multiple gene clusters of *A fumigatus*, was demonstrated to be important to allow the organism to establish invasive infection in the murine host [7]. The size, hydrophobicity, and cell wall pigments of conidia are thought to be important in conidia dissemination and interaction with the host immune response [2,7,8]. As reviewed elsewhere, proteases secreted from hyphae mediate tissue destruction, hinder the immune response, and also are important in the allergic manifestations of aspergillosis [2].

Both the acquired and innate immune systems have vital roles in defense against *Aspergillus* spp. As conidia enter the lung, resident pulmonary macrophages are ideally placed to phagocytose and destroy the conidia [9], presumably with little local cytokine response, because people inhale hundreds of conidia per day with no evident inflammation. Germination of conidia into the more invasive form hyphae, however, exposes β-glucans, and possibly other *Aspergillus* ligands, which interact with pattern recognition receptors (Toll-like receptors and Dectin) on macrophages, with the resultant production of proinflammatory cytokines [10,11]. Animal studies of invasive aspergillosis (IA) show a profound pulmonary neutrophil response to *A fumigatus* followed by a lymphocytic infiltrate, probably attracted by macrophage cytokines [12]. The vital role of neutrophils is demonstrated in animal models, in which neutropenic rabbits rapidly develop invasive disease [12], and in humans, for whom neutropenia is an independent risk factor for IA [13]. The development of a CD4 Th-1 lymphocyte response seems to be protective in animal studies of IA [14]. A CD4 Th-2 response in humans is associated with the allergic forms of aspergillosis, however [15,16]. The reasons some people develop a Th-2 rather than a Th-1 response to *Aspergillus* spp are not yet well described.

Clinical syndromes, epidemiology, diagnosis, and treatment

Allergy

The immune system of some individuals reacts inappropriately to *Aspergillus* spp and causes symptomatic local "allergic" disease that can be manifest by asthma, allergic bronchopulmonary aspergillosis (ABPA), and allergic sinusitis [16–18]. The risk of invasive disease is very low in these individuals.

Asthma

There is accumulating evidence to implicate fungi, including *Aspergillus* spp, as a cause of severe asthma [17]. Mold sensitivity has been associated with increased asthma severity and death [19].

Allergic bronchopulmonary aspergillosis

ABPA may be an extreme form of *Aspergillus* spp–driven asthma. The disease manifests as a vigorous CD4 Th-2 response in the lungs and production of *Aspergillus* spp–specific serum IgE [16,17,20]. The consequent inflammatory and obstructive bronchopulmonary injury produces steroid-dependent asthma, with the unusual symptoms of fever and hemoptysis, bronchiectasis, airway destruction, and, if inadequately treated, permanent lung injury with fibrosis [16,17,20]. The prevalence of ABPA is between 6% and 25% in people who have cystic fibrosis [16] and between 1% and 2% in asthmatic patients [17]. The underlying pathogenesis may be related to the host genetics of *Aspergillus* antigen presentation to the immune system, in particular with HLA-DR restriction [21]. Patients who have ABPA have been shown to have an increased frequency of the cystic fibrosis gene mutation, but a causative role of the gene has not yet been well described [22].

The diagnosis of ABPA is by a combination of clinical, radiologic, and laboratory parameters. Radiographic evidence includes pulmonary infiltrates that resolve with corticosteroids and central bronchiectasis (although infiltrates may not be evident in early disease) [17]. Detection of specific serum IgE against recombinant antigens of *A fumigatus* is sensitive and specific for ABPA, with levels of at least 500 IU/mL thought to be diagnostic [17,23]. This technique also has shown promise in the follow-up of patients after steroid therapy and the early detection of recurrences [23]. Other suggested criteria for diagnosis include detection of IgG specific for *Aspergillus* spp and a positive *Aspergillus* skin prick test, in the absence of response to other fungi [17].

Current treatment for ABPA is oral corticosteroids during an acute phase or exacerbation and itraconazole for antifungal therapy, but there is little evidence to suggest benefit from prolonged use of itraconazole [16,24,25]. Voriconazole and other currently investigational azole drugs probably have a future therapeutic role. In a small study, 13 children who had definitive ABPA were treated with voriconazole, with or without immunomodulatory

agents, and all demonstrated significant and sustained improvements in clinical and serologic parameters for up to 13 months [26].

Allergic sinusitis

Allergic fungal sinusitis is a noninvasive but recurrent inflammatory sinusitis that occurs as an allergic response to local *A fumigatus* infection [27]. Patients typically are young (in their early 30s) with a history of atopy and initially present with hypertrophic sinus disease and nasal polyps [18]. Diagnosis depends on the findings of type I hypersensitivity, nasal polyps, and mucus containing fungal elements and Charcot-Leyden crystals (allergic mucin) [27]. CT scan is almost always abnormal with evidence of destructive pansinusitis [18], but histology reveals no fungal invasion, only a local hyperinflammatory response [18,27]. Treatment centers on endoscopic removal of debris and hyperplastic tissue [18]. The role of antifungal agents is unclear, although systemic therapy with itraconazole and topical application of amphotericin have been attempted [28,29]. In a large retrospective review, corticosteroids showed some benefit, as assessed by symptoms [30].

Local saprophytic disease: mycelial balls without allergy or invasion

Aspergillomas are mycelial balls that grow in areas of devitalized lung such as a damaged bronchial tree, a pulmonary cyst, or from the cavities of patients who have underlying cavitary lung diseases [31]. They may manifest as asymptomatic radiographic abnormalities or lead to hemoptysis that can be life threatening [31]. Upper lobes are the most frequently involved sites, perhaps because of the prevalence of tuberculosis cavities [31]. Definitive treatment is surgical resection, but these patients often have inadequate lung function to tolerate thoracic surgery, which can carry a significant mortality (5% in one study) [31]. Other treatment options include azoles and percutaneous instillation of antifungal agents [32].

Mycelial balls can also be found in sinuses [18], and endoscopic removal is required. There is no established role for antifungal agents.

Semi-invasive disease

On the borderline between saprophytic and invasive disease is a group of diseases in which mycelial balls are present, but with progressive fibrosis and minimal fungal invasion [33]. The nomenclature of the disease is currently changing [33], and three distinct entities are suggested based on radiologic appearance [33]. The formation and expansion of multiple cavities, some containing fungus balls, has been termed "chronic cavitary pulmonary aspergillosis" (CCPA) [33]. Patients who have CCPA have positive aspergillus precipitins and raised inflammatory markers. In some cases, this condition progresses to marked and extensive pulmonary fibrosis, termed "chronic fibrosing pulmonary aspergillosis" (CFPA; second category) [33]. Pleural

involvement may occur, either as direct invasion of the pleural cavity or as fibrosis. The third category is the progressive enlargement of a single cavity occurring slowly over months or rapidly within weeks, with slowly progressive IA [33]. These patients differ slightly from those who have CCPA and CFPA because they usually have minor or moderate degrees of immune dysfunction, such as diabetes or corticosteroid use [33]. Treatment is with antifungal agents and surgery. Voriconazole is proving efficacious [34]. It may be difficult clinically to differentiate semi-invasive disease from noninvasive saprophytic aspergilloma, however. Factors that always must be considered are whether the patient is immunosuppressed (ie, at higher risk of invasive disease), whether the disease is progressing, and whether hyphae (signalling invasive disease) are seen in tissue on biopsy, if available [33].

Invasive sinopulmonary aspergillosis and disseminated disease

Epidemiology

Invasive sinopulmonary aspergillosis and disseminated aspergillosis represent a direct failure of the immune system to control local infection. With recent historical mortality rates approaching 100% in severely immunosuppressed populations, it is a deservedly feared infection.

In recipients of HSCT, the incidence of IA increased during the 1990s (Table 1). Suggested reasons include changes in conditioning chemotherapy regimens, changes in prophylaxis strategies for cytomegalovirus infection, the introduction of different sources of stem cells, and the use of therapeutic monoclonal antibodies [35,50]. In addition some centers report a much higher incidence than others, suggesting geographic influence or variability in diagnosis between institutions [3,51]. This difference should be considered when assessing incidence of IA disease. In contrast, the incidence of IA in patients receiving lung transplants may be declining, possibly because of effective prophylaxis with nebulized amphotericin [38,40].

The interval between transplantation and the development of IA has increased, particularly in recipients of allogeneic HSCT [13,35,36] and recipients of liver or heart transplants (see Table 1) [43,44]. Clinicians must have a high suspicion of IA long after transplantation, especially in patients who have long-term immunosuppression associated with graft-versus-host disease, organ rejection, or other posttransplantation complications such as cytomegalovirus (Table 2).

At highest risk from IA are recipients of allogeneic HSCT and persons who have hematologic cancer or neutropenia, especially if prolonged. At lower risk are recipients of autologous HSCT and solid-organ transplants. Also at risk are persons who are malnourished, recipients of corticosteroids, and patients who have HIV, diabetes, underlying pulmonary disease, and solid-organ cancer. At low risk, although often colonized with *Aspergillus* spp, are persons who have cystic fibrosis and connective tissue disease

Table 1
Epidemiology of invasive aspergillosis after transplantation

Type of transplant	HSCT Autologous	HSCT Allogeneic	Lung	Heart	Liver	Kidney
Incidence (%)	0.5–4 [3,13,35]	2.3–11 [3,13,35]	2.4–6 [3,38,39]	0.3–6 [3,38,42]	1–8 [38]	0.1–4 [3,38]
Median time to onset after transplantation	78 days –102 days [13,36,37]	78 days –102 days [13,36,37]	TRB = 3 months IA = 5–10 months [40]	75% of cases occur within 90 days [38,43]	17 days [44]	
Survival 3 months after diagnosis of IA (%)	47 [3]	15 [3] Probability of survival by time from transplantation[a] Early IA 0.35 Late IA 0.38 Very late IA 0.4 [35]	IA 18–33 TRB = 80 [3,40,41]	10–50 [3,3]	15–40 [40,45,46–48]	25–33 [3,38,49]

Abbreviations: HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; TRB, tracheobronchitis.

[a] Early IA, < 40 days after transplantation; late IA, 40 days to 6 months after transplantation; very late IA, > 6 months after transplantation.

[49,51]. In addition, specific factors affect the risk of IA within the cohorts of patients receiving HSCT and solid-organ transplants. These factors are summarized in Table 2.

The understanding of diseases that place a person at particular risk for IA is also changing. Multiple myeloma has emerged as a significant risk factor for IA, even in the absence of neutropenia [35]. In addition, IA is emerging as a devastating infection in ICU patients previously considered immunocompetent. Isolation of *Aspergillus* spp from these patients therefore must be regarded with a higher degree of clinical suspicion for IA than was previously thought necessary [60].

Survival in patients who have IA, particularly HSCT recipients [35], seems to be improving slowly (Box 1). The mortality of HSCT recipients was greater than 95% in 1990 [61] and was between 55% and 80% in recent studies [3,35,50]. This improvement probably reflects better antifungal agents (in particular voriconazole) and increased diagnostic capabilities.

Clinical manifestations of infectious aspergillosis

Invasive pulmonary aspergillosis manifests as pulmonary parenchymal invasion, inflammation, and the possibility of hematogenous spread of the fungus. Invasive pulmonary aspergillosis is the most common manifestation of *Aspergillus* spp infection in immunosuppressed patients.

There are also distinct bronchial diseases. *Aspergillus* tracheobronchitis (ATB) is an uncommon clinical presentation of pulmonary aspergillosis. Patients who have neutropenia and AIDS, and have received lung transplants are at risk. There are three recognized forms of ATB [64]. Obstructive ATB, described initially in patients who had AIDS and heart transplant recipients, is characterized by noninflammatory thick mucous plugs full of *Aspergillus* spp (demonstrated on CT scan in Fig. 1C) [65]. Pseudomembranous ATB shows extensive inflammation of the tracheobronchial tree, with a membrane overlying the mucosa containing *Aspergillus* spp [65]. Ulcerative ATB manifests as limited involvement of the tracheobronchial tree, usually at the suture line in lung transplant recipients [64,65]. Bilateral lung and right lung transplants are particularly susceptible to these infections [66]. The focus of infection is probably a nidus of *Aspergillus* infection in the native diseased lung [41,67]. Amphotericin prophylaxis and surveillance bronchoscopy, with surgery and antifungal therapy, have resulted in favorable outcomes for ulcerative ATB [65]. In contrast, for obstructive and pseudomembranous ATB the prognosis remains very poor [65].

Invasive sinus disease may present with headache, stuffiness, or nonspecifically with fever. In more advanced cases, proptosis and cranial nerve palsies become evident as *Aspergillus* spp invades the skull and neural tissue. The disease is very aggressive [45]. Systemic dissemination may present with infection of any organ, particularly the eyes and the skin [45].

Table 2
Factors reported to increase risk of invasive aspergillosis in hematopoietic stem cell and solid-organ transplantation

Transplant	Factors that increase risk of developing invasive aspergillosis
All HSCT	Type of transplant: allogeneic unrelated > allogeneic HLA matched > autologous
Allogeneic HSCT: early IA (within 40 days of transplantation)	Underlying disease: Hematologic malignancy in other than first remission [13], aplastic anemia, myelodysplastic syndrome, multiple myeloma [35]
	Cells from cord blood [35]
	Development of cytomegalovirus disease [35]
	Transplantation not done in room with laminar air flow [13]
	Transplantation done in summer [13]
Allogeneic HSCT: late IA (41–80 days after transplantation)	Unrelated donor transplant [13]
	Acute GVHD [13,35,36]
	Corticosteroids [13,35,36]
	Increased age [13,35]
	Transplant done at the time of building construction [13]
	Prolonged neutropenia [13,35]
	Delayed engraftment of T cells [35]
	Transplantation with T-cell–depleted or CD34-selected stem cells [35]
	Multiple myeloma [35]
	CMV+ donor /recipient, patients [35]
	Patients who developed CMV disease after day 40 [35,36].
	Respiratory virus infections after day 40; parainfluenza 3 and RSV [35]
HSCT 180+ days after transplantation	Neutropenia [35]
	Clinically extensive chronic GVHD [35]
	Receipt of unrelated or HLA-mismatched PBSCs [35]
	CMV disease [35]
Liver	Renal dysfunction [38,46]
	Retransplantation [38,46]
	Indications for transplant: fulminant hepatic failure [52] or HCV [44]
	CMV infection [53]
Lung	Single lung transplant [40,41]
	History of *Aspergillus* spp colonization before transplantation (eg, in COPD [40,38,54,55] except in patients who have cystic fibrosis [38]).
	CMV disease [56]
	Steroid therapy [6]
Heart	Reoperation [57]
	CMV disease [57]
	Posttransplantation hemodialysis [57]

Table 2 (*continued*)

Transplant	Factors that increase risk of developing invasive aspergillosis
Kidney	Existence of an episode of invasive aspergillosis in the institution's heart transplant program 2 months before or after the transplantation [57] High-dose and prolonged corticosteroids [58] Graft failure requiring hemodialysis, Potent immunosuppressive therapy [59,49]

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; GVHD, graft-versus-host disease; HCV, hepatitis C virus; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; PBSC, peripheral blood stem cell; RSV, respiratory syncytial virus.

Diagnosis of invasive aspergillosis

The clinical symptoms and signs associated with invasive pulmonary aspergillosis are notoriously vague but may be associated with fever, cough, pleuritic pain, and hemoptysis [45]. Early intervention in the high-risk patient is life saving. An ideal diagnostic test for IA would have very high sensitivity for early disease but would be sufficiently specific to allow a reduction in the use of empiric antifungal agents. In addition the test could be used to follow response to therapy. Current diagnostic methods have yet to reach this goal. Diagnosis is based on a combination of clinical risks, symptoms and signs, culture, histopathology, and detection of the fungal components such as the antigen galactomannan. These tests must be interpreted in the context of the patient's individual risk of infection to obtain a realistic probability of IA.

Radiology plays an important role in diagnosis and follow-up. Early findings on CT of invasive pulmonary aspergillosis are ground-glass attenuation surrounding a pulmonary nodule, the halo sign [68]. Although this sign is not specific to IA, use of CT for preemptive screening has been shown to improve early diagnosis and outcome [69]. Lesions may become bigger in the first 10 days of therapy and with neutrophil engraftment. This enlargement should not be taken as a sign of treatment failure [70]. Eventually nodules cavitate (Fig. 1A, B) and can produce the CT air-crescent sign [70]. None of the early CT signs seems to predict outcome of infection [70]. Radiographic presentation of IA in non-neutropenic patients, such as allogeneic HSCT recipients who have graft-versus-host disease, are less well described and may be more variable. The authors have seen cases in this setting diagnosed after appearance of isolated or multiple nodules, lobar infiltrates, and very diffuse ground glass opacities.

Bronchial aspergillosis can present radiographically with an obstructive pneumonia (Fig. 1C). Hence significant *Aspergillus* spp infection should be considered in immunocompromised patients, regardless of the radiographic presentation.

Box 1. Factors reported to affect risk of death from invasive aspergillosis

After hematopoietic stem cell transplantation
Graft-versus-host disease [13,62]
Neutropenia [13]
Cytomegalovirus seropositivity [13]
Prolonged use of corticosteroids [13,62,63]
Prolonged immunosuppression [63]
Disseminated invasive aspergillosis [63]
Fungal load [63]
Presence of pleural effusion [62]
Monocyte count of less than 120 cells/mm^3 [62]

After heart, lung, liver, and kidney transplantation
Hyper immunosuppression
Renal failure
More complicated postoperative course
Repeated bacterial infection
Older age [42]

The culture of *Aspergillus* spp is becoming increasingly important, given the emergence of antifungal drug–resistant non-fumigatus *Aspergillus* spp and a growing incidence of other molds causing invasive disease [3,50]. Growth from a sterile site is diagnostic of disease. A respiratory culture must be interpreted in the context of the risk for the patient, however. The positive predictive value for IA of a respiratory sample growing *Aspergillus* spp increases with rising immunosuppression [51,71]. One study showed a positive predictive value of 77% for respiratory cultures from patients who had hematologic malignancies, granulocytopenia, or HSCT, of 58% for patients who had received solid-organ transplants or steroids, and of 14% from patients who had HIV [71]. In HSCT recipients, the positive predictive value of a respiratory culture of 77% [71] makes preemptive screening for IA using respiratory cultures feasible in this cohort; however, the low negative predictive value raises questions regarding resource use.

Histology is being undertaken less frequently because biopsy is invasive. Identification of dichotomous acute-angle branching hyphae in a tissue section is definitive for fungal infection, however, and often is the only positive indication of etiology, although it is not specific for *Aspergillus* spp [1]. In situ hybridization and polymerase chain reaction (PCR) of fungi from histologic specimens are being analyzed for clinical utility when fungi are not cultured or the morphology is unclear [72,73].

The galactomannan assay (GM) is increasingly used as an aid for detecting IA. GM is the polysaccharide component cell wall of *Aspergillus* spp and is

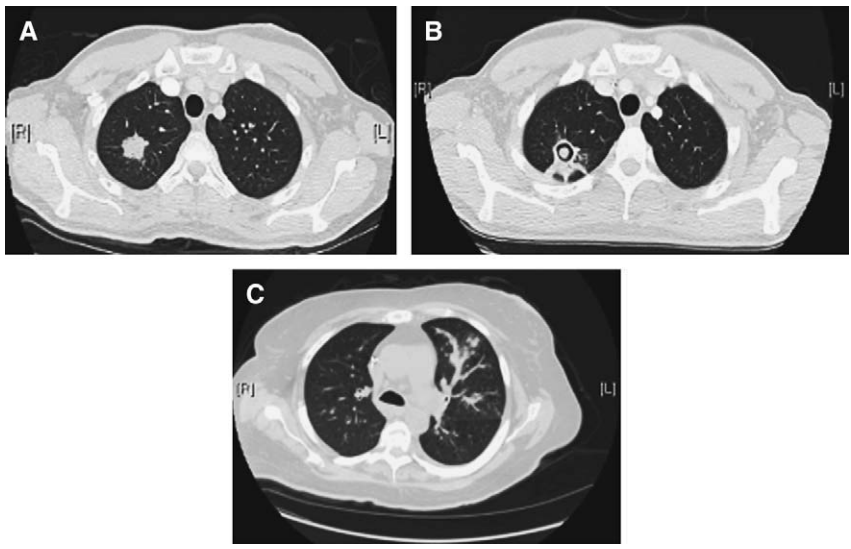

Fig. 1. CT appearances of invasive aspergillosis. (*A*) A 37-year-old man developed fever 40 days after allogeneic HSCT. His serum galactomannan (GM) EIA was positive. CT scan revealed a nodule. BAL was positive for *A fumigatus* by GM EIA and by PCR. No organisms grew. He was treated with voriconazole. (*B*) Fourteen days later the lesion had cavitated. (*C*) A 56-year-old woman with prolonged neutropenia after chemotherapy for multiple myeloma developed fever, wheeze, and cough. CT scan showed obstructive bronchial disease. Bronchoscopy revealed obstructing mucus plugs that grew *A fumigatus*.

released by growing hyphae [74]. A double-sandwich ELISA (EIA) is currently cleared by the Food and Drug Administration [74]. Recent studies suggest that the GM EIA has a sensitivity of 89% and specificity of 92% for detection of IA in the serum of HSCT recipients [74]. The sensitivity and specificity of the GM assay have been reported to be 55.6% and 93.9% to 98.5%, respectively, in liver transplant recipients [75,76] and 95% and 30%, respectively, in lung transplant recipients [77]. In lung transplant recipients, however, the GM EIA detected none of the cases of *Aspergillus* spp tracheobronchitis [77], and false positives have been reported in up to 20% of persons [77], particularly in patients with the underlying diagnosis of cystic fibrosis and chronic obstructive pulmonary disease [77]. Use of the GM EIA in bronchoalveolar lavage (BAL) fluid is less well defined, but studies demonstrate a BAL fluid sensitivity of 76% and specificity of 94% [78].

In addition to diagnosis in high-risk patients, use of the GM EIA is likely to have an increasing role for decreasing empiric antifungal therapy. A recent study examining regular serum screening for GM EIA and CT changes showed that empiric antifungal therapy could be reduced by at least 78% without apparent differences in clinical outcomes [79].

The GM EIA has important caveats, however. The antibiotic piperacillin-tazobactam produces false-positive results, probably because of GM in

the product [80]. In addition, concomitant use of GM screening with antifungal therapy produces false-negative results [81].

The β-glucan assay detects β-glucans located in the cell wall of multiple fungi, including *Candida*, *Fusarium*, *Acremonium*, *Aspergillus* spp, and *Pneumocystis jiroveci* [82]. Preliminary studies have reported sensitivity of 62% and specificity of 94% for diagnosing invasive fungal infections, although few IA cases were included in the studies [82].

Detection of *Aspergillus* spp nucleic acid by PCR is being used increasingly, and recent studies suggest that in HSCT recipients in combination with GM, sensitivity of IA using BAL fluid is 85% [78]. PCR methods and reagents are not standardized among centers, however, resulting in widely different reports of sensitivity and specificity. PCR also is being analyzed for use for preemptive screening, with promising initial results [83].

Therapeutic options for invasive aspergillosis

Until recently, amphotericin and itraconazole were the standard treatments for IA. In a landmark trial, voriconazole was found to be more effective than amphotericin B in treating IA, with patients having better survival and fewer toxic side effects [84].

Echinocandins inhibit the synthesis of cell wall β-glucan [85]. No large studies have been published for first-line therapy, although caspofungin is approved for use as a salvage agent in progressive infection or intolerance to other agents. There is evidence that dual therapy for IA including the echinocandins may be better than single-drug therapy. One report of experiences with amphotericin and caspofungin suggests a favorable outcome in 40% to 60% of patients [86]. In another retrospective report of outcomes, survival was higher with a combination of caspofungin and voriconazole than with voriconazole alone [87]. In addition, prospectively collected cases in which caspofungin and voriconazole were used for treatment of IA in patients who had received solid-organ transplants demonstrated that combination therapy improved survival, especially in patients who had renal failure [88]. Randomized, controlled trials are currently in development comparing single and double therapies for IA.

The duration of therapy for IA has not been established. In practice, patients are treated until immunosuppression is reduced and there is radiographic resolution. Treatment usually lasts several months but varies among patient cohorts.

There has been growing interest in accelerating or boosting immune reconstitution as an adjunct to antifungal therapy. Theoretically the use of granulocyte macrophage colony-stimulating factor should boost neutrophil counts and help clear *Aspergillus* spp. There is no evidence of improved outcome of IA, however. Likewise, granulocyte infusions have been used, but with no proven benefit. Large studies are currently in development.

Surgery in the severely immunosuppressed patient is a very high-risk option, and there are no controlled trials for its efficacy. In less severely ill patients, surgery is a therapeutic option, particularly using improved minimally invasive surgery techniques. Resection of isolated lesions seems to be particularly important in patients who have lesions next to large blood vessels and possibly in those who will receive additional courses of chemotherapy [89].

The future

Better preemptive methods for early diagnosis and intervention are mandatory to improve patient outcomes. With the availability of the galactomannan EIA, β-glucan test, and improvements in PCR this goal has become reasonable. New drugs are becoming available. In particular, posaconazole is effective in treating aspergillosis, fusariosis, and the emerging zygomycosis [90]. Broader antifungal activity is especially important in settings in which specific mycologic diagnoses remain elusive. Current antifungal agents continue to have limitations, which include drug interactions, toxicities, and cost. A better understanding of patient risks and immunity to these fungi is necessary to develop more rational strategies to prevent and treat diseases caused by *Aspergillus* spp.

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