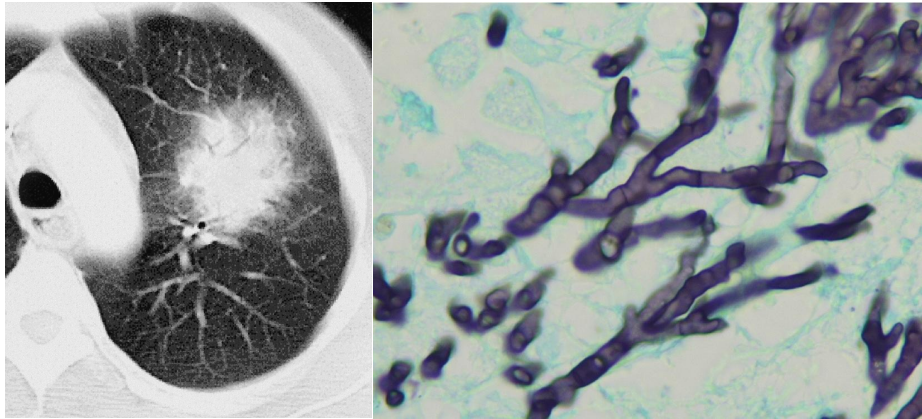


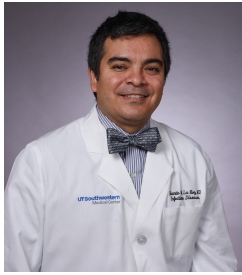
Invasive Pulmonary Aspergillosis



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University of Texas Southwestern Medical Center
Department of Internal Medicine Grand Rounds
October 13, 2017

This is to acknowledge that Dr. Ricardo M. La Hoz has disclosed financial interests related directly or indirectly to this program. Dr. La Hoz will be discussing off-label uses in his presentation.



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Biography

Dr. La Hoz received his medical degree from the Universidad Peruana Cayetano Heredia (UPCH) in Lima, Peru and was the “CONTENTA” award recipient for top medical student in his graduating class. He completed his Internal Medicine Residency and Infectious Diseases Fellowship at the University of Alabama at Birmingham (UAB). He currently serves as Assistant Professor of Internal Medicine in the Division of Infectious Diseases. Dr. La Hoz brings to UT Southwestern a strong background in transplant infectious diseases, as well as an interest in medical education. His commitment to patient care and medical education resulted in his induction to the Alpha Omega Alpha (AOA) Honor Medical Society and Fellowship of the American College of Physicians (FACP).

His activities in the American Society of Transplantation led to his election as an Executive Committee Member of the Infectious Diseases Community of Practice and will serve his term from 2016 to 2018. He was also selected to serve as the At Large Member of the Organ Procurement Transplantation Network/United Network of Organ Sharing Ad Hoc Disease Transmission Advisory Committee from 2016 to 2019. In 2017, he became a Fellow of the American Society of Transplantation (FAST) due to his commitment to the field of transplantation and outstanding service to the society. He has also served as a Panel Member for the Microbiology Devices Panel of the Medical Devices Advisory Committee of the Food and Drug Administration (FDA) on topics related to transplant-associated opportunistic viral infections. His research and clinical endeavors are focused on the prevention and treatment of infectious complications in hematopoietic stem cell and solid organ transplant recipients as well as medical mycology. He is a founding member of the Mycosis Study Group Education and Research Consortium.

Purpose and Overview

The purpose of this presentation is to provide an update of the epidemiology of invasive aspergillosis, describe the strengths and pitfalls of current diagnostic tools as well as recommended interventions for primary therapy of invasive aspergillosis.

Objectives

At the conclusion of this lecture, the learner should be able to:

- a. Identify populations at high risk for invasive aspergillosis
- b. Describe the clinical manifestations of invasive aspergillosis
- c. Interpret the results of common diagnostic tests for invasive aspergillosis
- d. List the antifungals recommended for primary therapy of invasive aspergillosis

Invasive Pulmonary Aspergillosis

Introduction

The term Aspergillosis refers to illness due to allergy or infection with fungi of the genus *Aspergillus*. In the lung, the spectrum of aspergillosis encompasses a broad range of clinical entities including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, chronic cavitary pulmonary aspergillosis, subacute invasive pulmonary aspergillosis, and acute invasive pulmonary aspergillosis (IA), which is the focus of this review.¹

In nature, *Aspergillus* species are saprophytic mold that live in the soil in decaying organic material and play a major role in plant degradation. There are more than 250 species of *Aspergillus*, with several subgenera and multiple sections. The most common species isolated in cases of invasive disease are: *A. fumigatus* (45-72.6%), *A. flavus* (5.8-9.9%), *A. terreus* (5.8-9.0%), and *A. niger* (4.3-6.0%).¹ Most *Aspergillus* species reproduce asexually (Figure 1). Within hours of arriving in a permissive environment, conidia germinate forming hyphae. Specific cells, known as foot cells, give rise to a conidiophore. The tip of the conidiophore swells into a globular multinucleate head called a vesicle. It forms many radially arranged tubular outgrowths called phialides. Conidia arise from the phialides, completing the asexual cycle. By virtue of their small size and hydrophobic exterior, conidia may remain airborne for hours once released.²

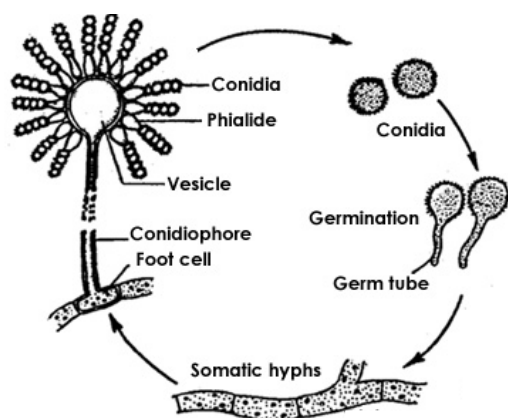


Figure 1: Asexual Reproduction of *Aspergillus* species.¹

Aspergillus species are ubiquitous; the mean concentration of *Aspergillus* conidia in the air is 0.2 to 15 conidia/m³.³ As a result, humans routinely inhale hundreds of conidia daily. Despite this constant exposure, it is remarkable that most humans do not develop any illness attributable to these organisms. The key determinant of the pathogenicity of this pathogen is the nature of the immune response of the host, and its clinical disease states may be conceptualized as points along a spectrum of abnormal immune responses of the host (Figure 2). On one extreme, there can be a strong aberrant Th2 response leading to ABPA and asthma while, on the other extreme, a deficient Th1 or Th17 response leads to IA.²

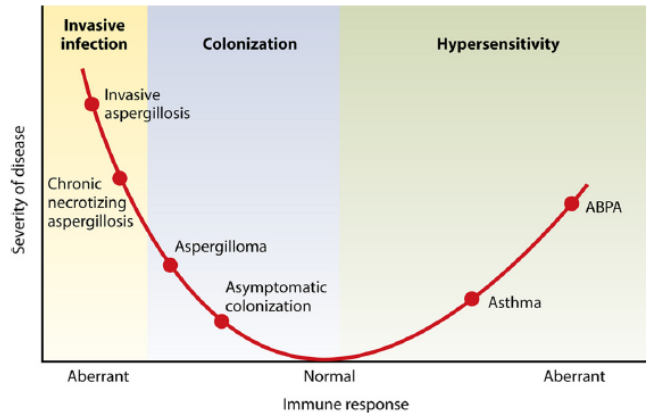


Figure 2: Diagrammatic representation of diseases attributed to *Aspergillus* species as a function of the host's immune response.²

Innate Immunity to *Aspergillus* sp.

Despite the constant exposure to *Aspergillus*, most humans have no evidence of acquired humoral or cell-mediated immunity to this organism. This suggests that, for most healthy humans, innate immunity is sufficient to clear the organism before an acquired immune response is mounted. We will now focus on a brief overview of these early events in the host's immune response against *Aspergillus* sp. (Figure 3).²

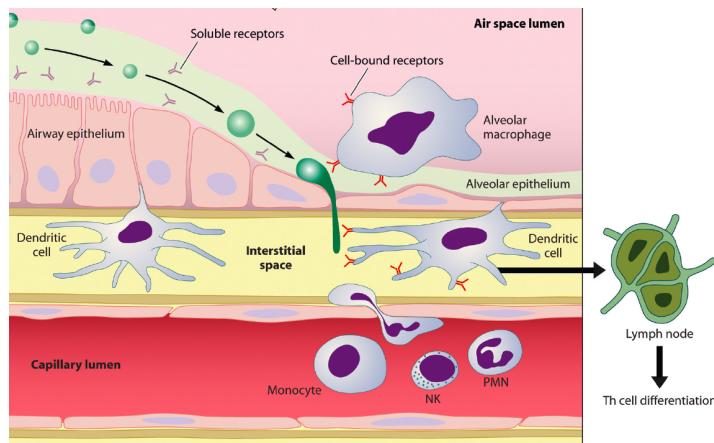


Figure 3: Schematic representation of the components of the host immune response to *Aspergillus* conidia.²

Once inhaled *Aspergillus* conidia reach the lower respiratory tract, they are trapped in the mucus lining the epithelium. Beyond its mechanical effects, the mucus contains soluble pattern recognition receptors (PRR) and microbicidal peptides. Examples of these soluble PRR include mannan-binding lectin and pentraxin-3. The former promotes activation of the lectin complement pathway while the latter promotes opsonization of the conidia, facilitating recognition by effector cells. The next step in the defense against *Aspergillus* sp. is activation of the effector mechanisms of the innate immunity; these include the resident alveolar macrophages, dendritic cells, and recruitment and activation of neutrophils. These cells recognize highly conserved structures expressed on the *Aspergillus* surface by

means of cell-bound PRR. Toll-like receptors, dectin-1 and DC-sign are cell bound PRR that play an important role in the innate immunity against *Aspergillus*. Toll-like receptors are mainly expressed on macrophages and dendritic cells; dectin-1 is expressed on macrophages, dendritic cells, and neutrophils and recognizes beta-D glucan, a component of *Aspergillus* cell wall. DC-sign is found on dendritic cells and macrophages and binds to galactomannan, another component of the fungal cell wall. Single-nucleotide polymorphisms (SNPs) in pentraxin-3, toll-like receptor 4, dectin-1, and DC-sign have been associated with an increased risk of IA.⁴

Epidemiology

The first cases of IA were described in the 1950's after the introduction of immunosuppressive agents such as corticosteroids and cytotoxic chemotherapy.¹¹ The incidence of IA appears to be increasing.¹² This may be secondary to the growing number of immunosuppressed patients, the use of more aggressive chemotherapy protocols, and more aggressive immunosuppressive practices in solid organ transplant recipients.¹ IA is a significant cause of morbidity and mortality in high-risk patients. Patients at high risk of invasive aspergillosis include: patients with acute myeloid leukemia (AML) especially on induction chemotherapy and in relapse, those that have undergone an allogeneic hematopoietic stem cell transplant (HSCT) and developed graft versus host disease (GVHD), and those that received a lung transplant. Populations at intermediate risk include patients that received an allogeneic hematopoietic stem cell transplant without the development of GVHD, heart and liver solid organ transplant recipients to mention a few. Patients at low risk include those with multiple myeloma, those who received an autologous stem cell transplant, kidney transplant recipients and patients with AIDS.¹ Figure 4 depicts the spectrum of risk for invasive aspergillosis for the different populations.

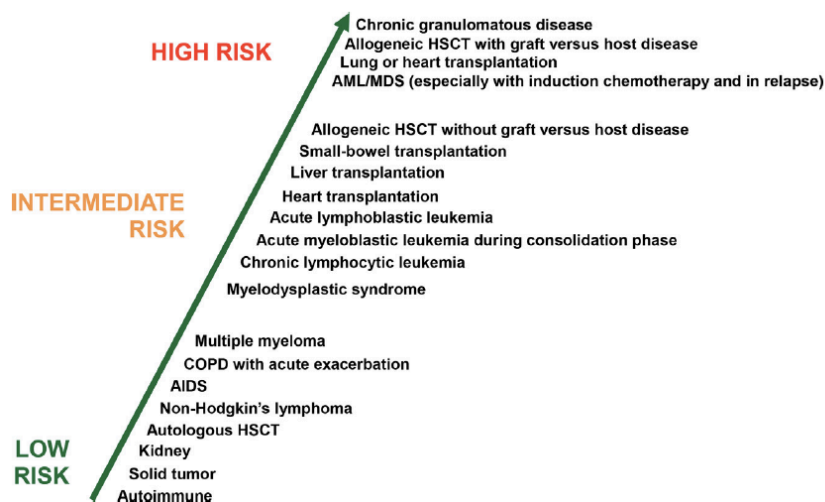


Figure 4 Spectrum of Risk for Invasive Aspergillosis amongst different populations.¹

High-Risk Patients: Acute Leukemias

A multicenter retrospective cohort study conducted in Italy from 1999 to 2003, which included 11,802 from 18 centers, revealed that the incidence of invasive aspergillosis in patients with hematologic malignancies is 0.3-7.1% depending on the type of malignancy.⁷ The incidence of invasive aspergillosis was highest amongst patients with acute myeloid leukemia (AML) (7.1%), patients with acute lymphoblastic leukemia (3.8%), and patients with chronic myeloid leukemia (2.4%). The risk of invasive aspergillosis in patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma was low, with an average incidence of about 0.5%.

In 1966, Bodey demonstrated that the frequency of all infections, including aspergillosis, in acute leukemia patients was correlated to the levels of circulating neutrophils, with the prevalence of all types of infection being inversely related to the absolute neutrophil count. The most important factor in predicting the risk of infection was the duration of neutropenia. If neutropenia persisted for ≥ 3 weeks, the risk of developing an infection, including those caused by fungi, was 60%. However, not only is the incidence of infections related to neutrophil count, but the outcome of bacterial and fungal infections also appears to be dependent on the evolution of the neutrophil count, with the highest fatality rates among patients with severe and refractory neutropenia ($< 0.1 \times 10^9/L$).⁸⁻⁹ Contemporary studies have confirmed these seminal observations from Bodey.

Few studies have addressed the specific risk factors for IA in patients with AML.¹⁰⁻¹¹ The proposed risk factors can be classified into the following categories: leukemia-related factors (lower probability of complete remission [adverse cytogenetics/gene mutation profiles, WBC $> 50,000/\mu L$, secondary AML], MDS-related phagocyte dysfunction, leukemia status [relapse-refractory $>$ first induction $>$ consolidation and persistence of blasts in day 15 bone marrow biopsy]), host factors (age > 65 , organ dysfunction with high comorbidity index or poor performance status > 2 , and chronic obstructive pulmonary disease) and fungal exposure (rooms without HEPA filtration, new building constructions or renovations, and colonization with *Aspergillus* species). Further studies are needed to refine risk factor identification to allow for targeted implementation of strategies to ameliorate the burden of this infectious complication.

Contemporary observational studies report a 38% attributable mortality due to invasive aspergillosis in patients with AML.⁷ Most experts agree that host factors significantly impact overall survival, and a lack of neutrophil recovery is strongly associated with a poor prognosis. Other prognostic factors included progression of underlying malignancy, renal impairment, disseminated disease and the burden of infection.¹²⁻¹³

High-Risk Patients: HSCT

Similar to hematologic malignancies, the risk of IA amongst patients receiving a hematopoietic stem cell transplant is heterogeneous. The Transplant Associated Infection Surveillance Network (TRANSNET), a consortium of 23 US academic transplant centers (22 performing HSCTs) and the Centers for Disease

Control and Prevention (CDC), provides contemporary data regarding the risk of invasive fungal infections amongst HSCT recipients. This study prospectively collected information on 15,820 patients from 2001-2006 (approximately 20% of the 80,000 persons who underwent an HSCT in the US during the same period). Aspergillosis was the most common invasive fungal infection in this study. The 12-month cumulative incidence of IA amongst HSCT recipients was 1.6%.¹⁴

Because of the poor outcomes associated with IA in HSCT recipients, there has been much interest in identification of risk factors and prevention. Amongst the high-risk group of allogeneic HSCT, IA occurs in a bi-modal temporal distribution. The first peak is early post-transplantation and associated with neutropenia, while a second peak > 100 days post-transplantation is associated with GVHD and the immunosuppressive agents used to treat it.¹ A single center retrospective study from Fred Hutchinson Cancer Research Center (FHCRC), which recruited 1682 patients who underwent a first allogeneic HSCT between 1993-1998, identified risk factors for early IA (<40 days) and late IA (40-180 days). In the early period, age > 20, requirement of an allo-HSCT for aplastic anemia and myelodysplastic syndrome, cord blood as the source of hematopoietic cells, and CMV disease were associated with increased IA risk. In the late period, receipt of T cell-depleted/CD34 selected stem cells, neutropenia, lymphopenia, acute or chronic GVHD, CMV disease and viral respiratory infections were associated with a higher risk of IA.¹⁵ One caveat is that this study was performed at a time when fluconazole was still being used as prophylaxis for invasive fungal infections. Newer studies are required to identify risk factors for IA amongst allo-HSCT recipients in the era of posaconazole prophylaxis. Other risk factors identified in other studies include the type of conditioning regimen, iron overload/high ferritin levels, and environmental factors such as hospital construction.¹⁶

Data derived from the TRANSNET revealed that the 12-week all-cause mortality for HSCT recipients with IA was 49.4%. Factors associated with a higher mortality included neutropenia, renal or hepatic insufficiency, early onset IA, proven IA, and methylprednisolone use; white race was associated with a decreased mortality risk.¹⁷ A single center study from the FHCRC, which included only allo-HSCT recipients revealed that the presence of severe pulmonary function abnormality before HSCT, HLA mismatch, neutropenia at the time of IA diagnosis, elevated creatinine or bilirubin levels, and treatment with corticosteroids \geq 2mg/kg were associated with a higher mortality. Conversely, a non-myeloablative conditioning regimen and peripheral blood HSCT were associated with a lower mortality risk.¹⁸

High-Risk Patients: Select Solid Organ Transplant Recipients

Solid organ transplantation (SOT) has been established as an accepted therapy for end stage disease of the kidneys, pancreas, liver, heart, and lungs. In the United States alone, more than 30,000 solid organ transplant procedures were performed in 2016. In spite of important advances in surgical techniques and immunosuppressive regimens, transplant recipients remain at substantial risk for infectious complications including invasive fungal disease (IFD).

A study conducted by the TRANSNET consortium prospectively followed 16,808 SOT recipients from 15 US transplant centers. The cumulative incidence of IFD at 12 months post-transplantation across transplant organ type ranged from 1.5% to 11.6%. The cumulative incidence for IFD was highest amongst small bowel and lung transplant recipients (11.6% and 8.6%, respectively) and intermediate amongst liver and pancreas or combined kidney-pancreas transplant recipients (4.6% and 4.0%, respectively). The risk was lowest amongst heart and kidney transplant recipients (3.4 and 1.3%, respectively). *Aspergillus* was the second most common IFD in the whole cohort and the most common IFD amongst lung transplant recipients.¹⁹ The cumulative incidence of IA in the entire cohort was 0.7% (4.1% in lung recipients).

A few single center studies have specifically analyzed factors associated with acquisition of IA in lung transplant recipients.¹⁶ However, because of the rarity of IA, most of the factors identified in these studies are derived from only univariate analysis. Factors associated with an increased risk of invasive aspergillosis in lung transplant recipients include single lung transplantation, rejection, development of bronchiolitis obliterans, ischemia reperfusion injury, *aspergillus* colonization pre- and post-transplantation, ischemia at the anastomotic site, acquired hypogammaglobulinemia (<400mg/dl), presence of bronchial stents and cytomegalovirus disease. An urgent need is for larger multicenter studies to better characterize the risk factors for developing IA in order to enhance targeting of preventive and prophylactic treatment strategies.

Data derived from the TRANSNET revealed that the 12-week all-cause mortality for SOT with IA was 34.4%.¹⁷ These rates compare favorably against HSCT recipients (57.5% vs. 34.4%; $P < 0.001$). Factors associated with a higher mortality include hepatic insufficiency, malnutrition, prednisone use and CNS disease.¹⁷

Clinical Manifestations of IA

IA primarily involves the pulmonary tract, reflecting that inhalation is the most common route of entry for *aspergillus* spores. In neutropenic patients, disease rarely occurs before 10-12 days of profound neutropenia. The signs and symptoms described with invasive pulmonary aspergillosis include fever, cough, shortness of air, pleuritic chest pain, and hemoptysis.¹ A higher burden of disease is associated with an increased risk of mortality.¹⁶ Thus, clinicians must keep a high index of suspicion in patients at risk presenting with these symptoms.

As mentioned above, the clinical manifestations depend on the interaction between the pathogen and the host's immune system. In patients with neutropenia, persistent fever may be the only clinical sign of invasive Aspergillosis, while fever occurs in less than a third of lung transplant recipients. As the disease progresses, cough or dyspnea on exertion may ensue although these symptoms are non-specific. *Aspergillus* has a particular predilection for angioinvasion, a phenomenon which can manifest clinically as pleuritic chest pain and hemoptysis from pulmonary infarction. Poorly controlled infection can lead to hematogenous dissemination which can involve virtually any organ. Involvement of the central nervous system is a devastating consequence of disseminated Aspergillosis and may manifest in seizures or focal neurologic signs from mass effect or stroke.

Lung transplant recipients may also present with tracheobronchial aspergillosis.¹ This syndrome is defined as infection confined to the tracheobronchial tree. The clinical features include cough, dyspnea on exertion, and declining lung function. Since the infection is localized to the bronchial tree, chest imaging is usually normal. Pseudo-membranes, ulcerated lesions, and masses are observed in bronchoscopy (Figure 5). These lesions often occur at the anastomotic site and can lead to dehiscence.

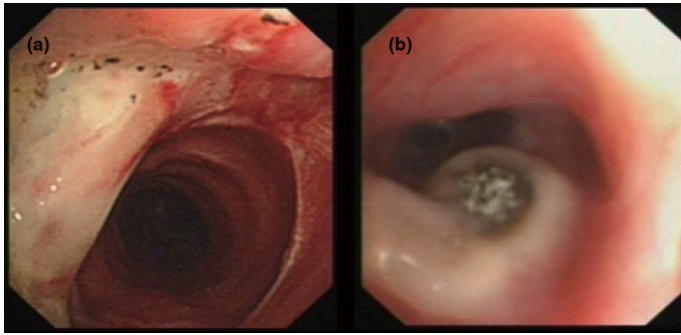


Figure 5: Characteristic bronchoscopy findings of tracheobronchial Aspergillosis. (a) pseudo-membrane and (b) ulcerated lesion.

Diagnosis of IA

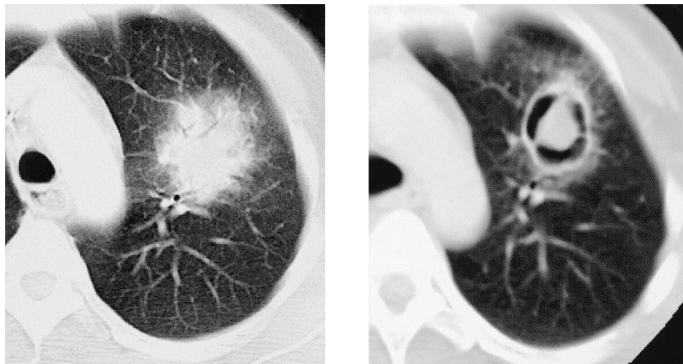


Figure 6: Characteristic halo sign (left) and air crescent sign (right) observed in CT.²⁰

Radiographic studies can be used in the diagnosis of invasive pulmonary aspergillosis. Plain chest radiographs are of limited diagnostic utility due to a lack of specificity. The type of radiographic abnormality present in computed tomography (CT) scan is variable and dependent on the host. A study primarily conducted in patients with hematologic malignancies and HSCT recipients (235 patients total) showed that most patients (94%) presented with at least 1 macronodule (nodule >1cm) while 79% had multiple nodules. Many patients (61%) had at least 1 halo sign (macronodule surrounded by groundglass opacity [Figure 6]), while a minority (27%) had nodules that were characterized by pulmonary infarction and even fewer (7.7%) presented with air crescent signs (figure 6). Consolidations were only identified in a third of the patients.²⁰ Conversely, a multicenter retrospective study

from Spain, revealed that nodules and consolidation were present in 35% and 6% of SOT recipients with invasive pulmonary aspergillosis.²¹

Non-culture based methods have been used to establish a rapid diagnosis of IA. Detection of galactomannan, an aspergillus cell wall component released during hyphal growth, in serum and bronchoalveolar lavage (BAL) has played an important role in non-culture-based diagnosis of IA (Figure 5).¹ In the United States, the galactomannan (GM) assay is approved by the Food and Drug Administration (FDA), though restricted to patients with hematologic malignancies or HSCT recipients. A positive serum result should be based on a cutoff index ≥ 0.5 from testing conducted on two separate serum samples or a single BAL sample. False positive assays may be seen with infections caused by organisms that share cross-reacting antigens (*Fusarium sp.*, *Paecilomyces sp.*, *Acremonium sp.*, *Alternaria sp.*, *Wangiella dermatitidis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans*).¹ Although cross reactivity was initially reported in patients receiving piperacillin-tazobactam, results of more recent studies demonstrate that current preparations of piperacillin-tazobactam rarely cross-react with the assay.²¹ False negatives are described with concomitant use of antifungals.¹

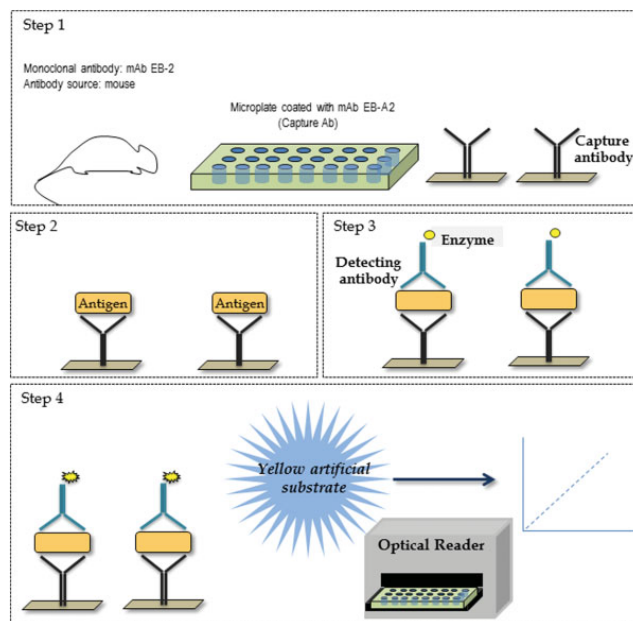


Figure 7: Schematic Representation of the Aspergillus Galactomannan ELISA immunoassay procedure.

In 2006, Pfeiffer et al. conducted a meta-analysis to evaluate the performance of serum GM.²³ The overall test performance demonstrated a sensitivity of 0.71 (95% CI, 0.68-0.74), specificity of 0.89 (95% CI, 0.88-0.90), positive likelihood ratio of 6.45, and negative likelihood ratio of 0.33. The test, however, did not perform equally in all patient groups. The test performed well in patients with hematologic malignancies (sensitivity 0.70 and specificity 0.92) and HSCT recipients (sensitivity 0.82 and specificity 0.86). Conversely, the test had substandard performance in solid organ transplant recipients (sensitivity 0.22 and specificity 0.84). GM is a water-

soluble molecule, and therefore, the test can be applied to specimens other than serum including BAL fluid. False positives have been described with the use of plasmalyte while false negatives have been described with the use of anti-fungals. A meta-analysis of GM in BAL fluid that included thirty studies showed a sensitivity of 0.87 (95% CI 0.79-0.92), specificity of 0.89 (0.85-0.92), positive likelihood ratio of 8.0 (95% CI 5.7-11.1), and negative likelihood ratio of 0.15 (95% CI 0.10-0.23).²⁴ The BAL GM assay had a higher sensitivity (0.85% [95% CI 0.72-0.92]) compared to the serum GM assay (0.65 [95% CI 0.54-0.75]) in this meta-analysis.

Cultures from sterile sites confirm the diagnosis of IA; cultures from non-sterile sites, (i.e. lower respiratory tract) in high risk patient help support the diagnosis of IA. Unfortunately, cultures have significant limitations as they lack both sensitivity and specificity. *Aspergillus sp.* can be cultured from lower respiratory tract samples of adult patients in whom no clinical illness is apparent. A multicenter study revealed that out of 1209 patients with positive cultures for *Aspergillus sp.* only 12% (148) had invasive disease.²⁵ Likewise, an autopsy study revealed that only 50% of autopsy-proven IA had positive cultures.²⁶ Thus, culture results need to be interpreted with caution. Positive cultures from a patient at low risk for IA and an alternative diagnosis likely represent culture contamination, while negative cultures in patients at high risk with a compatible clinical presentation for IA does not exclude the diagnosis of IA.

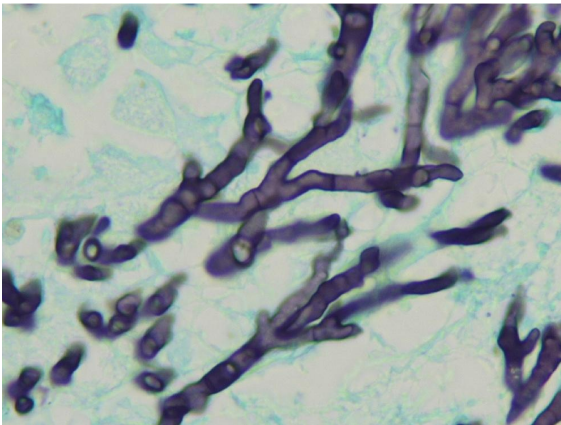


Figure 8: Gomori methenamine silver stain of tissue with proven invasive aspergillosis. *Aspergillus sp.* hyphal elements are septated, with dichotomous acute angle branching.

A proven diagnosis of IA can be demonstrated with hyphal invasion of tissue specimens together with a positive culture for *Aspergillus sp.* Hyphal elements and morphology are usually easily demonstrated in infected tissues using stains such as Gomori methenamine silver (see Figure 6) or periodic acid shift. *Aspergillus* hyphae are typically hyaline (non-pigmented), septate, 3-6 μm wide with parallel cross-walls and dichotomously branched at acute angles. These features usually allow distinction from *Zygomycete*; however a number of pathogenic molds including *Scedosporium*, *Fusarium*, and others will have virtually identical appearances to *Aspergillus sp.* on histopathology. Procedures to confirm the diagnosis of IA include bronchoscopy with transbronchial biopsy and imaging guided biopsy. Obtaining

tissue may be challenging as patients at highest risk for IA often have multiple comorbidities, high oxygen requirements, thrombocytopenia, coagulation disorders or pulmonary hypertension.

Given the shortcoming of the different diagnostic modalities, a consensus group of the European Organization of Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) developed diagnostic criteria to help design clinical trials, and foster communication between researchers. The definition assigns 3 diagnostic categories of IA: proven, probable and possible.²⁷ To meet the proven case definition of IA, histopathologic evidence of hyphal tissue invasion and culture confirmation or recovery of *Aspergillus sp.* from sterile sites associated with clinical or radiological abnormalities suggestive of infection is required. To meet the probable case definition of IA, patients need to meet host, clinical and mycological criteria (*Aspergillus sp.* isolated from a non-sterile site, positive serum of BAL galactomannan or positive serum (1,3)-beta-D glucan). The possible case definition only requires host and clinical criteria.

Treatment of IA

The Infectious Diseases Society of America (IDSA) recommends reduction of immunosuppression, surgery for localized disease accessible to surgical debridement, and primary therapy with voriconazole.²⁸ Alternative antifungals include liposomal amphotericin B, isavuconazole and other lipid formulations of amphotericin B. Primary therapy with echinocandins or posaconazole was not recommended by the IDSA guidelines due to lack of robust randomized trial data.

Voriconazole was approved by the FDA for primary therapy of IA in 2003. The best efficacy data come from the Global Comparative Aspergillus Study, an international multicenter randomized open-label trial in which voriconazole was compared with amphotericin B deoxycholate as initial therapy in 277 patients with proven or probable IA. The survival at 12 weeks (71 vs. 58%), and adverse effect profile favored voriconazole.²⁹ Based on this data, voriconazole is recommended as first line primary therapy for IA.

Isavuconazole was compared to voriconazole in a randomized controlled trial and found to be non-inferior to voriconazole by the primary endpoint of all-cause mortality at 6 weeks (19% [48 patients] in the isavuconazole group vs 20% [52 patients] in the voriconazole group) in an intention-to-treat population. The predefined 10% non-inferiority margin was met by an adjusted treatment difference in mortality of -1.0% (95% CI -7.8 to 5.7).³⁰ Based on this data, isavuconazole received FDA approval for first-line therapy of primary IA and is recommended as an acceptable alternative to voriconazole.

Based on randomized clinical trials and observational data, lipid formulations of amphotericin B are also an alternative for therapy in IA.²⁸ The panel of experts acknowledged some preliminary data with echinocandins and posaconazole, but it was considered that this was insufficient to recommend these anti-fungals for primary therapy of IA.

Combination therapy of amphotericin B formulations or azoles with echinocandins suggest additive or synergistic effects in some pre-clinical studies.

The strongest evidence for combination therapy with voriconazole and an echinocandin comes from a large randomized trial that assessed the safety and efficacy of voriconazole with or without anidulafungin for the treatment of IA.³¹ Results showed a non-statistical trend toward improved six-week survival with the combination compared with voriconazole monotherapy. In a post-hoc analysis of patients with probable IA, a statistically significant difference in mortality was observed (16 percent with combination therapy versus 27 percent with voriconazole monotherapy; 95% CI -22.7 to -0.4). Interpretation of these results leaves some uncertainty as to the efficacy of combination therapy with voriconazole and echinocandins. For these reason, the IDSA guidelines committee suggest only considering an echinocandin with voriconazole for primary therapy of IA in the setting of severe disease.²⁸

Monitoring response to therapy for IA

Response to therapy is monitored using the following criteria: clinical parameters, trends in biomarkers, and follow-up imaging. Improvements in the presenting symptoms have been associated with a favorable prognosis. Several studies have correlated the trend in GM during the initial treatment phase with outcomes in IA. A retrospective evaluation of the global aspergillus clinical trial²⁹ found that a GM reduction of > 35% between baseline and week 1 predicted a probability of a satisfactory clinical response.³² For IA patients with pre-treatment GM of <0.5, a rising galactomannan level to > 0.5 at week 2 despite antifungal treatment heralds a poor clinical outcome. Furthermore, every 0.1 unit increase in the GM from baseline to 2 weeks later increased the likelihood of an unsatisfactory clinical response by 21.6% (p=0.018). In summary, this data suggests that clinical outcomes can be anticipated by charting early GM trends during the first 2 weeks of antifungal therapy.

As it is usually the case, radiologic improvement lags behind clinical improvement, particularly in neutropenic patients. In this population, the size of the lesions can increase up to 4-fold despite antifungal treatment and then remains stable during the second week.³³ Progression of radiologic lesions was not associated with treatment failure and does not necessarily mean progression of the infection during the first 2 weeks.

Conclusions

The incidence of IA appears to be increasing as a consequence of the continually growing immunosuppressed population. Populations at high risk include patients with acute myeloid leukemia (AML) especially on induction chemotherapy and in relapse, those that have undergone an allogeneic hematopoietic stem cell transplant (HSCT) and developed graft versus host disease (GVHD), and those that received a lung transplant. Substantial progress has been made during the last decade with diagnostic tools, yet current modalities have significant pitfalls. The performance of these tools is dependent on the study population. Voriconazole, isavuconazole and amphotericin preparations are recommended by the IDSA guidelines as primary therapy for IA.

Despite advances in our understanding of the epidemiology, clinical manifestations, molecular diagnostic tools and novel antifungal implementation strategies, the mortality associated with IA remains unacceptably high. Further studies are required to minimize the burden of this disease in populations at risk.

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