CHEST®

THE CARDIOPULMONARY
AND CRITICAL CARE JOURNAL

FOR PULMONOLOGISTS, CARDIOLOGISTS, CARDIOTHORACIC SURGEONS,
CRITICAL CARE PHYSICIANS, AND RELATED SPECIALISTS

The Clinical Spectrum of Pulmonary Aspergillosis*

Ayman O. Soubani and Pranatharthi H. Chandrasekar

Chest 2002;121;1988-1999
DOI: 10.1378/chest.121.6.1988

This information is current as of April 12, 2006

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.chestjournal.org/cgi/content/full/121/6/1988

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2005 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder. ISSN: 0012-3692.

AMERICAN COLLEGE OF
CHEST
PHYSICIANS

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

The Clinical Spectrum of Pulmonary Aspergillosis*

Ayman O. Soubani, MD; and Pranatharthi H. Chandrasekar, MD

Aspergillus is a ubiquitous fungus that causes a variety of clinical syndromes in the lung, ranging from aspergilloma in patients with lung cavities, to chronic necrotizing aspergillosis in those who are mildly immunocompromised or have chronic lung disease. Invasive pulmonary aspergillosis (IPA) is a severe and commonly fatal disease that is seen in immunocompromised patients, while allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to Aspergillus antigens that mainly affects patients with asthma. In light of the increasing risk factors leading to IPA, such as organ transplantation and immunosuppressive therapy, and recent advances in the diagnosis and treatment of Aspergillus-related lung diseases, it is essential for clinicians to be familiar with the clinical presentation, diagnostic methods, and approach to management of the spectrum of pulmonary aspergillosis. ***(CHEST 2002; 121:1988–1999)***

Key words: allergic pulmonary aspergillosis; Aspergillus; fungal diseases; immunocompromised host; pulmonary infection

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BMT = bone marrow transplantation; CNA = chronic necrotizing aspergillosis; IPA = invasive pulmonary aspergillosis

Aspergillus is a ubiquitous soil-dwelling organism found in organic debris, dust, compost, foods, spices, and rotted plants. There are approximately 200 species of Aspergillus; however, only a few are known to be pathogenic for humans. *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger* are the most commonly encountered species, but other species, like *Aspergillus terreus*, *Aspergillus clavatus*, *Aspergillus niveus*, and *Aspergillus nidulans*, have rarely been reported to cause disease in humans.[1]

Aspergillus, like other filamentous fungi, is primarily acquired from an inanimate reservoir, usually by the inhalation of airborne spores. The organism grows best at 37°C, and the small spores (2 to 3 μm) are easily inhaled and deposited deep in the lungs, leading to a variety of clinical syndromes (Fig 1). Although these are distinct pulmonary entities, on rare occasions one condition may change to another; for example, an aspergilloma may change to invasive pulmonary aspergillosis (IPA).[2,3]

*From the Divisions of Pulmonary, Critical Care, and Sleep Medicine (Dr. Soubani) and Infectious Diseases (Dr. Chandrasekar), Wayne State University School of Medicine, Detroit, MI.
Manuscript received February 27, 2001; revision accepted August 29, 2001.
Correspondence to: Ayman O. Soubani, MD, Harper University Hospital, Division of Pulmonary, Critical Care, and Sleep Medicine, 3990 John R-3 Hudson, Detroit, MI 48201; e-mail: asoubani@intmed.wayne.edu

This article reviews the clinical spectrum of pulmonary aspergillosis, emphasizing the risk factors, clinical picture, and recent advances in diagnostic and therapeutic approaches.

Aspergilloma

This is the most common and best-recognized form of pulmonary involvement due to Aspergillus. The aspergilloma (fungal ball) consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus, and tissue debris, usually developing in a preformed lung cavity. Although other fungi may cause the formation of a fungal ball (for example, Zygomycetes and Fusarium), Aspergillus spp (specifically, *A fumigatus*) are by far the most common etiologic agents.

The true incidence of aspergilloma is not known. In a study[4] of 544 patients with pulmonary cavities secondary to tuberculosis, 11% had radiologic evidence of aspergilloma. The most common predisposing factor is the presence of a preexisting lung cavity formed secondary to tuberculosis, sarcoidosis, bronchiectasis, bronchial cysts and bullae, ankylosing spondylitis, neoplasm, or pulmonary infarction.[5,6] Of these, tuberculosis is the most frequently associated condition.[7] Occasionally, aspergilloma has been described in cavities caused by other fungal infections.[8,9] It is believed that inadequate drainage facilitates the growth of Aspergillus on the walls of these cavities.

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

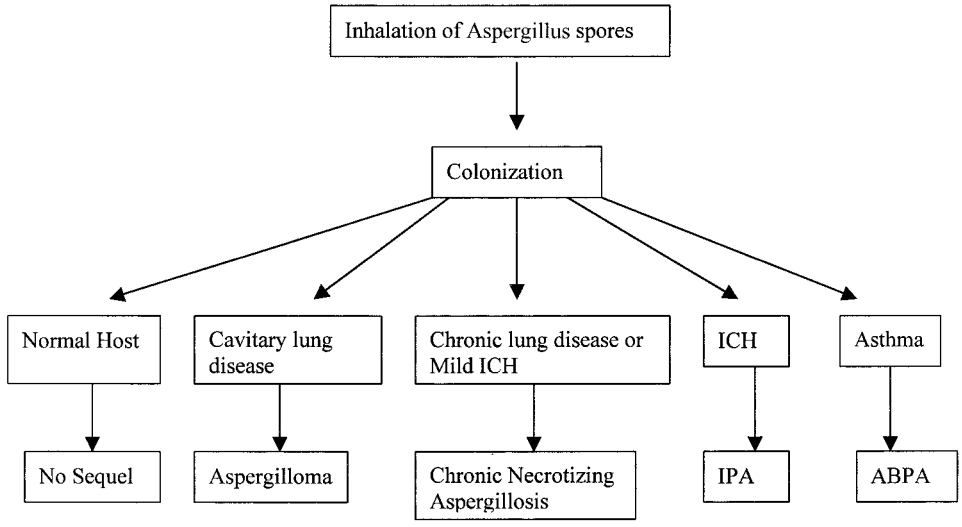

FIGURE 1. The clinical spectrum of conditions resulting from the inhalation of Aspergillus spores. ICH = immunocompromised host.

Usually, the fungus does not invade the surrounding lung parenchyma or blood vessels; exceptions, however, have been noted.[2,10]

The natural history of aspergilloma is variable. In the majority of cases, the lesion remains stable, however, in approximately 10% of cases, it may decrease in size or resolve spontaneously without treatment.[11] Rarely, the aspergilloma increases in size.[12]

Clinical Picture

An aspergilloma may exist for years without causing symptoms. Most patients will experience mild hemoptysis, but severe hemoptysis may occur, particularly in patients with underlying tuberculosis.[13] Bleeding usually occurs from bronchial blood vessels. Theories on the cause of the hemoptysis include local invasion of blood vessels lining the cavity, endotoxins released by the fungus with hemolytic properties, and mechanical friction of the aspergilloma with the cavity wall blood vessels.[2,14,15] The mortality rate from hemoptysis ranges between 2% and 14%.[16–20] Other symptoms include chronic cough and dyspnea that are probably more related to the underlying lung disease. Fever is rare unless there is secondary bacterial infection.

Risk factors associated with poor prognosis of aspergilloma are severe underlying disease, increasing size or number of lesions as seen on chest radiographs, immunosuppression (including corticosteroid treatment), increasing Aspergillus-specific IgG titers, recurrent large-volume hemoptysis, and underlying sarcoidosis or HIV infection.[21]

Diagnosis

Aspergilloma usually comes to clinical attention as an incidental finding on a routine chest radiograph or during an evaluation of hemoptysis. Radiologically, aspergilloma is evident as an upper-lobe, mobile, intracavitary mass with an air crescent in the periphery.[22] The adjacent pleura may be thickened. At times, the mass may be difficult to see on a routine chest radiograph, and tomography or chest CT scan may be necessary to visualize the aspergilloma [23] (Fig 2). A change in the position of the aspergilloma with a change of position of the patient is an interesting but variable sign.[23] The differential diagnosis of this radiologic appearance includes hematoma, neo-

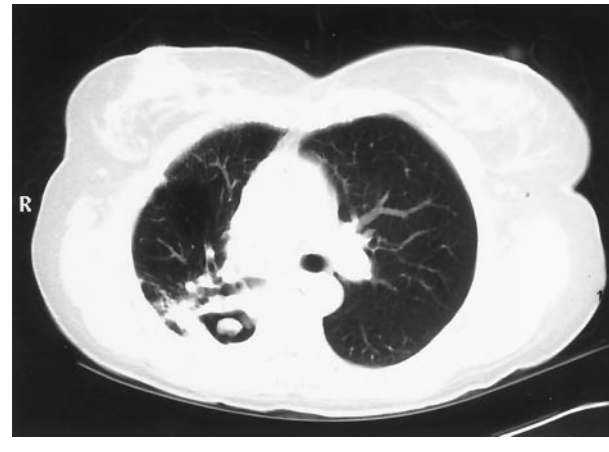

FIGURE 2. Chest CT scan of a patient with a history of lung cancer and tuberculosis, who developed aspergilloma after undergoing resection of the right upper lobe.

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

plasm, abscess, hydatid cyst, and Wegener granulomatosis. It is important to note that aspergilloma may coexist with any of the above conditions.[24,25]

A sputum examination may reveal the presence of Aspergillus but is negative in 50% of the cases.[26] Serum IgG antibodies to Aspergillus are positive in almost all cases; however, they may be falsely negative in the rare cases of aspergilloma due to species other than *A fumigatus* or in patients receiving corticosteroid therapy.[10] Immediate skin reactivity is much less helpful in the evaluation of aspergilloma and is positive only in a minority of patients.[26]

Treatment

In asymptomatic patients, no therapy is warranted. There is no consistent evidence that aspergilloma responds to antifungal agents, and these drugs rarely achieve the minimal inhibitory concentrations within the lung cavities.[27] Inhaled, intracavitary, and endobronchial instillations of antifungal agents have been tried with no consistent success.[19,28,29] In addition, systemic antifungal therapy using IV amphotericin B failed to show a benefit in patients with aspergilloma.[30] Itraconazole therapy has been tried with variable results.[31–33] Bronchial artery embolization rarely results in control of hemoptysis because of the massive collateral blood vessels; however, this procedure should be considered as a temporizing measure in patients with life-threatening hemoptysis.[34] The surgical treatment of aspergilloma is associated with relatively high mortality rate that ranges between 7% and 23%.[15–17,35–38] The most common causes of death following surgery are severe underlying lung disease, pneumonia, acute myocardial infarction, and IPA.[19,38] In addition, there is significant postoperative morbidity, including bleeding, residual pleural space, bronchopulmonary fistula, empyema, and respiratory failure. A recent report[39] of 87 patients who were operated on for pulmonary aspergilloma revealed a postoperative mortality rate of 5.7%. Another report[38] showed a lower mortality rate of 1.5% and morbidity of 18% in the surgical treatment of aspergilloma; however, most of the patients were young with adequate respiratory reserve, and tuberculosis was the underlying lung disease in the vast majority of the patients.

In summary, observation alone is adequate in most cases of aspergilloma. Medical therapy with bed rest, humidified oxygen, cough suppressants, and postural drainage is helpful in cases of mild hemoptysis. The surgical approach needs to be considered in patients with massive hemoptysis and adequate pulmonary reserves.[20] The role of itraconazole is yet to be determined.

Chronic Necrotizing Aspergillosis

Also called semi-invasive aspergillosis, this entity was first described in two reports in 1981 and 1982.[40,41] Chronic necrotizing aspergillosis (CNA) is an indolent, destructive process of the lung due to invasion by Aspergillus species (usually *A fumigatus*). This entity is different from aspergilloma in that there is local invasion of the lung tissue, and a preexisting cavity is not needed, although a cavity with a fungal ball may develop in the lung as a secondary phenomenon due to destruction by the fungus. On occasion, an aspergilloma may invade the cavity wall, causing local parenchyma destruction, as seen in patients with CNA.[42] CNA is also different from invasive aspergillosis. The former, in contrast to the latter, is a chronic process that progresses slowly over months to years, and there is no vascular invasion or dissemination to other organs.[40]

CNA is usually seen in middle-aged and elderly patients with documented or suspected underlying lung diseases like COPD, inactive tuberculosis, previous lung resection, radiation therapy, pneumoconiosis, cystic fibrosis, lung infarction, or, rarely, sarcoidosis.[43] It also has been described in patients with mild immunosuppression, including those with diabetes mellitus, those with poor nutrition, those undergoing low-dose corticosteroid therapy, and those with connective tissue diseases such as rheumatoid arthritis and ankylosing spondylitis.[40]

The patient usually presents with fever, cough, sputum production, and weight loss of 1 to 6 months' duration. A minority of the patients may be asymptomatic.[40] The chest radiograph usually shows an infiltrative process in the upper lobes or the superior segments of the lower lobes. A fungal ball may be seen in nearly one half of the cases.[40] Adjacent pleural thickening is a characteristic finding and may be an early indication of a locally invasive process.[41]

The diagnosis is confirmed by a histologic demonstration of tissue invasion by the fungus and the growth of Aspergillus species on a culture. However, the yield of transbronchial biopsy specimens or percutaneous aspirates is relatively poor, and a thoracoscopic or open-lung biopsy is rarely performed in these patients. So, a clinical diagnosis of CNA could be made using the following criteria:

- Clinical and radiologic features consistent with the diagnosis;
- Isolation of Aspergillus species by culture from sputum or from bronchoscopic or percutaneous samples; and
- Exclusion of other conditions with similar presentations, such as active tuberculosis, atypical mycobacterial infection, chronic cavitary histoplasmosis, or coccidioidomycosis.

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

Other helpful but nondiagnostic tests include serum IgG antibodies to Aspergillus (positive results in > 90% of the patients) and immediate skin reactivity for Aspergillus antigens.

Treatment with antifungal medications is indicated once the diagnosis is made. The response to therapy with IV amphotericin B is generally favorable.[40,42] However, therapy with itraconazole has emerged as an effective alternative to the relatively toxic amphotericin B.[42,44] Surgical resection is generally reserved for healthy young patients with focal disease and good pulmonary reserves, patients not tolerating antifungal therapy, and patients with residual localized but active disease despite adequate antifungal treatment. In the initial series by Binder et al,[40] 90% of patients who underwent surgical resections had good responses. However, there were significant postoperative complications, and one patient died.[40]

The long-term prognosis for patients with CNA is not well-documented. In the original series,[40] 73% of the patients were alive 1 to 2 years following therapy, and the majority of deaths was due to other causes.

IPA

The incidence of IPA has been on the rise since it was first described in 1953.[45] Groll et al[46] documented a rise in the rate of invasive mycoses from 0.4 to 3.1% of all autopsies performed between 1978 and 1992. In addition, invasive aspergillosis increased from 17% of all mycoses found on autopsy at the beginning of the study to 60% at the end of the 14-year study period.

The vast majority of IPA cases are seen in immunocompromised patients. The risk factors are summarized in Table 1.[47–51] Neutropenia is the most important risk factor, and it is estimated that IPA accounts for 7.5% of all infections in neutropenic patients following induction therapy for acute myelogenous leukemia.[47] The risk of IPA increases with the duration of neutropenia (*ie*, neutrophil count, < 500 cells/μL) and is estimated to be 1% per day for the first 3 weeks, after which time it increases to 4% per day.[47] Transplantation, especially lung and bone marrow transplantation (BMT), is another increasingly significant risk factor for IPA.[52] It is estimated that 5% of BMT recipients develop IPA with mortality rates ranging between 30% and 80%.[53–55] In BMT recipients, IPA may be seen in the first few weeks after the procedure with delayed engraftment or graft failure, and more commonly in the setting of treatment with corticosteroids for graft-vs-host disease. The increased risk of IPA in patients undergoing transplantation is related to multiple immune defects including prolonged neutropenia in the pre-engraftment phase of BMT, and the use of multiple antirejection or anti-graft-vs-host disease therapy, including corticosteroids and cyclosporine. In addition, other factors that predispose patients to fungal infections in general, such as parenteral nutrition, use of multiple antibiotics, and prolonged hospitalization, increase the risk of IPA following transplantation. IPA also has been reported increasingly in patients with HIV infection.[51] While most HIV-infected patients have the same risk factors for Aspergillus infection as those in other patient populations (such as patients with neutropenia and those receiving corticosteroid therapy), there are a growing number of reports of IPA in AIDS patients without the traditional risk factors.[56,57] Besides the usual clinical picture of IPA, there is increased incidence of tracheobronchial involvement.[58] The response to therapy is particularly poor in the HIV-infected population.[51]

Rarely, IPA has been reported[59,60] in apparently immunocompetent patients or in those individuals who are mildly immunocompromised, such as patients with alcoholism, chronic liver disease, or diabetic ketoacidosis. In addition, IPA is increasingly recognized in patients with advanced COPD, especially those treated with oral corticosteroids.[61,62] In a recent review[63] of 545 patients with invasive aspergillosis, BMT was the most frequent risk factor (32%; autologous BMT, 7%; allogeneic BMT, 25%), followed by hematologic malignancy (29%), solid organ transplantation (9%), and AIDS (8%). In 2% of patients, no underlying risk factors were identified.

Table 1—*Major Risk Factors for IPA*

1. Prolonged neutropenia (> 3 wk) or neutrophil dysfunction (chronic granulomatous disease)
2. Corticosteroid therapy (especially prolonged, high-dose therapy)
3. Transplantation (highest risk is with lung and bone marrow)
4. Hematologic malignancy (risk is higher with leukemia)
5. Cytotoxic therapy
6. AIDS (risk increases with lower CD4 count)

Clinical Picture

The lower respiratory tract is almost always the primary focus of infection as a result of the inhalation of the infectious spores. Less commonly, IPA may start in locations other than the lungs, like the sinuses, the GI tract, or the skin (*ie*, resulting from the insertion of IV catheters, prolonged skin contact with adhesive tapes, or burns).[64–67]

Consequently, patients usually present with respiratory symptoms that are consistent with bronchopneumonia, with fever, cough, sputum production,

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

and dyspnea. Two other symptoms that are significant and that raise the possibility of IPA in the appropriate clinical setting are pleuritic chest pain (due to small pulmonary infarctions secondary to vascular invasion) and hemoptysis that is usually mild but could be massive. IPA is one of the most common causes of hemoptysis in neutropenic patients; and has been reported to be associated with cavitation that occurs with neutrophil recovery.[68] Other pulmonary manifestations include isolated tracheobronchitis with severe inflammation of the airways that is associated with ulcerations and plaque formation. This may lead to airway obstruction and secondary atelectasis. This form of IPA has been most commonly reported in patients with AIDS and in lung transplant recipients [69,70]

With the predilection of Aspergillus to invade blood vessels, IPA commonly leads to areas of infarction and hemorrhage in the primary organ (usually the lungs), and the organism spreads hematogenously to other organs, most commonly the brain (leading to seizures, ring-enhancing lesions, cerebral infarctions, intracranial hemorrhage, meningitis, and epidural abscess), and less commonly skin, kidneys, pleura, heart, esophagus, liver, or any other site.[71]

Diagnosis

The diagnosis of IPA is difficult. A high index of suspicion is necessary in patients with risk factors for invasive aspergillosis. The diagnosis is best made by demonstrating the presence of septate, acute, branching hyphae in the lung tissue sample along with a culture that is positive for Aspergillus from the same site. Methenamine-silver and periodic acid-Schiff stains are the usual stains to demonstrate the characteristic hyphae. Other fungi such as Fusarium and Scedosporium may have similar appearances, thus increasing the importance of performing a culture for the accurate identification of the fungus.

The presence of the Aspergillus species in sputum samples could be due to colonization of the airway; however, in the immunocompromised patient sputum culture positivity may be the only indication of IPA. Studies[72–74] have shown that sputum samples that are positive for Aspergillus in patients with leukemia or in those who have undergone BMT have a positive predictive value of 80 to 90%. On the other hand, a sputum sample that is negative for Aspergillus does not exclude the diagnosis of IPA, since negative sputum studies have been noted in 70% of patients with confirmed IPA.[75] Blood cultures rarely have positive results.[76]

The chest radiograph often shows nonspecific changes. The lesions that are suggestive of IPA include rounded densities, pleural-based infiltrates that are suggestive of pulmonary infarctions, and cavitation. Pleural effusions are uncommon.[77,78] The chest CT scan, especially with high-resolution images, is a much more helpful tool in the diagnosis of IPA. It leads to earlier diagnosis, and aids further diagnostic studies like bronchoscopy and open-lung biopsy.[79,80] The routine use of high-resolution chest CT scans in patients with suspected IPA has been associated with better outcomes, probably due to earlier diagnosis. Of the 156 patients who underwent chest CT scans in the report by Patterson et al,[63] 85% had findings that were suggestive of IPA. Typical chest CT scan findings are multiple nodules (Fig 3), the halo sign, which is an early radiologic sign that appears as a zone of low attenuation due to hemorrhage surrounding the pulmonary nodule,[81] and the air crescent sign, which is a crescent-shaped lucency in the region of the original nodule secondary to necrosis.[82] The air crescent sign usually correlates with recovery from neutropenia and is a relatively late sign.[83] The last two radiologic signs are relatively specific for IPA, but they are neither sensitive nor pathognomonic; other infections like nocardiosis and zygomycoses may have a similar appearance.[81,82]

BAL is helpful in the diagnosis of IPA, especially in patients with diffuse lung involvement. The BAL fluid is tested by fungal smear and culture. The specificity of a positive result of BAL fluid testing is very high, reaching 97%,[84] but the sensitivity is reported to be approximately 30 to 50%.[84,85] Transbronchial biopsies have not been shown to add much to the results of BAL and are associated with increased risks.[19] Open or thoracoscopic lung biopsies are generally the "gold standard" in the diagnosis of

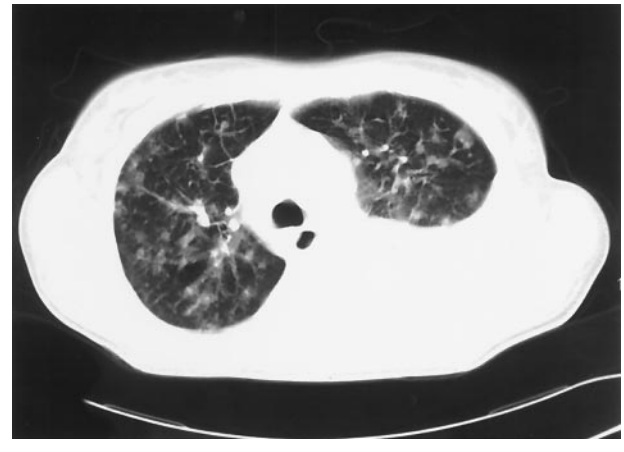

FIGURE 3. Chest CT scan of a patient with chronic lymphocytic leukemia and histologically proven IPA showing multiple pulmonary nodules.

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

pulmonary problems in immunocompromised patients; however, in the case of IPA, this procedure is known to be associated with false-negative results. In a study[86] of 15 patients who had undergone open-lung biopsies, the presence of IPA was missed in 3. Thus, open-lung biopsy is reserved for patients in whom the diagnosis of IPA remains uncertain despite results from the mentioned studies, and when such a procedure is expected to have an impact on the patients' management and outcome.

Serology has not been useful in the diagnosis of IPA. Aspergillus antibody detection is not useful, probably due to the poor immune response of patients with IPA and the rapidity with which the infection occurs, not giving enough time for an adequate antibody response.[87]

There has been increasing interest in Aspergillus antigen detection from serum and BAL samples. Some studies[88] suggest that antigenemia may be detected before the presence of clinical features of IPA. A sandwich enzyme-linked immunosorbent assay technique that utilizes monoclonal antibodies to galactomannan (*ie*, the cell wall glycoprotein that binds lectin) has been developed to detect the Aspergillus antigen in serum, urine, and BAL fluid and has a reported sensitivity and specificity of $> 90\%$.[88–92] This method, while commercially available in Western Europe, has not yet been approved in the United States.

Polymerase chain reaction is another experimental method with which to diagnose IPA by the detection of Aspergillus DNA in BAL fluid and serum. The extrasensitive nature of this method and the ubiquitous presence of the fungus create a high likelihood of false-positive results.[93,94]

The National Institute of Immunology, Allergy, and Infectious Diseases has provided a working case definition. The diagnosis of IPA is definite when tissue histopathology shows the hyphae, with or without a positive culture for Aspergillus from the same site, or a positive culture from tissue obtained by an invasive procedure such as transbronchial biopsy, percutaneous needle aspiration, or open-lung biopsy. The diagnosis of IPA is probable when the clinical picture is consistent with the diagnosis, and when two sputum cultures or one BAL fluid culture, a bronchial washing culture, or a brushing culture for Aspergillus species, or a cytologic examination of the BAL fluid shows the characteristic hyphae or positive Aspergillus antigen in the serum or BAL fluid. The diagnosis is possible when the clinical picture is compatible without documentation of any mycologic evidence of IPA.[63,95]

Treatment

The treatment of IPA is difficult, and the mortality rate remains high despite recent advances in therapy. Empiric therapy should be started as soon as there is clinical suspicion of IPA, and while a workup is underway. The outcome of therapy is dependent on an early diagnosis, the absence of dissemination, the instigation of intensive antifungal therapy, and the recovery of the underlying host defense defect, such as the resolution of neutropenia or the tapering of immunosuppression therapy.[96–98] In the review by Patterson et al,[63] patients who had severe immunosuppression, such as those who had undergone BMT and had hematologic malignancy, had poor responses to therapy compared to less severely immunosuppressed patients (28% vs 51%, respectively). Also, when IPA was limited to the lung, the response was better than in patients with disseminated infection (40% vs 18%, respectively). The most widely used drug in the treatment of IPA is amphotericin B. Its usual dose is 0.6 to 1.2 mg/kg/d; however, higher doses (*ie*, 1 to 1.5 mg/kg/d) may be necessary in severely immunocompromised patients with overwhelming infections.[99] The optimal duration of antifungal drug therapy is not known, but treatment is recommended to continue past the period of immunosuppression and until the disease appears to be clinically resolved.[19] Even with optimal therapy, the response rate varies widely between 20% and 83%.[100]

Amphotericin B is known to cause serious side effects such as nephrotoxicity, electrolyte disturbances, and hypersensitivity reactions. Newer lipid-based preparations of amphotericin B (*eg*, liposomal amphotericin B and lipid complex amphotericin B) have been introduced in an effort to minimize these side effects. These preparations enable the administration of higher doses of amphotericin B with less toxicity and are indicated in patients who are at high risk for nephrotoxicity, who develop toxicity while receiving amphotericin B, or who respond poorly to that medication.[19,101–104]

Itraconazole, a triazole, is another agent that is used in the treatment of IPA, in doses of 200 to 400 mg/d.[30,105] The drug is available in oral (*ie*, capsule and suspension) and IV formulations. The itraconazole capsule should be avoided in the treatment of IPA in view of its poor bioavailability. In a large nonrandomized study,[95] itraconazole was found to result in complete or partial response in 39% of patients with IPA, and in a failure to respond to treatment in 26%. The results were particularly poor in allogeneic BMT recipients and AIDS patients. It is reasonable to consider therapy with itraconazole as an alterative to that with amphotericin B in patients

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

with IPA who are less immunocompromised and in the late stages of therapy after the initial control of the infection with amphotericin B therapy. Because of drug-drug interactions, itraconazole needs to be used with caution. The use of combination therapy (for example, amphotericin B with 5-fluorocytosine, rifampin, itraconazole, or ketoconazole) has not been shown to be more effective in the treatment of patients with IPA.[106] Trials[19] are currently underway testing several new promising drugs like voriconazole, posaconazole, and echinocandin derivatives. Caspofungin, an echinocandin derivative was recently approved[107] for the treatment of IPA in patients with refractory infection or those intolerant to conventional therapy.

Other modalities of therapy include surgical resection, which should be considered in cases of massive hemoptysis,[108] or the resection of residual localized pulmonary lesions in patients with continuing immunosuppression or those who are expected to have further immunosuppressive therapy in the future.[109] Surgery has been performed safely in selected neutropenic patients.[109–111] The surgical outcome is poor in patients with multiple foci of infection, in those who have undergone allogeneic BMT, and those requiring mechanical ventilation.

The value of immunomodulatory therapy such as that using cytokines (*ie*, granulocyte colony-stimulating factor, granulocyte macrophage-colony-stimulating factor, or interferon-γ) as adjuvant therapy is not clear, and large studies on the safety and efficacy of these agents are lacking.[112]

Given the difficulties in the management of IPA, an important approach to this problem is prophylaxis for those patients who are at increased risk for IPA. Avoiding the hospitalization of patients in areas where there is construction and the use of high-efficiency particulate air or laminar air flow have been shown to decrease the rate of IPA in some studies.[113] Also chemoprophylaxis using low-dose amphotericin B and intranasal amphotericin B have been studied with variable results.[114,115] Currently chemoprophylaxis trials using itraconazole and posaconazole are underway in allogeneic BMT recipients.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to Aspergillus antigens, mostly due to *A fumigatus*. It is typically seen in patients with long-standing asthma or cystic fibrosis, and it is estimated that 7 to 14% of corticosteroid-dependent asthma patients and 6% of patients with cystic fibrosis meet the diagnostic criteria for ABPA.[116,117] The factors leading to ABPA are not clearly understood. It is believed that Aspergillus-specific, IgE-mediated type I hypersensitivity reactions and specific IgG-mediated type III hypersensitivity reactions play a central role in the pathogenesis of ABPA.[118,119] Other host factors, including cellular immunity, may contribute to the pathologic changes seen in ABPA.[120,121] Since the diagnosis of ABPA is usually made on clinical grounds, lung biopsies are rarely performed. In a study[122] of 18 pathologic specimens from patients with ABPA, the most significant findings involved the bronchi and bronchioles with bronchocentric granulomas in 15 specimens and mucoid impaction in 11. Other findings included granulomatous inflammation with histiocytes and lymphocytes, increased numbers of eosinophils, and exudative bronchiolitis. Fungal hyphae were commonly seen without evidence of tissue invasion.[122]

Diagnosis

ABPA is usually suspected on clinical grounds, and the diagnosis is confirmed by radiologic and serologic testing. The patient usually presents with wheezing, expectoration of brown mucus plugs, pleuritic chest pain, and fever.[123] The chest radiograph findings may be normal in the early stages of the disease. During acute exacerbations, the typical findings are fleeting pulmonary infiltrates that tend to be in the upper lobe and central in location. There may be loss of volume due to mucoid impaction of the airways. This latter manifestation may present as band-like opacities emanating from the hilum with rounded distal margins (gloved finger appearance).[124] At later stages, central bronchiectasis and pulmonary fibrosis develop. The chest CT scan is more sensitive in demonstrating the above changes. The IgE level serves as a marker for flare-ups and responses to therapy.[125] A positive sputum culture for *A fumigatus* is not essential for the diagnosis, and indeed in rare cases a syndrome similar to ABPA is triggered by fungi other than Aspergillus. Immediate skin reactivity to *A fumigatus* antigens and elevated levels of serum IgG antibodies to Aspergillus are usually present.[118] Lung biopsy is rarely performed for the diagnosis of ABPA.

Greenberger and Patterson recently modified the diagnostic criteria for ABPA (Table 2).[123,125] Not all of these criteria need to be present to diagnose ABPA. Withholding therapy until the development of all clinical symptoms and evidence of bronchiectasis may lead to a missed diagnosis in a significant number of patients and to delayed treatment resulting in irreversible pulmonary damage. Therefore, ABPA may be subdivided into the following two

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

Table 2—*Diagnostic Criteria for ABPA*

1. Asthma
2. Immediate skin reactivity to Aspergillus
3. Serum precipitins to *A fumigatus*
4. Increased serum IgE and IgG to *A fumigatus*
5. Total serum IgE > 1,000 ng/mL
6. Current or previous pulmonary infiltrates
7. Central bronchiectasis
8. Peripheral eosinophilia (1,000 cells/μL)

groups: patients with or without central bronchiectasis. The essential criteria for diagnosis of the group with ABPA and central bronchiectasis are asthma, immediate skin reactivity to Aspergillus antigens, serum IgE level > 1,000 ng/mL, and central bronchiectasis. Patients without central bronchiectasis are labeled ABPA-seropositive, and the minimal criteria for diagnosis are asthma, immediate skin reactivity to Aspergillus, serum IgE level > 1,000 ng/mL, history of pulmonary infiltrates, and elevated levels of serum IgE and IgG antibodies to *A fumigatus*.[127]

Patterson et al[128] divided this syndrome into five stages that help to guide the management of the disease. It is not necessary for a patient to progress through all of these stages. Stage 1 (acute stage) is characterized by asthma, a markedly elevated IgE level, peripheral eosinophilia, pulmonary infiltrates, and the presence of IgE and IgG antibodies to *A fumigatus*. In practice, patients are rarely identified in this stage. In stage II (remission stage), the IgE level falls, but not to the normal range, eosinophilia is absent, and the chest radiograph is clear. Serum IgG antibodies to Aspergillus may be slightly elevated. Stage III (exacerbation stage) is diagnosed in a patient who is known to have ABPA and is similar to stage I. The IgE level is usually double that at baseline. Stage IV (the corticosteroid-dependent stage) occurs when the patient becomes steroid-dependent and attempts to taper the steroid therapy, resulting in an obvious worsening of symptoms and the development of pulmonary infiltrates. The serum IgE level is usually elevated but may be normal. Frequently, the chest CT scan will show central bronchiectasis. Unfortunately, the syndrome is diagnosed in the majority of patients at this stage.[129] Stage V (fibrotic stage) is characterized by clinical features of end-stage lung disease with dyspnea, cyanosis, rales, and cor pulmonale. Clubbing may be present. The serum IgE level and eosinophil count may be low or high. A minority of patients progress to this stage.

Treatment

The mainstay of therapy for ABPA is oral corticosteroids to suppress the immunologic response to Aspergillus antigens and the secondary inflammatory reaction. Treatment with corticosteroids leads to the relief of bronchospasm, the clearing of pulmonary infiltrates, and a decrease in IgE level and peripheral eosinophilia.[130,131] Oral prednisone is administered at 0.5 mg/kg/d for 2 weeks then gradually is tapered.[132] The duration of therapy should be individualized according to the patient's clinical condition. Most patients, however, require prolonged low-dose corticosteroid therapy to control their symptoms and minimize relapses.[132,133] Inhaled steroids are not helpful in preventing the progression of lung damage associated with ABPA.[134]

Since there are side effects associated with long-term corticosteroid therapy, including an increased risk of invasive aspergillosis,[135] interest in other modalities of treatment of ABPA has developed. Recently, a randomized prospective study[136] was performed to evaluate the role of an antifungal agent, itraconazole, in the management of ABPA. The study showed that 46% of patients treated with itraconazole, 200 mg bid for 16 weeks, had a significant response, which was defined as a 50% reduction in the corticosteroid dose, a decrease of at least 25% in the serum IgE concentration, and a 25% improvement in exercise tolerance or pulmonary function test results, or the resolution or absence of pulmonary infiltrates. There was no significant toxicity related to this therapy. The study concluded that patients with ABPA generally benefit from concurrent itraconazole therapy and suggested that a lower dose of itraconazole (200 mg daily) was equally beneficial and may be useful as a maintenance therapy to sustain remission.

Syndromes Related to ABPA

Mucoid Impaction: This feature of ABPA may be seen without asthma or other features of the disease. The patient usually presents with a cough and expectoration of mucus plugs.[137] The mucus plugging may lead to atelectasis, which may arouse suspicion of endobronchial malignancy.[138]

Bronchocentric Granulomatosis: This syndrome is characterized by necrotizing granulomas that obstruct and destroy the bronchioles. The Aspergillus hyphae are identified within the granulomas in 40 to 50% of patients with bronchocentric granulomatosis.[99] The lung parenchyma is marked by the presence eosinophilic inflammatory infiltrates and fibrosis, however, there is no tissue or vascular invasion by the Aspergillus. Clinically, the patients are almost always asthmatic and have a persistent cough with peripheral eosinophilia and increased serum IgE levels. The chest radiograph usually shows solitary or

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

multiple pulmonary nodules that may be mistaken for malignancies. The patients usually respond to corticosteroid therapy.[139]

Eosinophilic Pneumonitis: Aspergillus rarely has been implicated in the etiology of this syndrome. The patient usually presents with cough, dyspnea, and fever associated with peripheral pulmonary infiltrates, and an elevation of Aspergillus IgE levels. The diagnosis usually is confirmed by biopsy, and patients respond well to corticosteroid therapy.[140,141]

Hypersensitivity Pneumonitis: Also known as extrinsic allergic alveolitis, it is a form of hypersensitivity granulomatous inflammation of the distal airways and lung parenchyma. It is related to intense or repeated inhalation of various antigens, including thermophilic bacteria, fungi, bird excreta, and chemical agents. This condition has been described in patients exposed to Aspergillus spores and has been implicated in farmer's lung disease and malt-worker's lung disease.[142] The acute form of the disease presents within hours of exposure to the antigens with dyspnea, cough, fever, and myalgia. The chest radiograph usually shows interstitial and alveolar nodular infiltrates. Repeated exposures to the offending antigens lead to a chronic form of hypersensitivity pneumonitis that is associated with irreversible pulmonary fibrosis.[142,143] Serum levels of IgG antibodies to Aspergillus are elevated when the disease is due to Aspergillus.[144] The management of the acute form includes avoiding further exposure to the offending agents and corticosteroid therapy.[142,145]

References

1 Rinaldi MG. Invasive aspergillosis. Rev Infect Dis 1983; 5:1061–1077
2 Tomee JF, van der Werf TS, Latge JP, et al. Serologic monitoring of disease and treatment in a patient with pulmonary aspergilloma. Am J Respir Crit Care Med 1995; 151:199–204
3 Safirstein BH. Aspergilloma consequent to allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1973; 108:940–943
4 Aspergilloma and residual tuberculous cavities: the results of a resurvey. Tubercle 1970; 51:227–245
5 Kauffman CA. Quandary about treatment of aspergillomas persists. Lancet 1996; 347:1640
6 Zizzo G, Castriota-Scanderbeg A, Zarrelli N, et al. Pulmonary aspergillosis complicating ankylosing spondylitis. Radiol Med (Torino) 1996; 91:817–818
7 Kawamura S, Maesaki S, Tomono K, et al. Clinical evaluation of 61 patients with pulmonary aspergilloma. Intern Med 2000; 39:209–212
8 Rosenheim SH, Schwarz J. Cavitary pulmonary cryptococcosis complicated by aspergilloma. Am Rev Respir Dis 1975; 111:549–553
9 Sarosi GA, Silberfarb PM, Saliba NA, et al. Aspergillomas occurring in blastomycotic cavities. Am Rev Respir Dis 1971; 104:581–584
10 Rafferty P, Biggs BA, Crompton GK, et al. What happens to patients with pulmonary aspergilloma? Analysis of 23 cases. Thorax 1983; 38:579–583
11 Gefter WB. The spectrum of pulmonary aspergillosis. J Thorac Imaging 1992; 7:56–74
12 British Tuberculosis Association. Aspergillus in persistent lung cavities after tuberculosis: a report from the Research Committee of the British Tuberculosis Association. Tubercle 1968; 49:1–11
13 Faulkner SL, Vernon R, Brown PP, et al. Hemoptysis and pulmonary aspergilloma: operative versus nonoperative treatment. Ann Thorac Surg 1978; 25:389–392
14 Addrizzo-Harris DJ, Harkin TJ, McGuinness G, et al. Pulmonary aspergilloma and AIDS: a comparison of HIV-infected and HIV-negative individuals. Chest 1997; 111: 612–618
15 Aslam PA, Eastridge CE, Hughes FA Jr. Aspergillosis of the lung: an eighteen-year experience. Chest 1971; 59:28–32
16 Garvey J, Crastnopol P, Weisz D, et al. The surgical treatment of pulmonary aspergillomas. Thorac Cardiovasc Surg 1977; 74:542–547
17 Daly RC, Pairolero PC, Piehler JM, et al. Pulmonary aspergilloma: results of surgical treatment. Thorac Cardiovasc Surg 1986; 92:981–988
18 Karas A, Hankins JR, Attar S, et al. Pulmonary aspergillosis: an analysis of 41 patients. Ann Thorac Surg 1976; 22:1–7
19 Jewkes J, Kay PH, Paneth M, et al. Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. Thorax 1983; 38:572–578
20 Glimp RA, Bayer AS. Pulmonary aspergilloma: diagnostic and therapeutic considerations. Arch Intern Med 1983; 143:303–308
21 Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by Aspergillus: Infectious Diseases Society of America. Clin Infect Dis 2000; 30:696–709
22 Tuncel E. Pulmonary air meniscus sign. Respiration 1984; 46:139–144
23 Roberts CM, Citron KM, Strickland B. Intrathoracic aspergilloma: role of CT in diagnosis and treatment. Radiology 1987; 165:123–128
24 Bandoh S, Fujita J, Fukunaga Y, et al. Cavitary lung cancer with an aspergilloma-like shadow. Lung Cancer 1999; 26: 195–198
25 Le Thi HD, Wechsler B, Chamuzeau JP, et al. Pulmonary aspergilloma complicating Wegener's granulomatosis [letter]. Scand J Rheumatol 1995; 24:260
26 McCarthy DS, Pepys J. Pulmonary aspergilloma: clinical immunology. Clin Allergy 1973; 3:57–70
27 Pennington JE. Aspergillus lung disease. Med Clin North Am 1980; 64:475–490
28 Yamada H, Kohno S, Koga H, et al. Topical treatment of pulmonary aspergilloma by antifungals: relationship between duration of the disease and efficacy of therapy. Chest 1993; 103:1421–1425
29 Munk PL, Vellet AD, Rankin RN, et al. Intracavitary aspergilloma: transthoracic percutaneous injection of amphotericin gelatin solution. Radiology 1993; 188:821–823
30 Hammerman KJ, Sarosi GA, Tosh FE. Amphotericin B in the treatment of saprophytic forms of pulmonary aspergillosis. Am Rev Respir Dis 1974; 109:57–62
31 Dupont B. Itraconazole therapy in aspergillosis: study in 49 patients. J Am Acad Dermatol 1990; 23:607–614
32 Campbell JH, Winter JH, Richardson MD, et al. Treatment

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

of pulmonary aspergilloma with itraconazole. Thorax 1991; 46:839–841
33 Jennings TS, Hardin TC. Treatment of aspergillosis with itraconazole. Ann Pharmacother 1993; 27:1206–1211
34 Uflacker R, Kaemmerer A, Picon PD, et al. Bronchial artery embolization in the management of hemoptysis: technical aspects and long-term results. Radiology 1985; 157:637–644
35 Soltanzadeh H, Wychulis AR, Sadr F, et al. Surgical treatment of pulmonary aspergilloma. Ann Surg 1977; 186:13–16
36 Massard G, Roeslin N, Wihlm JM, et al. Pleuropulmonary aspergilloma: clinical spectrum and results of surgical treatment. Ann Thorac Surg 1992; 54:1159–1164
37 Kilman JW, Ahn C, Andrews NC, et al. Surgery for pulmonary aspergillosis. Thorac Cardiovasc Surg 1969; 57:642–647
38 Chen JC, Chang YL, Luh SP, et al. Surgical treatment for pulmonary aspergilloma: a 28 year experience. Thorax 1997; 52:810–813
39 Regnard JF, Icard P, Nicolosi M, et al. Aspergilloma: a series of 89 surgical cases. Ann Thorac Surg 2000; 69:898–903
40 Binder RE, Faling LJ, Pugatch RD, et al. Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine (Baltimore) 1982; 61:109–124
41 Gefter WB, Weingrad TR, Epstein DM, et al. "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of Aspergillus infections of the lung. Radiology 1981; 140:313–321
42 Saraceno JL, Phelps DT, Ferro TJ, et al. Chronic necrotizing aspergillosis: approach to management. Chest 1997; 112: 541–548
43 Grahame-Clarke CN, Roberts CM, Empey DW. Chronic necrotizing pulmonary aspergillosis and pulmonary phycomycosis in cystic fibrosis. Respir Med 1994; 88:465–468
44 Caras WE, Pluss JL. Chronic necrotizing pulmonary aspergillosis: pathologic outcome after itraconazole therapy. Mayo Clin Proc 1996; 71:25–30
45 Bartlett JG. Aspergillosis update. Medicine (Baltimore) 2000; 79:281–282
46 Groll AH, Shah PM, Mentzel C, et al. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 1996; 33:23–32
47 Gerson SL, Talbot GH, Hurwitz S, et al. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984; 100:345–351
48 Schaffner A. Therapeutic concentrations of glucocorticoids suppress the antimicrobial activity of human macrophages without impairing their responsiveness to gamma interferon. J Clin Invest 1985; 76:1755–1764
49 Minamoto GY, Barlam TF, Vander Els NJ. Invasive aspergillosis in patients with AIDS. Clin Infect Dis 1992; 14:66–74
50 Hibberd PL, Rubin RH. Clinical aspects of fungal infection in organ transplant recipients. Clin Infect Dis 1994; 19(suppl):S33–S40
51 Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324:654–662
52 Soubani AO, Miller KB, Hassoun PM. Pulmonary complications of bone marrow transplantation. Chest 1996; 109: 1066–1077
53 Wald A, Leisenring W, van Burik JA, et al. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997; 175: 1459–1466
54 McWhinney PH, Kibbler CC, Hamon MD, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. Clin Infect Dis 1993; 17:397–404
55 Saugier-Veber P, Devergie A, Sulahian A, et al. Epidemiology and diagnosis of invasive pulmonary aspergillosis in bone marrow transplant patients: results of a 5 year retrospective study. Bone Marrow Transplant 1993; 12:121–124
56 Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases; French Cooperative Study Group on Aspergillosis in AIDS. Am J Med 1993; 95:177–187
57 Miller WT Jr, Sais GJ, Frank I, et al. Pulmonary aspergillosis in patients with AIDS: clinical and radiographic correlations. Chest 1994; 105:37–44
58 Kemper CA, Hostetler JS, Follansbee SE, et al. Ulcerative and plaque-like tracheobronchitis due to infection with Aspergillus in patients with AIDS. Clin Infect Dis 1993; 17:344–352
59 Karam GH, Griffin FM Jr. Invasive pulmonary aspergillosis in nonimmunocompromised, nonneutropenic hosts. Rev Infect Dis 1986; 8:357–363
60 Levitz SM, Diamond RD. Changing patterns of aspergillosis infections. Adv Intern Med 1984; 30:153–174
61 Pittet D, Huguenin T, Dharan S, et al. Unusual cause of lethal pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 154:541–544
62 Bulpa PA, Dive AM, Garrino MG, et al. Chronic obstructive pulmonary disease patients with invasive pulmonary aspergillosis: benefits of intensive care? Intensive Care Med 2001; 27:59–67
63 Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes; I3 Aspergillus Study Group. Medicine (Baltimore) 2000; 79:250–260
64 Iwen PC, Rupp ME, Langnas AN, et al. Invasive pulmonary aspergillosis due to *Aspergillus terreus*: 12-year experience and review of the literature. Clin Infect Dis 1998; 26:1092–1097
65 Young RC, Bennett JE, Vogel CL, et al. Aspergillosis: the spectrum of the disease in 98 patients. Medicine (Baltimore) 1970; 49:147–173
66 Prystowsky SD, Vogelstein B, Ettinger DS, et al. Invasive aspergillosis. N Engl J Med 1976; 295:655–658
67 Allo MD, Miller J, Townsend T, et al. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. N Engl J Med 1987; 317:1105–1108
68 Albelda SM, Talbot GH, Gerson SL, et al. Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis: influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 1985; 131:115–120
69 Judson MA, Sahn SA. Endobronchial lesions in HIV-infected individuals. Chest 1994; 105:1314–1323
70 Nathan SD, Shorr AF, Schmidt ME, et al. Aspergillus and endobronchial abnormalities in lung transplant recipients. Chest 2000; 118:403–407
71 Denning DW. Invasive aspergillosis. Clin Infect Dis 1998; 26:781–803
72 Yu VL, Muder RR, Poorsattar A. Significance of isolation of Aspergillus from the respiratory tract in diagnosis of invasive pulmonary aspergillosis: results from a three-year prospective study. Am J Med 1986; 81:249–254
73 Nalesnik MA, Myerowitz RL, Jenkins R, et al. Significance of Aspergillus species isolated from respiratory secretions in the diagnosis of invasive pulmonary aspergillosis. J Clin Microbiol 1980; 11:370–376
74 Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med 1996; 100:171–178

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

75 Tang CM, Cohen J. Diagnosing fungal infections in immunocompromised hosts. J Clin Pathol 1992; 45:1–5
76 Duthie R, Denning DW. Aspergillus fungemia: report of two cases and review. Clin Infect Dis 1995; 20:598–605
77 Libshitz HI, Pagani JJ. Aspergillosis and mucormycosis: two types of opportunistic fungal pneumonia. Radiology 1981; 140:301–306
78 Pagani JJ, Libshitz HI. Opportunistic fungal pneumonias in cancer patients. AJR Am J Roentgenol 1981; 137:1033–1039
79 Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 1985; 157:611–614
80 Kuhlman JE, Fishman EK, Burch PA, et al. CT of invasive pulmonary aspergillosis. AJR Am J Roentgenol 1988; 150: 1015–1020
81 Kuhlman JE, Fishman EK, Burch PA, et al. Invasive pulmonary aspergillosis in acute leukemia: the contribution of CT to early diagnosis and aggressive management. Chest 1987; 92:95–99
82 Curtis AM, Smith GJ, Ravin CE. Air crescent sign of invasive aspergillosis. Radiology 1979; 133:17–21
83 Gefter WB, Albelda SM, Talbot GH, et al. Invasive pulmonary aspergillosis and acute leukemia: limitations in the diagnostic utility of the air crescent sign. Radiology 1985; 157:605–610
84 Kahn FW, Jones JM, England DM. The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol 1986; 86:518–523
85 Albelda SM, Talbot GH, Gerson SL, et al. Role of fiberoptic bronchoscopy in the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am J Med 1984; 76:1027–1034
86 McCabe RE, Brooks RG, Mark JB, et al. Open lung biopsy in patients with acute leukemia. Am J Med 1985; 78:609–616
87 Tomee JF, Mannes GP, van der Bij W, et al. Serodiagnosis and monitoring of Aspergillus infections after lung transplantation. Ann Intern Med 1996; 125:197–201
88 Rogers TR, Haynes KA, Barnes RA. Value of antigen detection in predicting invasive pulmonary aspergillosis. Lancet 1990; 336:1210–1213
89 Verweij PE, Dompeling EC, Donnelly JP, et al. Serial monitoring of Aspergillus antigen in the early diagnosis of invasive aspergillosis: preliminary investigations with two examples. Infection 1997; 25:86–89
90 Verweij PE, Stynen D, Rijs AJ, et al. Sandwich enzyme-linked immunosorbent assay compared with Pastorex latex agglutination test for diagnosing invasive aspergillosis in immunocompromised patients. J Clin Microbiol 1995; 33: 1912–1914
91 Sulahian A, Tabouret M, Ribaud P, et al. Comparison of an enzyme immunoassay and latex agglutination test for detection of galactomannan in the diagnosis of invasive aspergillosis. Eur J Clin Microbiol Infect Dis 1996; 15:139–145
92 Rohrlich P, Sarfati J, Mariani P, et al. Prospective sandwich enzyme-linked immunosorbent assay for serum galactomannan: early predictive value and clinical use in invasive aspergillosis. Pediatr Infect Dis J 1996; 15:232–237
93 Melchers WJ, Verweij PE, van den HP, et al. General primer-mediated PCR for detection of Aspergillus species. J Clin Microbiol 1994; 32:1710–1717
94 Bretagne S, Costa JM, Marmorat-Khuong A, et al. Detection of Aspergillus species DNA in bronchoalveolar lavage samples by competitive PCR. J Clin Microbiol 1995; 33:1164–1168
95 Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994; 97:135–144
96 von Eiff M, Roos N, Schulten R, et al. Pulmonary aspergillosis: early diagnosis improves survival. Respiration 1995; 62:341–347
97 Ribaud P, Chastang C, Latge JP, et al. Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis 1999; 28:322–330
98 Schwartz RS, Mackintosh FR, Schrier SL, et al. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. Cancer 1984; 53:411–419
99 Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev Infect Dis 1990; 12:1147–1201
100 Denning DW. Therapeutic outcome in invasive aspergillosis. Clin Infect Dis 1996; 23:608–615
101 Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 1998; 26:1383–1396
102 Bowden RA, Cays M, Gooley T, et al. Phase I study of amphotericin B colloidal dispersion for the treatment of invasive fungal infections after marrow transplant. J Infect Dis 1996; 173:1208–1215
103 Mills W, Chopra R, Linch DC, et al. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: a single-centre experience of 133 episodes in 116 patients. Br J Haematol 1994; 86:754–760
104 Ng TT, Denning DW. Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections: evaluation of United Kingdom compassionate use data. Arch Intern Med 1995; 155:1093–1098
105 Denning DW, Tucker RM, Hanson LH, et al. Treatment of invasive aspergillosis with itraconazole. Am J Med 1989; 86:791–800
106 Schaffner A, Bohler A. Amphotericin B refractory aspergillosis after itraconazole: evidence for significant antagonism. Mycoses 1993; 36:421–424
107 Thompson CA. New type of antifungal approved for invasive aspergillosis. Am J Health Syst Pharm 2001; 58:558
108 Pagano L, Ricci P, Nosari A, et al. Fatal haemoptysis in pulmonary filamentous mycosis: an underevaluated cause of death in patients with acute leukaemia in haematological complete remission; a retrospective study and review of the literature—Gimema Infection Program. Br J Haematol 1995; 89:500–505
109 Bernard A, Caillot D, Couaillier JF, et al. Surgical management of invasive pulmonary aspergillosis in neutropenic patients. Ann Thorac Surg 1997; 64:1441–1447
110 Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997; 15:139–147
111 Robinson LA, Reed EC, Galbraith TA, et al. Pulmonary resection for invasive Aspergillus infections in immunocompromised patients. Thorac Cardiovasc Surg 1995; 109:1182–1196
112 Bernhisel-Broadbent J, Camargo EE, Jaffe HS, et al. Recombinant human interferon-gamma as adjunct therapy for Aspergillus infection in a patient with chronic granulomatous disease. J Infect Dis 1991; 163:908–911
113 Sherertz RJ, Belani A, Kramer BS, et al. Impact of air filtration on nosocomial Aspergillus infections: unique risk of bone marrow transplant recipients. Am J Med 1987; 83:709–718
114 Bohme A, Karthaus M, Hoelzer D. Antifungal prophylaxis in

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

neutropenic patients with hematologic malignancies. Antibiot Chemother 2000; 50:69–78
115 Donnelly JP. Febrile neutropenia: antifungal prophylaxis. Int J Antimicrob Agents 2000; 16:127–130
116 Basich JE, Graves TS, Baz MN, et al. Allergic bronchopulmonary aspergillosis in corticosteroid-dependent asthmatics. J Allergy Clin Immunol 1981; 68:98–102
117 Mroueh S, Spock A. Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Chest 1994; 105:32–36
118 Wang JL, Patterson R, Rosenberg M, et al. Serum IgE and IgG antibody activity against *Aspergillus fumigatus* as a diagnostic aid in allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1978; 117:917–927
119 Cockrill BA, Hales CA. Allergic bronchopulmonary aspergillosis. Annu Rev Med 1999; 50:303–316
120 Knutsen AP, Slavin RG. *In vitro* T cell responses in patients with cystic fibrosis and allergic bronchopulmonary aspergillosis. J Lab Clin Med 1989; 113:428–435
121 Chauhan B, Santiago L, Kirschmann DA, et al. The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. J Immunol 1997; 159:4072–4076
122 Bosken CH, Myers JL, Greenberger PA, et al. Pathologic features of allergic bronchopulmonary aspergillosis. Am J Surg Pathol 1988; 12:216–222
123 Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977; 86:405–414
124 Mintzer RA, Rogers LF, Kruglik GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. Radiology 1978; 127:301–307
125 Greenberger PA, Patterson R. Diagnosis and management of allergic bronchopulmonary aspergillosis. Ann Allergy 1986; 56:444–448
126 Varkey B. Allergic bronchopulmonary aspergillosis: clinical perspectives. Immunol Allergy Clin North Am 1998; 18: 479–501
127 Greenberger PA. Immunologic aspects of lung diseases and cystic fibrosis. JAMA 1997; 278:1924–1930
128 Patterson R, Greenberger PA, Radin RC, et al. Allergic bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med 1982; 96:286–291
129 Patterson R, Greenberger PA, Halwig JM, et al. Allergic bronchopulmonary aspergillosis: natural history and classification of early disease by serologic and roentgenographic studies. Arch Intern Med 1986; 146:916–918
130 Rosenberg M, Patterson R, Roberts M, et al. The assessment of immunologic and clinical changes occurring during corticosteroid therapy for allergic bronchopulmonary aspergillosis. Am J Med 1978; 64:599–606
131 Wang JL, Patterson R, Roberts M, et al. The management of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1979; 120:87–92
132 Capewell S, Chapman BJ, Alexander F, et al. Corticosteroid treatment and prognosis in pulmonary eosinophilia. Thorax 1989; 44:925–929
133 Safirstein BH, D'Souza MF, Simon G, et al. Five-year follow-up of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1973; 108:450–459
134 British Thoracic Association. Inhaled beclomethasone dipropionate in allergic bronchopulmonary aspergillosis: report to the Research Committee of the British Thoracic Association. Br J Dis Chest 1979; 73:349–356
135 Ganassini A, Cazzadori A. Invasive pulmonary aspergillosis complicating allergic bronchopulmonary aspergillosis. Respir Med 1995; 89:143–145
136 Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000; 342:756–762
137 Hewlett RI. Possible mucoid impaction of allergic bronchopulmonary aspergilloma [letter]. Chest 1974; 66:738
138 Cote CG, Cicchelli R, Hassoun PM. Hemoptysis and a lung mass in a 51-year-old patient with asthma. Chest 1998; 114:1465–1468
139 Sulavik SB. Bronchocentric granulomatosis and allergic bronchopulmonary aspergillosis. Clin Chest Med 1988; 9:609–621
140 Warnock ML, Fennessy J, Rippon J. Chronic eosinophilic pneumonia, a manifestation of allergic aspergillosis. Am J Clin Pathol 1974; 62:73–81
141 Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia: a report of 19 cases and a review of the literature. Medicine (Baltimore) 1988; 67:154–162
142 Salvaggio JE. Hypersensitivity pneumonitis. J Allergy Clin Immunol 1987; 79:558–571
143 Richerson HB, Bernstein IL, Fink JN, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis: report of the Subcommittee on Hypersensitivity Pneumonitis. J Allergy Clin Immunol 1989; 84:839–844
144 Hinojosa M, Fraj J, De La Hoz B, et al. Hypersensitivity pneumonitis in workers exposed to esparto grass (*Stipa tenacissima*) fibers. J Allergy Clin Immunol 1996; 98:985–991
145 Kokkarinen JI, Tukiainen HO, Terho EO. Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung. Am Rev Respir Dis 1992; 145:3–5

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006

The Clinical Spectrum of Pulmonary Aspergillosis*
Ayman O. Soubani and Pranatharthi H. Chandrasekar
Chest 2002;121;1988-1999
DOI: 10.1378/chest.121.6.1988

This information is current as of April 12, 2006

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://www.chestjournal.org/cgi/content/full/121/6/1988
References	This article cites 145 articles, 48 of which you can access for free at: http://www.chestjournal.org/cgi/content/full/121/6/1988#BIBL
Citations	This article has been cited by 12 HighWire-hosted articles: http://www.chestjournal.org/cgi/content/full/121/6/1988#other articles
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://www.chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

AMERICAN COLLEGE OF
CHEST
PHYSICIANS

Downloaded from www.chestjournal.org at Massachusetts General Hospital on April 12, 2006