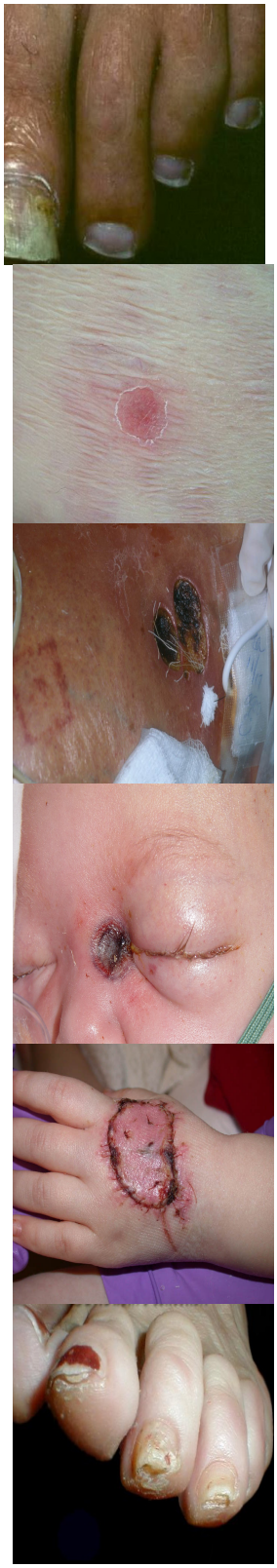

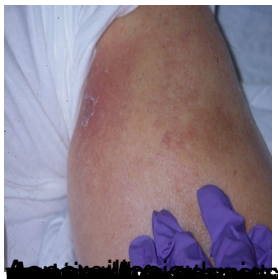

Laboratory Studies

Because *Aspergillus* infection may cause colonization, allergy, or invasive infection, its manifestations are quite variable and are best considered based on the disease process.

Allergic bronchopulmonary aspergillosis (ABPA) is defined by several abnormalities, including asthma, eosinophilia, a positive skin test result for *A fumigatus,* marked elevation of the serum immunoglobulin E (IgE) level to greater than 1000 IU/dL, fleeting pulmonary infiltrates, central bronchiectasis, mucoid impaction, and positive test results for
Aspergillus
precipitins (primarily immunoglobulin G [IgG], but also immunoglobulin A and immunoglobulin M, antibodies). Minor criteria for diagnosis include positive
Aspergillus
radioallergosorbent assay test results and culture findings for
Aspergillus
in sputum.

Diagnostic criteria for ABPA in persons with CF were revised by the Cystic Fibrosis Foundation. ABPA is considered a definite diagnosis requiring treatment if the following are noted: (1) clinical deterioration, including cough, wheeze, increased sputum production, diminished exercise tolerance, or diminished pulmonary function; (2) total serum IgE level greater than 1000 IU/mL or a greater than 2-fold rise from baseline; (3) positive serology results for *Aspergillus* (*Aspergillus*
precipitins or
Aspergillus
-specific IgG or IgE); and (4) new infiltrates on chest radiographs or CT scans. Treatment for ABPA is also recommended in patients with CF who have new radiographic findings and symptoms and a change in baseline IgE level to greater than 500 IU/mL.
[6]

Definitive diagnosis of invasive aspergillosis or chronic necrotizing *Aspergillus* pneumonia depends on the demonstration of the organism in tissue.

In the appropriate clinical setting of pulmonary infiltrates in a patient who is neutropenic or immunosuppressed, visualization of the characteristic fungi using Gomori methenamine silver stain or Calcofluor or a positive culture result from sputum, needle biopsy, or bronchoalveolar lavage (BAL) fluid should result in the prompt institution of therapy. This is especially important after bone marrow transplantation because a positive *Aspergillus* culture result from sputum has a 95% positive predictive value for invasive disease. However, a negative fungus result from culture of sputum or BAL fluid does not exclude pulmonary aspergillosis because *Aspergillus*
is cultured from sputum in 8-34% of patients and from BAL fluid in 45-62% of patients eventually found by biopsy or autopsy to have invasive disease.

An assay to detect galactomannan, a major component of the *Aspergillus* cell wall, is available.
[7]

Patients who are at high risk, such as those who have received stem cell transplants or who have prolonged neutropenia, may be screened for the development of invasive *Aspergillus*
infection by monitoring serum galactomannan levels weekly.
[8]

The presence of an elevated galactomannan level in BAL fluid may also be helpful in the diagnosis of pulmonary aspergillosis in patients in whom compatible radiographic changes are present and BAL testing is performed in the suspicious area.
[9]

A meta-analysis and systematic review determined that the measurement of BAL-galactomannan levels may help in diagnosing invasive aspergillosis early.

Aspergilloma does not cause many characteristic laboratory abnormalities. *Aspergillus* precipitin antibody test results (ie, for IgG) are usually positive

Treatment
Medical Care

The treatment of invasive aspergillosis and chronic necrotizing aspergillosis differs significantly from the treatment of allergic bronchopulmonary aspergillosis (ABPA) and aspergilloma.

Invasive aspergillosis

This is often rapidly progressive and has a high mortality rate; therefore, preventive therapy and rapid institution of therapy in patients in whom invasive aspergillosis is suggested may be lifesaving. Prophylactic antifungal therapy and the use of laminar airflow (LAF) or high-efficiency particulate air (HEPA) filtration of patient rooms in patients who receive bone marrow transplants and other high-risk patients may prevent invasive aspergillosis. In patients with solid organ transplants, especially lung, in whom *Aspergillus* is cultured from sputum without evidence of pneumonia (colonization), inhaled amphotericin B may be administered.

When high-risk patients develop a compatible clinical picture, empiric treatment for aspergillosis should be initiated as diagnostic testing is undertaken. Voriconazole is now considered the drug of choice for invasive aspergillosis because of better tolerance and improved survival with its use when compared with amphotericin.[17] Posaconazole, amphotericin B, or amphotericin B lipid formulations may be considered as empiric therapy in critically ill patients if the clinical picture, particularly the presence of sinusitis, could be compatible with mucormycosis, because voriconazole is ineffective for *Zygomycetes* infection. Caspofungin has also been approved for treatment of invasive aspergillosis in patients who are unable to tolerate or are resistant to other therapies.
[18]

Initial combination therapy is usually not indicated and should generally be reserved for treatment failures.
[19]

If possible, the level of immunosuppression should be decreased. For example, patients who are neutropenic may receive growth factors (ie, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor), and patients with certain types of transplants, in which transplanted organ dysfunction will not be life threatening (eg, renal transplant), may have immunosuppressive medications, including corticosteroids, reduced or discontinued.

Combination antifungal therapy is sometimes used for patients whose disease progresses while on single-drug therapy. Concomitant therapy with azole antifungals and amphotericin is

controversial because the azole antifungals decrease amphotericin-binding sites and may therefore diminish its effectiveness. Be alert to the possibility of diminished effectiveness of amphotericin in any patient who has received prior treatment with an azole antifungal, including voriconazole, itraconazole, fluconazole, or ketoconazole. Newer antifungal azoles are under study (eg, ravuconazole) and may be available for compassionate use in patients in whom other therapies have failed. Posaconazole, a new triazole, has been approved by the US Food and Drug Administration.[20]

Aspergilloma

Treatment is considered when patients become symptomatic, usually with hemoptysis. Surgical resection is curative but may not be possible in patients with limited pulmonary function. Oral itraconazole may provide partial or complete resolution of aspergillomas in 60% of patients. Successful intracavitary treatment, using CT-guided, percutaneously placed catheters to instill amphotericin alone or in combination with other drugs, including acetylcysteine and aminocaproic acid, has been reported in small numbers of patients.[21]

Bronchial artery embolization may be used for life-threatening hemoptysis in patients thought to have insufficient pulmonary reserve to tolerate surgery or in patients with recurrent hemoptysis (eg, patients with CF in whom hemoptysis may be related to underlying bronchiectasis with or without aspergilloma).[22] Bronchial artery embolization requires a skilled and experienced radiologist because localizing the abnormal vessel(s) may be challenging. Because the anterior spinal arteries may originate from the bronchial vessels, serious neurologic complications, although rare, may occur.

Allergic bronchopulmonary aspergillosis

This is a hypersensitivity reaction that requires treatment with oral corticosteroids. Inhaled steroids are not effective.

Adding oral itraconazole to steroids in patients with recurrent or chronic ABPA may be helpful.[23, 24,25,26]

This may allow more rapid resolution of infiltrates and symptoms, facilitating steroid tapering or lowering the needed maintenance corticosteroid dosage. In CF patients with ABPA, the

concomitant use of itraconazole and inhaled corticosteroids may increase the risk of adrenal insufficiency.

Patients who have associated allergic fungal sinusitis benefit from surgical resection of obstructing nasal polyps and inspissated mucus in addition to corticosteroid therapy. Nasal washes with amphotericin or itraconazole have also been used.

Case reports have described the beneficial use of the anti-IgE monoclonal antibody omalizumab (Xolair) in patients with ABPA.[27]

Chronic necrotizing pulmonary aspergillosis

Treatment consists of therapy with voriconazole, or, in some cases, itraconazole (if expense is an issue), caspofungin, or amphotericin B or amphotericin lipid formulation. A prolonged course of therapy with the goal of radiographic resolution is needed. In addition, reduction or elimination of immunosuppression should be attempted, if possible.

Surgical resection may be considered when localized disease fails to respond to antifungal therapy.

Surgical Care

Invasive aspergillosis and CNPA

Surgical resection is a consideration for localized chronic necrotizing pulmonary aspergillosis (CNPA) that has failed to respond to prolonged antifungal therapy.[28] Aspergillomas may occasionally form in areas of necrotizing pneumonia. These necrotic areas may bleed, sometimes massively, necessitating consideration of surgical resection. Patients may be high-risk surgical candidates because of underlying disease, coagulopathy, or thrombocytopenia and limited pulmonary reserve.

Aspergilloma

Surgical resection may be considered for massive hemoptysis if pulmonary function is sufficient enough for this sort of intervention. Assessment of operative risk necessitates obtaining pulmonary function studies, arterial blood gas determinations, and, possibly, split lung function studies (eg, quantitative perfusion lung scanning). Because aspergilloma occurs in cavitary areas, the affected lung may not be functional. Surgical resection may be difficult because of scarring, pleural adhesion, and the presence of abnormal vasculature.

Allergic bronchopulmonary aspergillosis

Areas of mucoid impaction may have a masslike appearance and are sometimes resected as an undiagnosed lung mass; however, steroid therapy and oral itraconazole therapy are preferred. Allergic fungal sinusitis usually requires endoscopic sinus surgery to improve drainage.

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