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223 Aspergillosis

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Aspergillosis Aspergillosis is the collective term used to describe all disease entities caused by any one of ~50 pathogenic and allergenic species of *Aspergillus*. Only those species that grow at 37°C can cause invasive infection, although some species without this ability can cause allergic syndromes. Each common pathogenic species is actually a complex of many species (many of them cryptic) but is referred to as a single species here for simplicity. *A. fumigatus* is responsible for most cases of invasive aspergillosis, >95% of cases of chronic aspergillosis, and most allergic syndromes. *A. flavus* is more prevalent in some hospitals and causes a higher proportion of cases of sinus infections, cutaneous infections, and keratitis than *A. fumigatus*. *A. niger* can cause invasive infection but more commonly colonizes the respiratory tract and causes external otitis. *A. terreus* causes only invasive disease, usually with a poor prognosis. *A. nidulans* occasionally causes invasive infection, primarily in patients with chronic granulomatous disease (CGD). ■

■ **EPIDEMIOLOGY AND ECOLOGY** *Aspergillus* has a worldwide distribution, most commonly growing in decomposing plant materials (i.e., compost) and in bedding. This hyaline (nonpigmented), septate, branching mold produces vast numbers of conidia (spores) on stalks above the surface of mycelial growth. Aspergilli are found in indoor and outdoor air, on surfaces, and in water from surface reservoirs. Daily exposures vary from a few to many millions of conidia; high numbers of conidia are encountered in hay barns and other very dusty environments. The required size of the infecting inoculum is uncertain; however, only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) are demonstrated to cause disease—acute community-acquired pulmonary aspergillosis—in healthy immunocompetent individuals or exacerbations of COPD. Allergic syndromes are exacerbated by continuous antigenic exposure arising from sinus or airway colonization or from nail infection. High-efficiency particulate air (HEPA) filtration is often protective against infection; thus, HEPA filters should be installed and monitored for efficiency in operating rooms, burn units and in areas of the hospital that house high-risk patients. The incubation period of invasive aspergillosis after exposure is highly variable, extending in documented cases from 2 to 90 days. Thus, community acquisition of an infecting strain frequently manifests as invasive infection during hospitalization, although nosocomial acquisition is also common. Outbreaks usually are directly related to a contaminated air source or construction in the hospital. Global aspergillosis incidence and prevalence have been estimated (Table 223-1). The frequency of different manifestations of aspergillosis varies considerably with geographic location; most notably, chronic granulomatous sinusitis is rare outside the Middle East and India. Fungal (mycotic) keratitis is particularly common in Southeast Asia but occurs globally. Chronic pulmonary aspergillosis follows pulmonary tuberculosis in ~6–13% of treated cases and also mimics pulmonary tuberculosis as smear-negative or “clinically diagnosed” tuberculosis.

Aspergillus onychomycosis, usually of the toenail, has been reported in as low as <1% and as high as 35% of cases of onychomycosis and is more common in diabetes. ■ ■RISK FACTORS AND PATHOGENESIS The primary risk factors for invasive aspergillosis are profound neutropenia, glucocorticoid use, and underlying respiratory disease; risk increases with longer duration of these conditions. Higher doses of glucocorticoids increase the risk of both acquisition of invasive aspergillosis and death from the infection. Neutrophil and/or phagocyte dysfunction also is an important risk factor, as evidenced by aspergillosis in CGD, advanced HIV infection, and relapsed leukemia. Invasive aspergillosis is increasingly recognized (if actively sought) in medical intensive care units (2–5%), those with severe influenza (8–25%) and

TABLE 223-1 Disease Frequency and Diagnostic Sensitivity for Different Manifestations of Aspergillosis

TYPE OF DISEASE	INVASIVE	CHRONIC	ALLERGIC	PARAMETER	Incidence/100,000a	27.6	23.6	?b	Prevalence/100,000a	—	55.4	286c	Global burdena	~2,116,000	~6,141,000	~11,690,000	Mortality rate without treatmenta	~100%	~50%	<1%	Respiratory	Diagnostic Sensitivityd	Culturee	✓	✓-✓✓e	✓-✓✓e	Microscopy	✓	✓	✓	Antigen	✓✓✓	✓✓	?	Real-time PCR	✓✓	✓✓	✓✓	Blood	Diagnostic Sensitivityd	Culture	x	x	x	Antigen	✓✓	✓	✓	β-D-Glucan	✓✓	✓	?	Real-time PCR	✓✓	x	x	IgG antibodyf	✓✓f	✓✓✓	✓✓✓	IgE antibody	x	✓✓	✓✓✓✓	a	Denning DW: Global incidence and mortality of severe fungal disease. Lancet Infect Dis 24:e428, 2024.
Abbreviation: PCR, polymerase chain reaction.																																																																		

CHAPTER 223 Aspergillosis severe COVID-19 (~10%), and patients admitted to hospital with chronic obstructive pulmonary disease (COPD; 1.3–3.9%). Temporarily abrogation of protective responses from glucocorticoid use or compensatory anti-inflammatory response syndrome is a significant risk factor. Many patients have some evidence of prior pulmonary disease—typically, a history of pneumonia or COPD. Many new immunomodulating agents, such as infliximab and ibrutinib, increase the risk of invasive aspergillosis, as does severe liver disease. Patients with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary disease, including current and prior tuberculosis, sarcoidosis, prior pneumothorax, or COPD. These patients are apparently immunocompetent, but natural killer and/or interleukin 12 or gamma interferon production defects are common. Their inflammatory immune (TH1-like) response is suboptimal, and persistent inflammation is typical. Glucocorticoids accelerate disease progression. Allergic bronchopulmonary aspergillosis (ABPA) usually complicates asthma and cystic fibrosis. Many genetic associations indicate a strong basis for the development of a TH2-like and “allergic” response to *A. fumigatus*. Remarkably, high-dose glucocorticoid treatment for exacerbations of ABPA almost never leads to invasive aspergillosis. Fungal, and especially *Aspergillus*, sensitization is especially common in those with poorly controlled asthma. Environmental exposure and *Aspergillus* sensitization drive some COPD exacerbations. Most patients with *Aspergillus* bronchitis have bronchiectasis, with or without cystic fibrosis, including heterozygous CFTR mutations. Different genetic traits are associated with invasive, chronic, and allergic aspergillosis; the majority of people probably are not at risk for aspergillosis. Multiple gene variants appear to be necessary for susceptibility to each form of aspergillosis. ■ ■CLINICAL FEATURES AND APPROACH

TO THE PATIENT (Table 223-2) Invasive Pulmonary Aspergillosis Both the frequency of invasive disease and the pace of its progression increase with greater

TABLE 223-2 Major Manifestations of Aspergillosis

ORGAN	INVASIVE (ACUTE AND SUBACUTE)	CHRONIC SAPROPHYTIC ALLERGIC
Lung	Angioinvasive (in neutropenia), nonangioinvasive, granulomatous	Chronic cavitary, chronic fibrosing, bronchitis, Aspergillus nodule
Sinus	Acute invasive	Chronic invasive, chronic granulomatous
Brain	Abscess, hemorrhagic infarction, meningitis	Granulomatous, meningitis
None	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis
None	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None
None	None	None
Eye	Keratitis, endophthalmitis	None
None	None	None

described degrees of immunocompromise. Invasive aspergillosis is arbitrarily classified as acute and subacute, with courses of ≤ 1 month and 1–3 months, respectively. More than 80% of cases of invasive aspergillosis involve the lungs, and most are community acquired. The most common clinical features are no symptoms at all, fever, cough (some times productive), nondescript chest discomfort, trivial hemoptysis, and shortness of breath. Although the fever often responds to glucocorticoids, the disease progresses. In ventilated patients, screening for Aspergillus antigen on tracheobronchial lavage fluid is necessary for diagnosis as radiology is not distinctive. The keys to early diagnosis in at-risk patients are a high index of suspicion, screening for circulating antigen (in leukemia), and urgent computed tomography (CT) of the thorax. Invasive aspergillosis is one of the most common diagnostic errors revealed at autopsy.

Invasive Sinusitis The sinuses are involved in 5–10% of cases of invasive aspergillosis, especially affecting patients with leukemia and recipients of hematopoietic stem cell transplants. In addition to fever, the most common features are nasal or facial discomfort, blocked nose, and nasal discharge (sometimes bloody). Endoscopic examination of the nose reveals pale, dusky or necrotic-looking tissue in any location. CT or magnetic resonance imaging (MRI) of the sinuses is essential but does not distinguish invasive Aspergillus sinusitis from preexisting allergic or bacterial sinusitis early in the disease process. Tracheobronchitis

Occasionally, only the airways are infected by Aspergillus. The resulting manifestations seen on bronchoscopy range from acute or chronic bronchitis to ulcerative or pseudomembranous tracheobronchitis. These entities are particularly common among lung transplant recipients and patients on artificial ventilation. Obstruction with mucous plugs may occur and is called obstructing bronchial aspergillosis in immunocompromised patients and mucous impaction in other patients, such as those with ABPA.

Aspergillus Bronchitis Recurrent chest infections that only partially improve with antibiotic treatment and are associated with significant breathlessness or coughing up of thick sputum plugs are typical features of Aspergillus bronchitis. Patients are not significantly immunocompromised and usually have bronchiectasis or cystic fibrosis. Occasional patients present with respiratory failure because of airway obstruction with mucus. Concurrent bacterial bronchitis is common. The diagnosis rests on recurrent detection of Aspergillus in the airway by microscopy, culture, or polymerase chain reaction (PCR). Aspergillus IgG is usually detectable.

Disseminated Aspergillosis In the most severely immunocompromised patients, Aspergillus disseminates from the lungs to multiple organs—most often to the brain but also to the skin, thyroid, bone, kidney, liver, gastrointestinal tract, eye (endophthalmitis), and heart valve. Aside from cutaneous lesions, the most common features are gradual clinical deterioration over 1–3 days, with low-grade fever and features of mild sepsis, and nonspecific abnormalities in laboratory tests. In most cases, at least one localization becomes apparent before death. Blood cultures are almost always negative.

PART 5 Infectious Diseases

TYPE OF DISEASE Aspergilloma (single), airway colonization Allergic bronchopulmonary, severe asthma with fungal sensitization, hypersensitivity pneumonitis Maxillary fungal ball Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis Cerebral Aspergillosis Hematogenous dissemination to the brain is a devastating complication of invasive aspergillosis. Single or multiple lesions may develop. In acute disease, hemorrhagic infarction is most typical, and cerebral abscess is common. Rarer manifestations include meningitis, mycotic aneurysm, and cerebral granuloma (mimicking a brain tumor). Local spread from cranial sinuses also occurs. Postoperative infection develops rarely and is exacerbated by glucocorticoids, which are often given after neurosurgery. The presentation can be either acute or subacute, with mood changes, focal signs, seizures, and decline in mental status. MRI is the most useful immediate investigation; unenhanced CT of the brain is usually nonspecific, and contrast is often contraindicated because of poor renal function. Cerebral aspergillosis is disproportionately common in those on imatinib. Endocarditis Most cases of Aspergillus endocarditis are prosthetic-valve infections resulting from contamination during surgery. Native-valve disease is reported, especially as a feature of disseminated infection and in persons using illicit IV drugs. Culture-negative endocarditis with large vegetations is the most common presentation; embolectomy occasionally reveals the diagnosis. Cutaneous Aspergillosis Dissemination of Aspergillus occasionally results in cutaneous features, usually an erythematous or purplish nontender area that progresses to a necrotic eschar. Direct invasion of the skin occurs in neutropenic patients at the site of IV catheter insertion and in burn patients. Surgical, burn, and trauma wounds may become infected with Aspergillus (especially *A. flavus*). Chronic Pulmonary Aspergillosis The hallmark of chronic cavitary pulmonary aspergillosis (Fig. 223-1) is one or more pulmonary cavities expanding over a period of months or years in association with pulmonary symptoms and systemic manifestations such as fatigue and weight loss. Often mistaken initially for tuberculosis, >90% of chronic cavitary pulmonary aspergillosis cases occur in patients with prior pulmonary disease (e.g., current or past tuberculosis or nontuberculous mycobacterial infection, sarcoidosis, rheumatoid lung disease, pneumothorax, bullae) or lung surgery. The onset is insidious, and systemic features (weight loss, fatigue) may be more prominent than pulmonary symptoms. On CT scan, an irregular internal cavity surface and thickened cavity walls are typical and indicative of disease activity. Irregular material, fluid level, and a well-formed fungal ball are seen in some cavities. Multiple cavities are more common than a single cavity, and most cavities are in the upper lobes. Pleural thickening and pericavitary infiltrates are typical and most obvious if a positron emission tomography scan has been done as part of the workup. Chronic cavitary pulmonary aspergillosis is usually caused by *A. fumigatus*, but *A. niger* has been implicated, particularly in diabetic patients, as have other species. IgG antibodies to Aspergillus are detectable in ~90% of patients with chronic cavitary pulmonary aspergillosis. Some patients have concurrent infections with mycobacteria and/or other bacterial pathogens. The most significant complication is life-threatening hemoptysis, which may be the presenting manifestation. If untreated, chronic cavitary pulmonary aspergillosis typically

FIGURE 223-1 Computed tomography (CT) scan image of the chest in a patient with long-standing bilateral chronic cavitary pulmonary aspergillosis. This patient had a history of several bilateral pneumothoraces and had required bilateral pleurodesis in 1990. CT then demonstrated multiple bullae, and sputum cultures grew *A. fumigatus*. The patient had initially weakly and later strongly positive serum IgG Aspergillus antibody tests. This scan (2003) shows a mixture of thick- and thin-walled cavities in both lungs (each marked with C), with a probable fungal ball (black arrow) protruding into the large cavity on the patient's right side (R). There is also considerable

pleural thickening bilaterally. progresses (sometimes relatively rapidly) to unilateral or upper-lobe fibrosis. This end-stage entity is termed chronic fibrosing pulmonary aspergillosis (destroyed lung). Aspergilloma Aspergilloma (fungal ball) is a late manifestation of chronic cavitary pulmonary aspergillosis, but some patients are asymptomatic. The inside of a pulmonary cavity allows fungal growth that peels off, forming the layers of the fungal ball. Signs and symptoms associated with single (simple) aspergillomas are minor, including cough (sometimes productive), hemoptysis, wheezing, and mild fatigue. More significant signs and symptoms are associated with chronic cavitary pulmonary aspergillosis and should be treated as such. About 10% of fungal balls resolve spontaneously (by being coughed up), but the cavity may still be infected and the patient symptomatic. Aspergillus Nodule A recently recognized form of chronic pulmonary aspergillosis is the Aspergillus nodule, which may resemble early lung carcinoma and may cavitate. Nodules may be single or multiple and 5–50 mm in diameter. Larger mass lesions are rarely seen. Nodules are usually avid on positron emission tomography. IgG antibodies to Aspergillus are detectable in ~65% of patients with an Aspergillus nodule. Chronic Aspergillus Sinusitis Three entities are subsumed under this broad designation: fungal ball of the sinus, chronic invasive sinusitis, and chronic granulomatous sinusitis. Fungal ball of the sinus is limited to the maxillary sinus (except in rare cases involving the sphenoid sinus) in which the sinus cavity is filled with a fungal ball. Maxillary disease is associated with prior upper-jaw root canal work and chronic (bacterial) sinusitis. About 90% of CT scans show focal hyperattenuation related to concretions; on MRI scans, the T2-weighted signal is decreased, whereas it is increased in bacterial sinusitis. Removal of the fungal ball is curative. No tissue invasion is demonstrable histologically or radiologically. In contrast, chronic invasive sinusitis is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses. Patients are usually but not always immunocompromised to some degree (e.g., as a result of diabetes or HIV infection). Imaging of the cranial sinuses shows opacification of one or more sinuses, local bone destruction, and invasion of local structures. The differential diagnosis is wide, including other infections. Apart from a history of chronic nasal discharge and blockage, loss of the sense of smell, and persistent headache, the usual presenting features are related to local involvement of critical structures. The orbital apex syndrome (blindness and proptosis) is characteristic. Facial swelling, cavernous sinus thrombosis,

carotid artery occlusion, and pituitary fossa and brain and skull-base invasion are complications.

Chronic granulomatous sinusitis due to Aspergillus is most commonly seen in the Middle East and India and is often caused by *A. flavus*. It typically presents late, with facial swelling and unilateral proptosis. The prominent granulomatous reaction histologically distinguishes this disease from chronic invasive sinusitis, in which tissue necrosis with a low-grade mixed-cell infiltrate is typical. IgG antibodies to *A. flavus* are usually detectable. Allergic Bronchopulmonary Aspergillosis In almost all cases, ABPA represents a hypersensitivity reaction to *A. fumigatus*; other causes are other aspergilli and other fungi. ABPA occurs in ~2.5% of patients with asthma who are referred to secondary care, although it may be less common in the United States and more common in those from the Indian subcontinent. In cystic fibrosis, up to 15% of teenagers are affected. Episodes of bronchial obstruction with mucous plugs leading to coughing fits, “pneumonia,” consolidation, and breathlessness are typical. Many patients report coughing up thick sputum casts, often brown in color. Eosinophilia commonly develops before systemic glucocorticoids are given. The cardinal diagnostic test is detection of Aspergillus-specific IgE (or a positive skin-prick test in response to *A. fumigatus* extract) together with an elevated serum level of total IgE (usually >1000 IU/mL). The

presence of hyperattenuated mucus in airways is highly specific. Bronchiectasis is characteristic, and a few patients develop chronic cavitary pulmonary aspergillosis. Severe Asthma with Fungal Sensitization (SAFS) Many adults with severe asthma do not fulfill the criteria for ABPA and yet are allergic to fungi. Although *A. fumigatus* is a common allergen, numerous other fungi (e.g., *Cladosporium* and *Alternaria* species) are implicated by skin-prick testing and/or specific IgE testing. Serum total IgE concentrations are <1000 IU/mL, and bronchial-wall thickening is common. ABPA and SAFS are collectively referred to as fungal asthma.

CHAPTER 223 Aspergillosis Allergic Fungal Rhinosinusitis

Like the lungs, the sinuses manifest allergic responses to *Aspergillus* and other fungi. The affected patients present with chronic (i.e., perennial) sinusitis that is relatively unresponsive to antibiotics. Many of these patients have nasal polyps, and all have congested nasal mucosae and sinuses full of mucoid material. The histologic hallmarks of allergic fungal sinusitis are local eosinophilia and Charcot-Leyden crystals. Removal of abnormal mucus and polyps, with local and occasionally systemic administration of glucocorticoids, usually leads to resolution. Persistent or recurrent signs and symptoms may require more extensive surgery (ethmoidectomy) and sometimes oral antifungal therapy. Recurrence is common, often after another bacterial or viral infection.

Superficial Aspergillosis

Aspergillus can cause keratitis, onychomycosis, and otitis externa. The first can be difficult to diagnose early enough to save the patient's sight. Natamycin (5%) eye drops are the optimal therapy for fungal keratitis, often with surgery. Otitis externa usually resolves with debridement and local application of antifungal agents. ■

■DIAGNOSIS

Several techniques are required to establish the diagnosis of any form of aspergillosis with confidence (Table 223-1). Acute Invasive Aspergillosis Patients with acute invasive aspergillosis have a relatively heavy load of fungus in the affected organ; thus, antigen detection, PCR, microscopy, culture, and/or histopathology usually confirm the diagnosis. However, the pace of progression leaves only a narrow window for making the diagnosis without losing the patient, and some invasive procedures are not possible because of coagulopathy, respiratory compromise, and other factors. Many cases of invasive aspergillosis are missed clinically and are diagnosed only at autopsy. Histologic examination of affected tissue reveals either infarction, with invasion of blood vessels by many fungal hyphae, or acute necrosis, with limited inflammation and fewer hyphae. *Aspergillus* hyphae are hyaline, narrow, and septate, with branching at 45° in infected tissue. Hyphae can be seen in cytology or microscopy

preparations, which therefore provide a rapid means of presumptive diagnosis.

One *Aspergillus* antigen test relies on detection of galactomannan release from *Aspergillus* organisms during growth, the other a novel protein antigen. Respiratory sample antigen detection is more sensitive than serum and is critical in the intensive care unit patient in whom radiology is nonspecific. Positive serum antigen results usually precede clinical or radiologic features by several days. The sensitivity of antigen detection is reduced by antifungal therapy. A positive culture supports the diagnosis, given that multiple other (rarer) fungi can mimic *Aspergillus* species histologically, but only 10–30% of patients with invasive aspergillosis have a positive culture. Bacterial agar is less sensitive than fungal media for culture; thus, if physicians do not request fungal culture, the diagnosis may be missed. High-volume fungal cultures enhance yield. A positive culture may represent noninvasive forms of aspergillosis or airway colonization. Both antigen detection and real-time PCR are faster and much more sensitive than culture of respiratory samples and blood. Definitive confirmation of a diagnosis of invasive aspergillosis requires (1) a positive culture of a sample taken directly from an ordinarily sterile site (e.g., a brain abscess) or

(2) positive results of both histologic testing and culture (or molecular confirmation of *Aspergillus* spp.) of a sample taken from an affected organ (e.g., sinuses or skin). Most diagnoses of invasive aspergillosis are inferred from fewer data, including the presence of the halo sign on a thoracic CT scan—a localized ground-glass appearance representing hemorrhagic infarction surrounds a nodule or consolidation. Halo signs are present for ~7 days early in the course of infection in neutropenic patients and are a good prognostic feature, reflecting an early diagnosis. Nodules with halo signs are a feature of COVID-19 itself; invasive aspergillosis diagnosis requires supportive evidence. Other characteristic radiologic features of invasive pulmonary aspergillosis include nodules and pleural-based infarction or cavitation, but nonspecific consolidation is common (Fig. 223-2).

PART 5 Infectious Diseases Chronic Aspergillosis For chronic aspergillosis, *Aspergillus* antibody testing combined with characteristic imaging is sufficient for the diagnosis. Biopsy of *Aspergillus* nodules reveals hyphae surrounded by cells of chronic inflammation and sometimes granulomas. Antibody titers fall slowly with successful therapy. Cultures are infrequently positive but are important in checking for azole resistance. PCR of sputum is often strongly positive. Some patients with chronic pulmonary aspergillosis often have elevated titers of total and *Aspergillus*-specific IgE. ABPA, SAFS, and Allergic *Aspergillus* Sinusitis ABPA and SAFS are diagnosed serologically with elevated specific and total serum IgE levels or with skin-prick tests. Allergic *Aspergillus* sinusitis is usually diagnosed histologically, accompanied by *Aspergillus* IgE antibody.

TREATMENT Aspergillosis Antifungal drugs active against *Aspergillus* include voriconazole, itraconazole, posaconazole, isavuconazole, caspofungin, micafungin, and amphotericin B (AmB). Possible interactions with other drugs must be considered before azoles are prescribed. In addition, plasma itraconazole and voriconazole concentrations vary substantially from one patient to another, and many authorities recommend monitoring levels to ensure that drug concentrations are adequate but not excessive. Initial IV administration is preferred for acute invasive aspergillosis and oral administration for all other diseases that require antifungal therapy. Current recommendations are shown in Table 223-3. Voriconazole, isavuconazole, and posaconazole are the preferred agents for invasive aspergillosis; caspofungin, micafungin, and lipid-associated AmB are second-line agents. AmB is not active against *A. terreus* or *A. nidulans*; multi-azole resistance in *A. fumigatus* is present in 3–20% of isolates but is increasing, especially in Southeast Asia; and *A. niger* is resistant to isavuconazole. An infectious disease consultation is advised for patients with invasive disease, given the

FIGURE 223-2 Markedly different appearances of invasive aspergillosis on computed tomography scan of the thorax. A. Patient with myelodysplasia and moderate neutropenia showing small right-sided nodules with minimal surrounding ground glass and a separate area of ground glass only on the left laterally. B. Patient with multiple myeloma undergoing intensive chemotherapy with corticosteroids showing bilateral areas of consolidation and some nonspecific atelectasis with probable ground glass surrounding the right-sided lesion. The anterior component of the left-sided lesion is demarcated by the fissure.

complexity of management. Immune reconstitution can complicate recovery. The duration of therapy for invasive aspergillosis varies from ~3 months to several years, depending on the patient's immune status and response to therapy. Relapse occurs if the response is suboptimal and immune reconstitution is not complete. Voriconazole is currently the preferred oral agent for chronic aspergillosis with itraconazole or posaconazole as substitutes when failure, emergence of resistance, or adverse events occur. Because chronic cavitary pulmonary aspergillosis responds slowly, therapy for at least 12 months is necessary, and disease control may require years of treatment, whereas the duration of treatment for other forms of chronic and allergic aspergillosis requires case-by-case evaluation.

Glucocorticoids should be avoided in chronic cavitary pulmonary aspergillosis unless covered by adequate antifungal therapy; mortality is increased by 240% with corticosteroids. Acute exacerbations of ABPA respond well to voriconazole, itraconazole, or a short course of glucocorticoids—long-term azole therapy usually helps minimize corticosteroid exposure and maintain remission. Antifungal response in *Aspergillus* bronchitis is gratifying, but relapse after 4 months of therapy is common. Resistance in *A. fumigatus* to one or more azoles, although uncommon, is increasingly found globally. Resistance may be derived from azole fungicide use for crops. Resistance arising from multiple mechanisms may develop during long-term treatment, and a positive culture during antifungal therapy is an indication for susceptibility testing. Surgical treatment is important in several forms of aspergillosis, including fungal ball of the sinus and single aspergillomas, in which

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