Severe Asthma with Fungal Sensitization 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 radioallergosorbent testing. Serum total IgE concentrations are <1000 IU/mL, and bronchiectasis is moderately common.

Allergic Sinusitis 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 possibly local antifungal therapy. Recurrence is common, often after another bacterial or viral infection.

Superficial Aspergillosis *Aspergillus* can cause keratitis and otitis externa. The former may be difficult to diagnose early enough to save the patient's sight. Treatment requires local surgical debridement as well as intensive topical antifungal therapy. 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 241-1). Patients with acute invasive aspergillosis have a relatively heavy load of fungus in the affected organ; thus culture, molecular diagnosis, antigen detection, and 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. Currently, ~40% of 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°; no yeast forms are present in infected tissue. Hyphae can be seen in cytology or microscopy preparations, which therefore provide a rapid means of presumptive diagnosis.

Culture is important in confirming the diagnosis, given that multiple other (rarer) fungi can mimic *Aspergillus* species histologically. Bacterial agar is less sensitive than fungal media for culture. Thus, if physicians do not request fungal culture, the diagnosis may be missed. Culture may be falsely positive (e.g., in patients whose airways are colonized by *Aspergillus*) or falsely negative. Only 10–30% of patients with invasive aspergillosis have a positive culture at any time. Both antigen detection and real-time polymerase chain reaction (PCR) are faster and much more sensitive than culture of respiratory samples and blood.

The *Aspergillus* antigen test relies on detection of galactomannan release from *Aspergillus* organisms during growth. Positive serum antigen results usually precede clinical or radiologic features by several days. The sensitivity of antigen detection is reduced by antifungal prophylaxis and empirical therapy.

Definitive confirmation of the diagnosis 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 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 high-resolution thoracic CT scan, in which a localized ground-glass appearance representing hemorrhagic infarction surrounds a nodule. While a halo sign may be produced by other fungi, *Aspergillus* species are by far the most common cause. 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. Thick CT sections can give the false appearance of a halo sign, as can other technical factors. Other common radiologic features of invasive pulmonary aspergillosis include nodules and pleural-based infarction or cavitation, with pleural fluid apparent in 10% of patients.

For chronic invasive aspergillosis, *Aspergillus* antibody testing is invaluable although relatively imprecise. Biopsy of new nodules reveals hyphae surrounded by cells of chronic inflammation and sometimes granulomas. Antibody titers fall with successful therapy. Cultures are infrequently positive but are important in checking for azole resistance. Real-time PCR of sputum is often strongly positive. Some patients with chronic pulmonary aspergillosis also have elevated titers of total serum IgE and *Aspergillus*-specific IgE.

ABPA and severe asthma with fungal sensitization are diagnosed serologically with elevated total and specific serum IgE levels and with skin-prick tests. Allergic *Aspergillus* sinusitis is usually diagnosed histologically, although precipitating antibodies in blood also may be useful.

TREATMENT ASPERGILLOSIS

Antifungal drugs active against *Aspergillus* include voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and amphotericin B (AmB). Drug interactions with azoles must be considered before these agents are prescribed. In addition, plasma azole concentrations vary substantially from one patient to another, and many authorities recommend monitoring 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 disease that requires antifungal therapy. Current recommendations are shown in **Table 241-3**.

Voriconazole is the preferred agent for invasive aspergillosis; caspofungin, posaconazole, and lipid-associated AmB are second-line agents. AmB is not active against *A. terreus* or *A. nidulans*. An infectious disease consultation is advised for patients with invasive disease, given the complexity of management. Combination therapy (voriconazole plus an echinocandin) for acute invasive aspergillosis may be beneficial for non-neutropenic patients. 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.

Itraconazole is currently the preferred oral agent for chronic and allergic forms of aspergillosis. Voriconazole or posaconazole can be substituted when failure, emergence of resistance, or adverse events occur. An itraconazole dose of 200 mg twice daily is recommended, with monitoring of drug concentrations in the blood. Chronic cavitary pulmonary aspergillosis probably requires lifelong therapy, whereas the duration of treatment for other forms of chronic and allergic aspergillosis requires case-by-case evaluation.

Resistance to one or more azoles, although uncommon, is present in isolates from the environment in many regions, including northern Europe, India, China, and North America. Resistance may be derived from azole fungicide use for crops. In addition, resistance arising from multiple mechanisms may develop during long-term treatment, and a positive culture during antifungal therapy is an indication for susceptibility testing. Combined resistance to itraconazole and voriconazole is the most common type of cross-resistance. Glucocorticoids should be used in chronic cavitary pulmonary aspergillosis only if covered by adequate antifungal therapy.

Surgical treatment is important in several forms of aspergillosis, including fungal ball of the sinus and single aspergillomas, in which surgery is curative; invasive aspergillosis involving bone,