TABLE 241-1 DISEASE FREQUENCY AND DIAGNOSTIC SENSITIVITY FOR DIFFERENT MANIFESTATIONS OF ASPERGILLOSIS

	Type of Disease		
Parameter	**Invasive**	**Chronic**	**Allergic**
Incidence/100,000[a]	8.6	10.4	?[b]
Prevalence/100,000[a]	—	32.8	286[c]
Global burden[d]	~200,000	~3,000,000	~10,000,000
Mortality rate without treatment	~100%	~50%	<1%
Respiratory Diagnostic Sensitivity[e]			
Culture	✓	✓	✓
Microscopy	✓	?	?
Antigen	✓✓✓	?	✓✓✓
Real-time PCR	✓✓✓	✓✓✓	✓✓✓
Blood Diagnostic Sensitivity[e]			
Culture	✗	✗	✗
Antigen	✓✓	✓	✗
β-D-glucan	✓✓	✓	?
Real-time PCR	✓✓	?	?
IgG antibody	✓	✓✓✓✓	✓✓
IgE antibody	✗	✓✓	✓✓✓✓

[a]Incidence and prevalence figures are for Europe. From *www.ecdc.europa.eu/en/publications/publications/risk-assessment-impact-environmental-usage-of-triazoles-on-aspergillus-spp-resistance-to-medical-triazoles.pdf.* [b]People are not born with allergic fungal disease; the annual frequency with which it occurs is not known. [c]Allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. [d]GD Brown et al: Human fungal infections: the hidden killers. Sci Transl Med 2012:4:165rv13. [e]Key for sensitivity: 1 check = limited (as the text indicates, 10–30% for culture); 2 checks = higher; 3 checks = >80%; and 4 checks = ~95%.

Abbreviation: PCR, polymerase chain reaction.

patients have some evidence of prior pulmonary disease—typically, a history of pneumonia or chronic obstructive pulmonary disease. Therapy with infliximab, adalimumab, alemtuzumab, daclizumab, rituximab, and possibly bevacizumab therapy also carries an increased risk of invasive aspergillosis, as do severe liver disease and high levels of stored iron in bone marrow.

Patients with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary disease, including tuberculosis, prior pneumothorax, or chronic obstructive pulmonary disease. These patients are immunocompetent except for some cytokine regulation defects, most of which are consistent with an inability to mount an inflammatory immune (T_H1-like) response or to control it adequately. Glucocorticoids accelerate disease progression.

Allergic bronchopulmonary aspergillosis (ABPA) is associated with polymorphisms of interleukin (IL) 4Ra, IL-10, and SPA2 genes (and others) and with heterozygosity of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. These associations suggest a strong genetic basis for the development of a T_H2-like and "allergic" response to *A. fumigatus*.

CD4+CD25+ T (T_{reg}) cells also appear to be pivotal in determining disease phenotype. Remarkably, high-dose glucocorticoid treatment for exacerbations of ABPA almost never leads to invasive aspergillosis.

CLINICAL FEATURES AND APPROACH TO THE PATIENT (Table 241-2)

Invasive Pulmonary Aspergillosis Both the frequency of invasive disease and the pace of its progression increase with greater 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. The most common clinical features are no symptoms at all, fever, cough (sometimes productive), nondescript chest discomfort, trivial hemoptysis, and shortness of breath. Although the fever often responds to glucocorticoids, the disease progresses. The keys to early diagnosis in at-risk patients are a high index of suspicion, screening for circulating antigen (in leukemia), and urgent 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 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 range from acute or chronic bronchitis to ulcerative or pseudomembranous tracheobronchitis. These entities are particularly common among lung transplant recipients. Obstruction with mucous plugs occurs in normal individuals; in persons with ABPA, cystic fibrosis, and/or bronchiectasis; and in immunocompromised patients.

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.

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

TABLE 241-2 MAJOR MANIFESTATIONS OF ASPERGILLOSIS

	Type of Disease			
Organ	**Invasive (Acute and Subacute)**	**Chronic**	**Saprophytic**	**Allergic**
Lung	Angioinvasive (in neutropenia), non-angioinvasive, granulomatous	Chronic cavitary, chronic fibrosing	Aspergilloma (single), airway colonization	Allergic bronchopulmonary, severe asthma with fungal sensitization, extrinsic allergic alveolitis
Sinus	Acute invasive	Chronic invasive, chronic granulomatous	Maxillary fungal ball	Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis
Brain	Abscess, hemorrhagic infarction, meningitis	Granulomatous, meningitis	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None	None	None
Eye	Keratitis, endophthalmitis	None	None	None described