CHEST™

Diagnosis and Treatment of Pulmonary Aspergillosis Syndromes

Karen C. Patterson, MD; and Mary E. Strek, MD, FCCP

Both inherited and acquired immunodeficiency and chronic pulmonary disease predispose to the development of a variety of pulmonary syndromes in response to *Aspergillus*, a fungus that is ubiquitous in the environment. These syndromes include invasive aspergillosis, which is now recognized to occur in patients with critical illness without neutropenia and in those with mild degrees of immunosuppression, including from corticosteroid use in the setting of COPD. Chronic pulmonary aspergillosis includes simple aspergilloma, which is occasionally complicated by life-threatening hemoptysis, and progressive destructive cavitary disease requiring antifungal therapy. Allergic bronchopulmonary aspergillosis occurs almost exclusively in patients with asthma or cystic fibrosis. Recent advances in each of these syndromes include a greater understanding of the underlying pathophysiology and hosts at risk; improved diagnostic algorithms; and the availability of more effective and well-tolerated therapies. Improvement in outcomes for *Aspergillus* pulmonary syndromes requires that physicians recognize the varied and sometimes subtle presentations, be aware of populations at risk of illness, and institute potentially life-saving therapies early in the disease course.

CHEST 2014; 146(5):1358-1368

ABBREVIATIONS: ABPA = allergic bronchopulmonary aspergillosis; IFN-γ = interferon γ; SAFS = severe asthma with fungal sensitization; Th = T-helper

Pulmonary aspergillosis refers to a spectrum of diseases that result from *Aspergillus* becoming resident in the lung. These include invasive aspergillosis from angioinvasive disease, simple aspergilloma from inert colonization of pulmonary cavities, and chronic cavitary pulmonary aspergillosis from fungal germination and immune activation (Table 1). Allergic bronchopulmonary aspergillosis (ABPA), driven by allergic responses, has an important place along this spectrum as well.

Aspergillus is a ubiquitous and hardy organism. It grows best in moist environments, although spore aerosolization and dispersion occur most effectively in dry climates. Spores survive harsh external conditions and adapt to a range of internal environments.[1-3] Although there are hundreds of *Aspergillus* species, *Aspergillus fumigatus* is by far the most common pathogenic species in humans, where the small size and hydrophobicity of its spores confer a dispersion advantage.[4-6] Although less common,

Manuscript received April 17, 2014; revision accepted June 29, 2014.

AFFILIATIONS: From the Pulmonary, Allergy and Critical Care Division (Dr Patterson), University of Pennsylvania, Pennsylvania, PA; and the Section of Pulmonary and Critical Care (Dr Strek), University of Chicago, Chicago, IL.

CORRESPONDENCE TO: Karen C. Patterson, MD, Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, 828 Gates, 3600 Spruce St, Philadelphia, PA 19104; e-mail: karen.patterson@uphs.upenn.edu

DOI: 10.1378/chest.14-0917

TABLE 1] Pulmonary Aspergillosis Syndromes

Aspergillus Syndrome	Syndrome	Clinical Features	Recent Updates
Allergic aspergillosis	ABPA	Worsening of underlying asthma Markedly elevated total IgE Sensitization: (+) skin testing and/or elevated *Aspergillus*-specific IgE Bronchiectasis	Cystic fibrosis is a risk factor for ABPA Bronchiectasis may be absent early in the disease course Antifungal agents benefit some patients Case reports of benefit from anti-IgE therapy
Chronic pulmonary aspergillosis	Simple aspergilloma	Quiescent mycetoma in a preexisting lung cavity Hemoptysis may occur	Small case series suggests benefit of percutaneous intracavitary amphotericin for refractory hemoptysis
	Chronic cavitary pulmonary aspergillosis	Systemic symptoms: malaise, fevers, weight loss Elevated *Aspergillus*-specific IgG New or expanding cavities in setting of chronic lung disease ± Intracavitary mycetoma ± Extensive parenchymal destruction ± Fibrosis	Immune dysfunction may contribute to risk of disease Long-term antifungal therapy generally recommended Surgical resection is often risky but may benefit those with focal disease and limited pleural involvement
Invasive disease	Angioinvasive disease	Seen in neutropenia and stem cell transplant Presentation ranges from asymptomatic macronodules to overt respiratory failure CT scan more sensitive than plain chest radiograph	Expanded populations at risk Positive *Aspergillus* respiratory culture may require further evaluation Serum and BAL galactomannan testing may aid in diagnosis Voriconazole first-line therapy; dual therapy in some
	Invasive tracheobronchial disease	Neutropenia and lung transplant are risk factors Ulcerative, pseudomembranous, and obstructive variants Atelectasis and unilateral wheeze are suggestive	Expanded populations at risk: COPD, critical illness, HIV infection Requires bronchoscopy for diagnosis

ABPA = allergic bronchopulmonary aspergillosis.

Aspergillus flavus and *Aspergillus niger* also contribute to the total burden of pulmonary aspergillosis. When inhaled, spores deposit by sedimentation in distal airways and alveolar spaces. In healthy hosts, spores are eliminated by mucociliary clearance and immune defenses. Germination is the conversion of dormant spores into growing hyphal elements.

Aspergillus is an inadvertent human pathogen, and pulmonary aspergillosis is largely the result of impaired airway clearance from a compromised immune function or a chronic lung disease such as COPD and sarcoidosis. Advances in the domains of stem cell transplant and immunosuppressive therapies and an increased prevalence of chronic pulmonary diseases have inadvertently led to a rise in pulmonary aspergillosis syndromes. Now commonly encountered by pulmonologists and intensivists worldwide, these syndromes have a high associated morbidity and can be fatal. In this review, we highlight advances in the diagnosis and treatment of pulmonary aspergillosis relevant to clinical care. These include the recognition of additional hosts at risk of invasive disease, as well as an expanded array of diagnostic and treatment options; a delineation of the features and outcomes of chronic pulmonary aspergillosis; and, updated diagnostic criteria and an evolving understanding of the role of triazole and anti-IgE treatment options in ABPA.

Invasive Aspergillosis: Epidemiology, Diagnostic Testing, and Treatment Updates

Invasive aspergillosis has been described classically in patients with neutropenia in the setting of hematologic malignancy but is seen increasingly in patients with even milder immune compromise from immunosuppression, chronic pulmonary or liver disease, or critical illness.[7] As the portal of entry, the upper and lower respiratory tracts are most commonly infected, although dissemination to any organ may occur. *Aspergillus*