Because these agents are also the initial treatment of choice for EGPA patients, institution of these therapies in patients with EGPA who are perceived to have severe asthma may delay the diagnosis of EGPA because signs of vasculitis may be masked. Corticosteroids dramatically alter the course of EGPA: up to 50% of those who are untreated die within 3 months of diagnosis, whereas treated patients have a 6-year survival of over 70%. Common causes of death include heart failure, cerebral hemorrhage, renal failure, and GI bleeding. Recent data suggest that clinical remission may be obtained in over 90% of patients treated; approximately 25% of those patients may relapse, often due to corticosteroid tapering, with a rising eosinophil count heralding the relapse. Myocardial, GI, and renal involvement most often portend a poor prognosis. In such cases, treatment with higher doses of corticosteroids or the addition of cytotoxic agents such as cyclophosphamide is often warranted. Although survival does not differ between those treated or untreated with cyclophosphamide, cyclophosphamide is associated with a reduced incidence of relapse and an improved clinical response to treatment. Other therapies that have been used successfully in the management of EGPA include azathioprine, methotrexate, intravenous gamma globulin, and interferon α. Plasma exchange has not been shown to provide any additional benefit. Recent studies examining the efficacy of anti-IL-5 therapy have shown promise.

HYPEREOSINOPHILIC SYNDROMES

Hypereosinophilic syndromes (HES) constitute a heterogeneous group of disease entities manifest by persistent eosinophilia >1500 eosinophils/μL in association with end organ damage or dysfunction, in the absence of secondary causes of eosinophilia. In addition to familial, undefined, and overlap syndromes with incomplete criteria, the predominant HES subtypes are the myeloproliferative and lymphocytic variants. The myeloproliferative variant may be divided into three subgroups: (1) chronic eosinophilic leukemia with demonstrable cytogenetic abnormalities and/or blasts on peripheral smear; (2) the platelet-derived growth factor receptor α (PDGFRα)–associated HES, attributed to a constitutively activated tyrosine kinase fusion protein (Fip1L1-PDGFRα) due to a chromosomal deletion on 4q12; this variant is often responsive to imatinib; and (3) the FIP1-negative variant associated with clonal eosinophilia and at least four of the following: dysplastic peripheral eosinophils, increased serum vitamin B_{12}, increased tryptase, anemia, thrombocytopenia, splenomegaly, bone marrow cellularity >80%, spindle-shaped mast cells, and myelofibrosis.

Extrapulmonary Manifestations of HES More common in men than in women, HES occurs between the ages of 20 and 50 and is characterized by significant extrapulmonary involvement, including infiltration of the heart, GI tract, kidney, liver, joints, and skin. Cardiac involvement includes myocarditis and/or endomyocardial fibrosis, as well as a restrictive cardiomyopathy.

Pulmonary Manifestations of HES Similar to the other pulmonary eosinophilic syndromes, these HES are manifest by high levels of blood, BAL, and tissue eosinophilia. Lung involvement occurs in 40% of these patients and is characterized by cough and dyspnea, as well as pulmonary infiltrates. Although it is often difficult to discern the pulmonary infiltrates and effusions seen on chest x-ray from pulmonary edema resulting from cardiac involvement, CT scan findings include interstitial infiltrates, ground-glass opacities, and small nodules. HES are typically not associated with ANCA or elevated IgE.

Course and Response to Therapy Unlike the other pulmonary eosinophilic syndromes, less than half of patients with these HES respond to corticosteroids as first-line therapy. Although other treatment options include hydroxyurea, cyclosporine, and interferon, the tyrosine kinase inhibitor imatinib has emerged as an important therapeutic option for patients with the myeloproliferative variant. Anti-IL-5 therapy with mepolizumab also holds promise for these patients and is currently being investigated.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is an eosinophilic pulmonary disorder that occurs in response to allergic sensitization to antigens from *Aspergillus* species fungi. The predominant clinical presentation of ABPA is an asthmatic phenotype, often accompanied by cough with production of brownish plugs of mucus. ABPA has also been well described as a complication of cystic fibrosis. A workup for ABPA may be beneficial in patients who carry a diagnosis of asthma but have proven refractory to usual therapy. ABPA is a distinct diagnosis from simple asthma, characterized by prominent peripheral eosinophilia and elevated circulating levels of IgE (>417 IU/mL). Establishing a diagnosis of ABPA also requires establishing sensitivity to *Aspergillus* antigens by skin test reactivity, positive serum precipitins for *Aspergillus*, and/or direct measurement of circulating specific IgG and IgE to *Aspergillus*. Central bronchiectasis is described as a classic finding on chest imaging in ABPA but is not necessary for making a diagnosis. Other possible findings on chest imaging include patchy infiltrates and evidence of mucus impaction.

Systemic glucocorticoids may be used in the treatment of ABPA that is persistently symptomatic despite the use of inhaled therapies for asthma. Courses of glucocorticoids should be tapered over 3–6 months, and their use must be balanced against the risks of prolonged steroid therapy. Antifungal agents such as fluconazole and voriconazole given over a 4-month course reduce the antigenic stimulus in ABPA and may therefore modulate disease activity in selected patients. The use of monoclonal antibody against IgE (omalizumab) has been described in treating severe ABPA, particularly in individuals with ABPA as a complication of cystic fibrosis.

ABPA-like syndromes have been reported as a result to sensitization to several non-*Aspergillus* species fungi. However, these conditions are substantially rarer than ABPA, which may be present in a significant proportion of patients with refractory asthma.

INFECTIOUS PROCESSES

Infectious etiologies of pulmonary eosinophilia are largely due to helminths and are of particular importance in the evaluation of pulmonary eosinophilia in tropical environments and in the developing world (Table 310-4). These infectious conditions may also be considered in recent travelers to endemic regions. Loffler syndrome refers to transient pulmonary infiltrates with eosinophilia that occurs in response to passage of helminthic larvae through the lungs, most

TABLE 310-4 INFECTIOUS CAUSES OF PULMONARY EOSINOPHILIA

Löffler Syndrome
Ascaris
Hookworm
Schistosomiasis
Heavy Parasite Burden
Strongyloidiasis
Direct Pulmonary Penetration
Paragonimiasis
Visceral larval migrans
Immunologic Response to Organisms in Lungs
Filariasis
Dirofilariasis
Cystic Disease
Echinococcus
Cysticercosis
Other Nonparasitic
Coccidioidomycosis
Basidiobolomycosis
Paracoccidioidomycosis
Tuberculosis

Source: Adapted from P Akuthota, PF Weller: Clin Microbiol Rev 25:649, 2012.