can develop before other symptoms such as arthritis manifest, making the diagnosis more difficult.

Clinical manifestations of CTD-ILD are nonspecific and include exertional dyspnea and dry cough. Exertional dyspnea may be obscured by disabilities caused by the underlying connective tissue disorder. CTD-ILD may be relatively asymptomatic, manifesting as an incidental finding on imaging. Lung examination in patients with CTD-ILD may reveal bibasilar crackles, and pulmonary function tests often show a restrictive pattern with decreased diffusion capacity. If obstruction is identified on pulmonary function testing, airway manifestations of the connective tissue disorder, such as obliterative bronchiolitis in the setting of rheumatoid arthritis, must be considered.

Chest imaging studies are useful because they may reveal typical patterns associated with the underlying connective tissue disorder, often obviating the need for biopsy. These patterns include apical fibrocavitary disease in ankylosing spondylitis and basilar fibrotic changes in rheumatoid arthritis, polymyositis, and systemic sclerosis. Imaging may also reveal pulmonary nodules in RA or pleural disease in the setting of rheumatoid arthritis or systemic lupus erythematosus.

Pulmonary hypertension in the absence of fibrosis can occur in these patients, especially those with limited scleroderma (e.g., CREST syndrome [*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia]) and systemic lupus erythematosus. Echocardiography may be helpful in patients with these disorders and otherwise unexplained dyspnea.

Drug-induced lung disorders related to immunosuppressant therapy should always be considered in patients with connective tissue disorders. Although CTD-ILD typically is chronic in nature, acute or fulminant pneumonitis that may be difficult to distinguish from opportunistic infection can be seen in systemic lupus erythematosus, Sjögren syndrome, polymyositis, and dermatomyositis.

Bronchoscopy with BAL is often used to rule out infection in acute presentations or when imaging reveals areas of consolidation, as may occur with organizing pneumonia in rheumatoid arthritis. Lung biopsy may be necessary if the clinical presentation or imaging findings are atypical. Biopsies of areas of typical basilar fibrosis in connective tissue disorders frequently reveal patterns consistent with NSIP or UIP. In Sjögren syndrome with ILD, LIP or lymphoma may be found on biopsy. Diffuse alveolar damage is found in the setting of acute lupus pneumonitis.

Immunosuppressants are the mainstay of treatment for CTD-ILD. These disorders are more responsive to this therapy than IPF.

DRUG-INDUCED LUNG DISORDERS

A large number and variety of drugs can induce adverse reactions in the lung, often in the form of an ILD (Table 17-4). These reactions vary in severity from self-limited hypersensitivity reactions (E-Fig. 17-5) to diffuse alveolar damage resulting in respiratory failure and death. A high index of suspicion is needed to make the association between a drug and a pulmonary reaction, and a careful review of medications and other pharmacologic substances used by a patient is necessary in the setting of diffuse lung disease. Illicit drugs such as heroin and cocaine commonly produce adverse pulmonary reactions. Substances such as talc may be injected or inhaled inadvertently during the use of illicit drugs, resulting in pulmonary vascular or interstitial disease.

The clinical presentation of a drug-induced ILD is often nonspecific, with fever, cough, and dyspnea accompanied by radiographic infiltrates. Eosinophilia is sometimes found. Tests results for antinuclear antibodies are positive, but those for anti–double-stranded DNA antibodies are negative in the setting of drug-induced lupus. Pulmonary function tests, if performed, usually reveal decreases in DLCO and often show a restrictive pattern. ILD caused by medications usually does not produce a unique radiographic or histologic pattern of lung injury but may result in a variety of nonspecific reactions, including pulmonary infiltrates with peripheral eosinophilia, an HP pattern, and interstitial fibrosis. Alveolar filling may also occur in the setting of drug-induced organizing pneumonia and acute lung injury or diffuse alveolar damage. Pleural and pericardial effusions may occur in lupus-like drug reactions. Because the clinical presentation of patients with drug-induced ILDs lacks specificity, ILDs are typically diagnoses of exclusion.

There are settings in which drug-induced lung disease may be especially relevant and should be strongly considered in the differential diagnosis. They include the use of chemotherapeutic agents, the use of illicit drugs, patients with lupus-like illness, and patients using agents known to produce pulmonary toxicity, such as amiodarone or nitrofurantoin. Many chemotherapeutic agents, ranging from the newer tyrosine kinase inhibitors to older agents such as bleomycin and methotrexate, may produce lung injury and ILD. Diagnosis of a drug-induced ILD may be challenging in patients treated with chemotherapy because atypical infections and chemotherapy-induced heart failure may result in similar symptoms and radiographic findings.

Heroin use typically results in pulmonary edema or aspiration injury rather than ILD. Cocaine use can produce a variety of pulmonary effects, including organizing pneumonia, alveolar hemorrhage, and diffuse alveolar damage. "Crack lung" is a clinical diagnosis typified by dyspnea, hemoptysis, and pulmonary infiltrates occurring in the setting of crack cocaine use. Drug-induced lupus occurs with drugs such as procainamide or hydralazine. Amiodarone lung toxicity is a classic drug-induced lung disorder that results in alveolar or interstitial infiltrates accompanied by dyspnea on exertion. Although foamy macrophages can be detected by BAL, they indicate amiodarone use, not toxicity. Nitrofurantoin may cause an acute pulmonary syndrome with fever, dyspnea, and cough soon after initiation of the drug or cause a chronic pulmonary fibrosis with long-standing use. Amiodarone and nitrofurantoin reactions necessitate drug withdrawal and often require corticosteroids for resolution.

Pulmonary toxicity from drugs may be dose dependent, as with bleomycin, for which the risk of lung toxicity increases with cumulative doses exceeding 450 U. Amiodarone lung disease typically occurs with dosages greater than 400 mg per day. Synergistic lung toxicities may occur. For example, exposure to high levels of inspired oxygen may precipitate bleomycin lung injury and should be avoided if possible in exposed patients.

An online drug reference website (http://www.pneumotox.com) is available. It tabulates the reported pulmonary