Drug-Induced Lung Diseases

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Objectives:

1. To appreciate the diverse clinical syndromes of drug-induced pulmonary diseases.
2. To understand the general approach to the patient with suspected drug toxicity.
3. To review the common abnormalities associated with specific chemotherapeutic agents.
4. To comprehend the typical manifestations of pulmonary toxicity due to non-chemotherapeutic agents.

Key words: acute lung injury, drugs, hypersensitivity pneumonitis, pulmonary fibrosis

Drug-induced lung diseases have challenged clinicians since the dawn of modern medicine. In 1880, William Osler described a patient with pulmonary edema associated with opiate exposure and suggested that there was a pathophysiologic relationship. In 1972, Edward Rosenow extensively reviewed this topic and identified 20 drugs that clearly caused pulmonary toxicity. [1] A decade later, Cooper and colleagues expanded the list to 37 drugs. [2] Since then, over 340 drugs have been implicated in causing a wide array of pulmonary manifestations that involve virtually all components of the respiratory system including the airways, parenchyma, pleura, pulmonary circulation, mediastinum, vocal cords, and respiratory muscles (Table 1). The number of drugs that cause lung disease will undoubtedly continue to grow as new agents and biologic response modifiers are developed.

Although the clinical syndromes associated with certain drugs are well defined, the full scope of the epidemiology of drug-induced lung disease is not firmly established. This is partly due to the fact that the diagnosis is one of exclusion (*eg*, infection, tumor, etc.). Notably, there are no pathognomonic clinical, laboratory, physiologic, radiographic or histologic findings. Also, most reactions are idiosyncratic without any clear relationship to dose or time of exposure. Indeed, some drugs can cause toxicity years after exposure (*eg*, cyclophosphamide). With few exceptions, the risk factors for drug-induced lung diseases are poorly defined. Moreover, confounding variables such as the use of other drugs, oxygen or radiation therapy, each of which can cause pulmonary injury or have interactive effects (*eg*, bleomycin and oxygen), often hamper the diagnosis. Rechallenge with the implicated drug is rarely done because effective alternative agents are nearly always available. Thus, clinicians evaluating patients with possible drug-induced pulmonary symptoms must obtain a thorough drug exposure history, maintain a high index of suspicion, and utilize a systematic diagnostic approach that is reviewed below.

The management of patients with drug-induced pulmonary side effects is largely supportive. Typically the implicated drug is withdrawn and a trial of corticosteroids is considered, particularly in the setting of significant symptoms and/or gas exchange abnormalities. The scientific basis for using corticosteroids is, unfortunately, supported by anecdotal reports rather than well-designed controlled studies.

Table 1— *Major Clinical Syndromes of Drug-Induced Pulmonary Disease*

1.	Chronic pneumonitis/fibrosis
2.	Hypersensitivity-type lung disease
3.	Bronchiolitis obliterans with organizing pneumonia
4.	Acute noncardiogenic pulmonary edema
5.	Alveolar hypoventilaton
6.	Bronchospasm
7.	Cough
8.	Concentric bronchiolitis obliterans
9.	Pleural effusions
10.	Venous thromboembolism
11.	Pulmonary vasculitis
12.	Pulmonary hypertension
13.	Drug-induced systemic lupus erythematosus
14.	Alveolar hemorrhage
15.	Pulmonary renal syndrome
16.	Alveolar proteinosis
17.	Mediastinal abnormalities (*eg*, adenopathy, lipomatosis, mediastinitis)
18.	Panlobular emphysema
19.	Pulmonary calcinosis
20.	Pseudosepsis syndrome

Major Clinical Syndromes of Drug-Induced Pulmonary Disease

Chronic Pneumonitis/Fibrosis

A wide array of drugs have been implicated in causing chronic interstitial pneumonitis and/or fibrosis making it the most common manifestation of drug-induced lung disease. Some of the agents implicated are listed in Table 2. Antidepressants, especially tricyclic-related agents, may account for nearly 10% of patients with idiopathic pulmonary fibrosis (IPF) (odds ratio: 1.79 [95% confidence interval: 1.09-2.95]).[3] These patients commonly present with insidious onset of cough and dyspnea. Weight loss and clubbing may also be present raising the possibility of an underlying malignancy or IPF, respectively. The chest radiograph and high resolution chest CT (HRCT) scan generally reveal reticular infiltrates beginning in the basilar subpleural regions and progressing to diffuse disease. Pulmonary function tests (PFT) typically show reduced lung volumes (*eg*, restrictive physiology), a reduced diffusion capacity for carbon monoxide (D_{LCO}), and arterial hypoxemia at rest or with exercise.

Hypersensitivity-Type Lung Disease

Virtually any drug can cause a generalized hypersensitivity-type reaction with respiratory symptoms that are associated with pulmonary infiltrates and eosinophilia (PIE). The agents commonly implicated are listed in Table 3. Patients can present with Loeffler's syndrome consisting of an acute onset over several days of cough, dyspnea, fever, rash, myalgias, peripheral eosinophilia, and fleeting infiltrates. Alternatively, they may present with chronic eosinophilic pneumonia consisting of a subacute onset over several months of low grade fever, night sweats, nonproductive cough, and weight loss. Establishing a diagnosis may be challenging because not all findings, especially peripheral eosinophilia, are present in each patient. The diagnosis is often secured by bronchoscopy with lavage and biopsy and, in some instances, after a prompt response to corticosteroids. The prognosis is generally favorable with a mortality rate of less than 1%.

Bronchilolitis Obliterans With Organizing Pneumonia

Bronchilolitis obliterans with organizing pneumonia (BOOP) can occur after exposure to a variety of drugs (Table 4) and presents similarly as cryptogenic organizing pneumonia (Table 4). These patients typically present with cough, dys-

Table 2 — *Some Drugs That Cause Chronic Pneumonitis/Fibrosis*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Azathioprine	• Amiodarone*
• BCNU	• Cocaine
• Bleomycin*	• Gold
• Busulfan	• Heroin
• Chlorambucil	• Methysergide
• Cyclophospamide	• Mexiletine
• Fludarabine	• Nitrofurantoin
• 6-Mercaptopurine	• Penicillamine
• Methotrexate	• Phenytoin
• Mitomycin C	• Sirolimus
	• Statins
	• Sulfasalazine
	• Tocainide

* Most commonly implicated.

Table 3 — *Some Drugs That Cause Hypersensitivity-Type Lung Disease*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Azathioprine	• Antibiotics (β-lactam and sulfa-containing)*
• Bleomycin	• Carbamazepine
• Busulfan	• Isoniazide
• Fludarabine	• Nitrofurantoin
• Methotrexate*	• Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Nitrogen mustards	• Penicillamine
• Procarbazine	• Phenytoin
	• Statins

* Most commonly implicated.

Table 4 — *Some Drugs That Cause BOOP*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Bleomycin	• Amiodarone
• Cyclophosphamide	• Amphotericin B
• Methotrexate	• Carbamazepine
• Mitomycin C	• Cocaine
	• Gold
	• Nitrofurantoin
	• Penicillamine
	• Phenytoin
	• Sulfasalazine
	• Ticlodipine

pnea, crackles on physical examination and patchy airspace infiltrates on the chest radiograph. Lung function tests reveal a mixed obstructive and restrictive defect. Gold and penicillamine, the two best-characterized etiologic agents, are often used in the management of rheumatoid arthritis, a disease that can also cause BOOP. Thus, it may be difficult to distinguish drug-induced BOOP from the patient's underlying collagen vascular disorder. Management requires a high clinical suspicion, lung biopsy, prompt withdrawal of the implicated drug and therapy with corticosteroids. The outcome is generally favorable as it is with idiopathic BOOP.

Acute Noncardiogenic Pulmonary Edema

Noncardiogenic pulmonary edema can occur after exposure to a variety of drugs (Table 5). These patients generally present with acute dyspnea and a nonproductive cough that develops over a period of hours. Physical examination of the chest reveals inspiratory crackles while arterial blood gases show hypoxemia. The chest radiograph film generally demonstrates diffuse acinar and/or ground-glass infiltrates. The histopathology can be similar to ARDS. Several mechanisms have been implicated in causing drug-induced noncardiogenic pulmonary edema. First, some drugs increase the filtration coefficient of the respiratory membrane making it more permeable (*eg*, overdose of narcotics/sedatives). Second, certain agents depress the central nervous system resulting in neurogenic pulmonary edema. Finally, some drugs cause an idiosyncratic reaction resulting in noncardiogenic pulmonary edema within hours of absorption. The prognosis varies depending upon the offending agent. For example, pulmonary edema associated with an overdose of salicylates is potentially reversible with appropriate management while carmustine-induced pulmonary edema generally has a poor prognosis.

Alveolar Hypoventilation

Alveolar hypoventilation is caused by drugs that induce respiratory depression or block respiratory muscle function. Patients with underlying pulmonary or neuromuscular disorders are particularly prone to developing acute hypercarbic respiratory failure. Some of the agents implicated in causing neuromuscular blockade or motor neuropathies/myopathies are listed in Table 6. Aminoglycoside-induced neuromuscular blockade is a rare, but potentially life-threatening adverse effect that has been described in patients exposed to neomycin, streptomycin, tobramycin, gentamicin, amikacin, kanamycin, and netilmicin.[4] The risk of aminoglycoside-induced neuromuscular blockade is increased in the presence of a disease or drug that promotes neuromuscular blockade, rising aminoglycoside drug levels, hypomagnesemia, and hypocalcemia. Management of these disorders requires a high clinical suspicion to identify the offending drug and withdrawal of the agent to avoid further respiratory failure.

Table 5— *Some Drugs That Cause Acute Noncardiogenic Pulmonary Edema*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Azathioprine	• Amiodarone
• Cytosine arabinoside	• Aspirin and NSAID overdose
• Gemcitabine	• Cocaine
• Interleukin 2	• Opiate overdose (*eg*, heroin)
• Methotrexate	• Sedative/hypnotic drug overdose
• Mitomycin C	• Sulfasalazine
• Nitrogen mustards	• Tocolytic therapy (*eg*, terbutaline, ritodrine)
• Retinoic acid	
• Tumor necrosis factor	
• Vinblastine (with mitomycin)	

Table 6 — *Some Drugs Causing Alveolar Hypoventilation*

Neuromuscular blockade	
• Aminoglycosides	• Opiates (*eg*, heroin)
• Cocaine	• Polymixins
• Gamma-hydroxy butyrate (GHB)	• Sedative/hypnotic drugs
Motor neuropathies or myopathies	
• Amiodarone	• Isoniazid
• Captopril	• Phenytoin
• Corticosteroids	• Procainamide
• Diuretics	

Table 7 — *Some Drugs That Cause Bronchospasm*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
• Interleukin 2	• Aspirin and NSAIDs
• Methotrexate	• β-blockers
• Vinblastine	• Contrast media
• Vinca alkaloids plus mitomycin	• Corticosteroids
	• Dipyridamole
	• Gold
	• Nitrofurantoin (acute)
	• Opiates (cocaine, heroin)
	• Penicillamine
	• Protamine

Bronchospasm

Drug-induced bronchospasm is caused by various agents (Table 7). Patients generally present with wheezing, cough, and/or dyspnea. Spirometry typically shows airways obstruction. The mechanism of drug-induced bronchospasm varies with the particular agent. In patients with asthma, unlike normal individuals, β-adrenergic blockers induce bronchospasm within minutes by mechanisms involving inhibition of adrenergic bronchodilator tone. Virtually any route of administration (*eg*, oral, IV, or ophthalmic) can induce bronchospasm. Aspirin-induced bronchospasm is mediated by an enhanced 5-lipoxygenase pathway resulting in the production of bronchoconstricting cysteinyl-leukotrienes and, to a lesser extent, by a reduction in bronchodilating prostaglandins (*eg*, prostaglandin E_2). Dipyridamole causes bronchospasm by augmenting the levels of adenosine, a bronchoconstricting agent. Gold and penicillamine cause irreversible airways obstruction due to concentric bronchiolitis obliterans.

Isolated Cough

Cough, which is one of the most common manifestations of drug-induced lung disease, is a vagus nerve-mediated reflex caused by various chemical and mechanical stimuli virtually anywhere within the upper and lower respiratory tract. Cough often occurs in patients with drug-induced bronchospasm or drug-induced interstitial lung disease. However, angiotensin-converting enzyme (ACE) inhibitors induce an isolated nonproductive cough without associated bronchospasm or parenchymal lung disease in nearly 10% of patients receiving any type of ACE inhibitor. [5]

Pleural Effusions

Although several drugs can cause a pleural effusion (Table 8), the number is much less than those that involve the lung parenchyma. [6] Pleural effusions with an acute onset occur as part of a hypersensitivity reaction after exposure to amiodarone, methotrexate, nitrofurantoin, as well as a number of other chemotherapeutic agents. Anticoagulants can induce an acute bloody effusion. Chronic pleural effusion may occur after long-term exposure to drugs that induce a delayed hypersensitivity-type response (*eg*, methotrexate or procarbazine) or in association with the development of interstitial pulmonary inflammation/fibrosis (*eg*, busulfan and methotrexate).

Pulmonary Vascular Disease

Drugs that affect the pulmonary vascular circulation by causing venous thromboembolism (VTE), pulmonary hypertension, vasculitis or pulmonary veno-occlusive disease are listed in Table 9. Oral contraceptives and other estrogen-containing agents can induce VTE. The VTE risks are relatively small in patients using second- and third-generation oral contraceptives as compared to nonusers (15, 30 and 5 per 100,000 patients treated, respectively). [7] The Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) study was unable to detect an increased risk from oral contraceptives but the number of patients studied was insufficient to exclude a role for these agents. [8] There is a synergistic interaction between hypercoagulable conditions (*eg*, factor V Leiden deficiency) and VTE risks from hormonal replacement therapy.[9] Thus, the risk from hormonal replacement in the absence of other VTE risk factors appears too small to recommend against using these agents.

Drug-induced pulmonary hypertension can occur after exposure to a variety of drugs by mechanisms that are unclear. A case-control study showed that appetite suppressants (*eg*, amphetamines, fenfluramine and dexfenfluramine) are associated with an increased risk of primary pulmonary hypertension (odds ratio: 6.3 overall and >20 if the drugs were used for over 3 months). [10] Although fenfluramine and dexfenfluramine have been withdrawn from the market worldwide, clinicians should remain vigilant for drug-induced pulmonary hypertension as an estimated 5 million adults in the United States continue to use appetite suppressants. Oral contraceptives and other estrogen-containing agents

Table 8 — *Some Drugs Causing Pleural Effusions*

Chemotherapeutic Agents	Nonchemotherapeutic Agents
Bleomycin	Amiodarone
Busulfan	Anticoagulants
Etoposide	Bromocriptine
Methotrexate	Dantrolene
Mitomycin	Esophageal sclerosing agents
Nitrogen mustards	Methysergide
Procarbazine	Nitrofurantoin

have also been associated with an increased risk of pulmonary hypertension.

An inflammatory vasculitis has been noted in conjunction with a generalized hypersensitivity reaction in patients exposed to busulfan, nitrofurantoin, or illicit drugs such as cocaine and heroin. However, it is uncertain whether the vascular response represents a primary or secondary effect of the drug. Zafirlukast and montelukast rarely (1 case per 15,000 to 20,000 patient-years treated) induce an idiosyncratic syndrome similar to Churg-Strauss vasculitis with peripheral eosinophilia, eosinophilic vasculitis, and cardiac failure.[11] Since most of the reported patients were receiving either high-dose inhaled or systemic corticosteroids, a preexisting vasculitis may have accounted for their symptoms. Pulmonary veno-occlusive disease is a rare adverse effect noted after exposure to bischlorethylnitrosurea (BCNU), bleomycin, busulfan or mitomycin.

Miscellaneous Drug-Induced Pulmonary Reactions

There are a variety of less common drug-induced adverse pulmonary effects (Table 10). Systemic lupus erythematosus (SLE) is associated

Table 9 — *Some Drugs Causing Pulmonary Vascular Disease*

Complication	Chemotherapeutic Agents	Nonchemotherapeutic Agents
Thromboembolic disease		Estrogens/hormonal Rx Phenytoin Steroids
Pulmonary hypertension	Mitomycin Interleukin 2	Aminorex (recalled) Amphetamines Dexfenfluramine (recalled) Fenfluramine (recalled) L-tryptophan (recalled) Oral contraceptives
Vasculitis	Busulfan	Cocaine/heroin Nitrofurantoin Zafirlukast/montelukast
Veno-occlusive disease	Bleomycin Busulfan BCNU Mitomycin	Oral contraceptives

Table 10 — *Miscellaneous Drug-Induced Pulmonary Reactions*

Drug-induced lupus erythematosus	Hydralazine Isoniazide Quinidine	Procainamide Penicillamine
Alveolar hemorrhage	Abciximab Amphotericin B Amiodarone Anticoagulants	Cocaine Mitomycin C Nitrofurantoin Penicillamine
Alveolar proteinosis	Busulfan	
Churg-Strauss vasculitis	Zafirlukast	Montelukast
Mediastinal abnormalities Adenopathy Lipomatosis Mediastinitis	 Methotrexate Corticosteroids Esophageal sclerosing agents	 Phenytoin
Panlobular emphysema	Methylphenidate	
Pulmonary calcification	Antacids Calcium	High-dose vitamin D
Pseudosepsis syndrome	Chronic salicylate intoxication	

with the use of a wide variety of drugs, although 5 agents are involved in over 90% of the cases (Table 10). Five to twelve percent of all cases of SLE are due to drugs. It is unclear whether these agents cause or unmask a latent case of SLE. Hydralazine- and isoniazid-induced SLE occur more frequently in slow acetylators of these drugs. Hydralazine-induced SLE occurs in up to 20% of patients receiving doses ≥ 400 mg/d but can develop in patients on low-dose therapy. Procainamide-induced SLE is time- rather than dose-related in that positive antinuclear antibodies (ANA) develop in approximately 50% of patients after 3 months of therapy and in nearly all patients by 1 year. Notably, the double-stranded DNA ANA is usually negative in drug-induced SLE unlike other patients with SLE. Typically, pleurisy and dyspnea, in conjunction with systemic complaints of fever and arthralgias, develop in an insidious manner after using the drug for several months or even years. Chest radiograph abnormalities include pleural effusions, atelectasis, diffuse interstitial infiltrates, and alveolar infiltrates. Withdrawal of the offending agent generally results in prompt resolution of symptoms within days but occasionally corticosteroids are required for symptomatic relief.

Alveolar hemorrhage and hemoptysis can occur after exposure to certain drugs (Table 10). Drug-induced hemoptysis is most commonly due to pulmonary embolism with infarction. Penicillamine can cause a pulmonary-renal syndrome similar to Goodpasture's syndrome. Oral anticoagulants can induce spontaneous pulmonary hemorrhage days to years after the onset therapy. Abciximab, a chimeric monoclonal antibody directed against platelet glycoprotein IIb/IIIa receptor that reduces restenosis after angioplasty and stent placement, can cause severe alveolar hemorrhage. [12] This relatively rare complication (7/2533 patients; 0.3% as compared to 0/5412 controls) should be suspected in patients presenting with hemoptysis, hypoxemic respiratory failure, diffuse alveolar infiltrates and progressive decline in the hemoglobin within hours to 2 d of the first dose of abciximab.

Mediastinal abnormalities can be a manifestation of an adverse drug effect (Table 10). Phenytoin can induce a pseudolymphoma syndrome associated with peripheral adenopathy and, rarely, mediastinal adenopathy. Methotrexate may cause transient hilar adenopathy during a hypersensitivity-type response. Typically the adenopathy regresses 1 to 2 weeks after drug withdrawal. Mediastinal fullness due to lipomatosis is an unusual manifestation of an adverse effect of corticosteroids. Although mediastinal widening in patients receiving corticosteroids may raise the suspicion of adenopathy, the diagnosis of lipomatosis is suggested by the characteristic chest radiograph appearance of a straight mediastinal border without the lumpy features of adenopathy and the typical CT findings of lipid-containing tissue. Mediastinitis associated with fever and chest pain is a relatively rare adverse effect of esophageal variceal sclerotherapy.

Other rare pulmonary adverse drug effects reported in the literature include busulfan-induced alveolar proteinosis, methylphenidate-induced panlobular emphysema, and pulmonary parenchymal calcium deposition associated with hypercalcemic conditions or drugs such as antacids, calcium, and high-dose vitamin D. Chronic salicylate ingestion can cause a pseudosepsis syndrome (reviewed later).

Approach to the Patient With Suspected Drug-Induced Lung Disease

Differential Diagnosis

As mentioned earlier, the diagnosis of drug-induced lung disease is one of exclusion since there are no pathognomonic criteria. The differential diagnosis is broad, especially in cancer patients receiving multiple drugs that often include immunosuppressive agents. However, the differential diagnosis can be narrowed based upon the presenting clinical syndrome reviewed above as well as by the presence of localized or diffuse infiltrates (Table 11). In some instances, the patient may have minimal or absent symptoms and findings

Table 11—*Differential Diagnosis of Radiographic Abnormalities*

Diffuse Disease	Localized Disease
Infection	Infection
Malignancy	Malignancy
Lymphangitic metastasis	Pulmonary emboli
Pulmonary edema	Radiation pneumonitis
Pulmonary fibrosis	Drug toxicity
Radiation pneumonitis/fibrosis	
Leukoagglutinin reaction	
Acute respiratory distress syndrome	
Hypersensitivity pneumonitis	
Pulmonary hemorrhage	
Drug toxicity	

but demonstrate abnormalities on the chest radiograph or PFTs. A high level of clinical suspicion is required since drug-induced disease may occur years after initial exposure and the radiographic abnormalities may be subtle.

Diagnostic Approach

Because drug-induced pulmonary toxicity has a profound impact on patient management, it is important to establish a diagnosis as firmly as possible. This begins with an understanding of the clinical syndromes caused by various agents combined with the prudent use of noninvasive studies and invasive procedures. Evaluation of the chest radiograph, PFTs, and, on occasion, chest CT scan help narrow the differential diagnosis. Noninvasive studies that may be useful include: (1) an echocardiogram to assess cardiac function, (2) sputum studies to identify an infectious pathogen (*eg*, Gram stain, culture, direct fluorescent antibody for *Pneumocystis carinii* or *Legionella*, and acid-fast bacteria stain and culture), and (3) immunologic studies to exclude collagen vascular disorders and vasculitis.

If a firm diagnosis is not established, then the judicious use of invasive diagnostic procedures is warranted. Typically, fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy is the next step in the evaluation of patients with localized or diffuse pulmonary disease of unclear etiology. Although this procedure has an excellent diagnostic yield for infections and malignant lesions (approximately 70% to 90%), it has a lower diagnostic yield for interstitial inflammatory lesions including those due to drug-induced toxicity. In the proper clinical setting, a nondiagnostic bronchoscopy may be sufficient to suggest the diagnosis of drug-induced injury. A thoracoscopic or, less commonly these days, an open lung biopsy is recommended in patients where the diagnosis remains unclear and the differential diagnosis includes other pulmonary abnormalities, especially interstitial lung disease. These procedures have the highest diagnostic yield and a relatively low complication rate, even in critically ill patients. The histopathologic changes associated with drug toxicity are nonspecific, revealing elements of diffuse alveolar damage, fibrinous exudate, atypical or reactive alveolar type II cells, inflammatory cells and fibrotic foci. One study showed that up to 20% of patients with diffuse infiltrates undergoing an open lung biopsy had histologic changes that could be attributed to a drug reaction. [13]

Pulmonary Function Tests

The role of PFTs for detecting adverse drug-induced pulmonary effects has been extensively investigated. The majority of the studies have focused on bleomycin, busulfan and amiodarone. The most common PFT abnormalities are diminished lung volumes and a reduced D_{LCO}. However, it is controversial whether these abnormalities accurately predict that clinically overt disease will develop. [14,15] Patients can develop overt drug-induced disease in the absence of PFT abnormalities and conversely can have abnormal PFTs in the absence of drug-induced lung disease. Patient effort and anemia are important confounding variables that impact on PFT results. For most drugs, well-designed clinical studies validating the role of PFTs to detect adverse pulmonary effects are not available. Until definitive data are available, it is reasonable for clinicians to continue utilizing PFTs in select settings with the goal of identifying subclinical disease as long as the physiologic interpretation is made in the context of the entire clinical situation.

Chemotherapy-Associated Pulmonary Toxicity

Azathioprine/Mercaptopurine

Azathioprine, a purine analogue that inhibits DNA synthesis, is an immunosuppressive agent used in the treatment of nonmalignant disease (*eg*, IPF, organ transplantation). Mercaptopurine, the active metabolite of azathioprine, is an antineoplastic agent. Azathioprine rarely (< 1%) causes pulmonary fibrosis, hypersensitivity-type reactions / PIE, or diffuse alveolar damage.

BCNU

Bischloroethylnitrosurea (BCNU), or carmustine, is the best known and extensively studied member of the nitrosurea family of drugs that includes lomustine (chloroethylnitrosurea or CCNU), semustine (methyl-CCNU), and chlorozotocin. These cytotoxic agents, which are unique in their ability to cross the blood brain barrier, are active

against a variety of neoplasms including central nervous system malignancies. BCNU causes interstitial pulmonary fibrosis and granulomatous inflammation that can progress after drug withdrawal. The pathogenesis of BCNU-induced pulmonary toxicity is unclear. BCNU promotes oxidant-induced lung injury by inhibiting glutathione reductase and thereby reducing glutathione stores, an important antioxidant defense. BCNU causes cytotoxic changes characterized by alveolar type II cell hyperplasia and dysplasia, fibroblastic foci of proliferation, and interstitial fibrosis.

Patients presenting with BCNU-induced pulmonary toxicity will typically note an insidious onset of a nonproductive cough and dyspnea associated with reticular nodular interstitial infiltrates on the chest radiograph. However, the onset of symptoms is highly variable, appearing within days to as many as 17 years after beginning BCNU. [16] Risk factors include: (1) total dose: the incidence of pulmonary toxicity with high-dose BCNU (> 1500 mg/m^2) varies from 20% to50% while with low-dose BCNU it is on the order of 1% to 5%, primarily when administered concurrently with other agents; (2) other agents: cyclophosphamide and radiation increase the risk of BCNU-induced lung injury, however a synergistic interaction has not been documented; (3) preexisting lung disease: patients with preexisting symptomatic pulmonary disorders, especially with a reduced vital capacity or DLCO, are typically excluded from receiving BCNU. A reduced DLCO without chest radiographic abnormalities occurs in patients receiving BCNU. Although there are no prospective studies to support the following, it is recommended that PFTs be obtained during therapy to monitor for subclinical disease and also long-term given the extended latency period between treatment and pulmonary toxicity. This approach is supported in part by the poor outcome of patients who develop BCNU-induced pulmonary fibrosis. It is associated with a mortality rate of nearly 90%. Corticosteroid therapy has little impact in preventing or treating BCNU-induced lung injury. Primary treatment is to withdraw BCNU promptly and provide supportive care. Although there is less information about the frequency of pulmonary injury caused by the other nitrosureas, each has been reported to have similar effects as BCNU.

Bleomycin

Bleomycin, a cytotoxic antibiotic isolated from *Streptomyces verticillus*, is very useful for treating patients with head and neck carcinomas, germ cell tumors, and Hodgkin's and non-Hodgkin's lymphomas. Bleomycin accumulates in the skin and lung resulting in skin ulcerations and pulmonary fibrosis. Bleomycin-induced pulmonary damage, which is the major dose-limiting side effect, was first recognized in 1972.[17] The overall incidence of pulmonary toxicity is 10% (range: 3% to 40%) and is fatal in 1% to 2%.

The pathogenesis of bleomycin-induced lung injury is not firmly established.[15] Because bleomycin reproducibly causes interstitial pneumonitis and fibrosis in animal models, it has become a paradigm for the study of the pathogenic mechanisms underlying pulmonary fibrosis. Early bleomycin-induced pulmonary injury shows acute and organizing diffuse alveolar damage that is similar to the fibroproliferative phase of ARDS. Bleomycin binds to intracellular iron in alveolar epithelial and vascular endothelial cells and, in the presence of oxygen, generates highly reactive oxygen species (ROS), such as hydroxyl radicals. ROS alter important cellular components (*eg*, DNA, lipids, and proteins) resulting in damage to the respiratory membrane. Intratracheal or IV bleomycin increases cytokine levels within the lung in animal models. The important cytokines implicated in the pathogenesis of bleomycin-induced pulmonary toxicity include transforming growth factor-β (TGF-β), tumor necrosis factor alpha (TNFα), interleukin (IL) -1, and others. Pathogenic roles for ROS and certain cytokines are supported by the protective effects various agents including antioxidants, iron chelators, IL-1 receptor antagonists, IL-12, keratinocyte growth factor, CD36 peptides (binds TGF-β_1) or antibodies against TGF-β, TNFα, or CD3 receptors.[15] A crucial role for alveolar epithelial cell injury is suggested by the finding that transgenic mice deficient in the epithelial cell restricted integrin beta 6 do not develop bleomycin-induced pulmonary inflammation or fibrosis in part because they are unable to activate latent TGF-β.[18] Bleomycin lung toxicity can also be prevented by blocking excessive alveolar epithelial cell apoptosis or DNA damage, by enhancing DNA repair, and by augmenting fibrinolysis. [19-24] For example, expression of the bleomycin-resistant *Streptoalloteichus hindustanus ble*

gene, that encodes a protein that binds bleomycin and blocks DNA damage, can prevent bleomycin-induced fibrosis.[22] Although the pathogenic mechanisms underlying bleomycin toxicity are better understood, it is unclear why certain patients are predisposed to pulmonary fibrosis.

There are three major clinical manifestations of bleomycin-induced lung toxicity: (1) chronic interstitial fibrosis, (2) hypersensitivity-type disease, and (3) BOOP. Interstitial fibrosis is by far the most common, occurring in approximately 11% of those treated. Patients typically present with a subacute onset of a nonproductive cough and dyspnea within a few weeks to 6 months after treatment.[15] Pleuritic substernal chest pain occurs in approximately 3%. However, nearly 20% of patients with bleomycin-induced lung injury will be asymptomatic. Physical examination may show tachypnea, bibasilar crackles, and hyperpigmented skin lesions. Chest radiographs typically reveal basilar, predominant reticular or fine nodular infiltrates that often originate from the costophrenic angles. Other less common radiographic patterns include patchy alveolar infiltrates, lobar consolidation, and lung nodules. PFTs generally show reduced lung volumes and DLCO. Patients with bleomycin-induced hypersensitivity-type disease may have similar symptoms but often with an associated fever, malaise, and chest radiographic changes of chronic pneumonitis and ground glass appearing parenchyma with little fibrosis. The radiographic and pathologic distinction between fibrosis and pneumonitis are not always clear.

Risk factors for developing bleomycin-induced pulmonary toxicity include: (1) total dose: a dose relationship has been described with an incidence of 3% to 5% when the total dose is below 300 U but over 20% when the total dose is above 500 U,[15] however, pulmonary toxicity can occur after receiving only 20 U; (2) oxygen: bleomycin, more than any other drug, has a well known synergistic toxic interaction with oxygen that can occur years after bleomycin exposure, although not all patients develop this reaction, the inspired oxygen concentration for patients who have ever received bleomycin should be kept below 25% if possible; (3) radiation: radiation, even years after bleomycin exposure, increases the risk; (4) age: persons over the age of 70 years are at an increased risk of lung injury; (5) abnormal renal function: patients with reduced renal function are more susceptible to bleomycin-induced pulmonary toxicity, due to the fact that the kidneys primarily excrete bleomycin; (6) concurrent use of other cytotoxic agents: some drugs may increase the risk of bleomycin-related injury including cyclophosphamide, doxorubicin, granulocyte colony stimulating factor (G-CSF), methotrexate, and vincristine.

Management of patients with bleomycin-induced pulmonary toxicity centers on withdrawing the drug. Although the overall mortality is approximately 1% to 2%, mortality varies from 10% to 83% in patients with pulmonary disease. Corticosteroids (60 to 100 mg/d) are generally administered to all patients with clinically significant toxicity and then slowly tapered according to the patient's clinical response. Clinical improvement typically occurs within weeks and may take 2 years to completely resolve. Select patients will be left with residual radiographic and PFT abnormalities.

Busulfan

Busulfan, an alkylating agent used in the management of chronic myeloproliferative disorders, was the first chemotherapeutic agent implicated in causing chronic pneumonitis/pulmonary fibrosis. In general, alkylating agents (*eg*, busulfan, cyclophosphamide, chlorambucil, melphalan) have a lower frequency of inducing lung injury than other cytotoxic agents. Like bleomycin, these agents can induce synergistic pulmonary damage when exposed to oxygen, radiation, or other cytotoxic chemotherapeutic agents. The incidence of symptomatic busulfan-induced pulmonary fibrosis is approximately 4% to 5%. However, histologically evident fibrosis and cytotoxic changes (hyperplastic and dysplastic type II cells) occur in up to 46% of busulfan-treated patients, most of whom are asymptomatic.[25] A threshold dose has not been established.

The clinical presentation is an insidious onset, often > 3 years after initiating therapy, of cough, dyspnea, fever, malaise and weight loss. The PFTs show restrictive lung volumes, a reduced DLCO, and hypoxemia. The chest radiograph typically shows diffuse interstitial and alveolar infiltrates with a basilar predominance. Occasionally pleural effusions, nodular densities or a normal chest radiograph are noted. Management centers on drug withdrawal and administration of corticosteroids. The prognosis is poor, with mortality ranging from

50% to 80%. Alveolar proteinosis has also been reported after exposure to busulfan. Unlike primary alveolar proteinosis, it does not respond to therapeutic bronchoalveolar lavage.

Cyclophosphamide

Cyclophosphamide, an alkylating agent that causes pulmonary toxicity less frequently than busulfan, is widely used to treat malignant (*eg*, lymphomas, breast carcinoma, ovarian carcinoma) and nonmalignant (*eg*, collagen vascular disorders, IPF, Wegener's granulomatosis) diseases. The incidence of adverse pulmonary effects is < 1%. The extensive clinical indications for cyclophosphamide and its frequent use in conjunction with other cytotoxic drugs increases the likelihood that lung toxicity will be seen by pulmonologists. Although cyclophosphamide alone induces pulmonary toxicity in humans relatively infrequently, [26,27] it clearly does so in animals. [28] The pathogenesis of pulmonary toxicity is not established but likely involves oxidant-mediated mechanisms. Cyclophosphamide is metabolized to two active agents: phosphoramide mustard and acrolein, both of which reduce hepatic glutathione stores.

Chronic pneumonitis and/or fibrosis are the most common clinical manifestations of pulmonary toxicity. Symptoms develop as soon as 2 weeks to as long as 13 years after initiation of therapy without any clear dose relationship. The patients present with cough, dyspnea, fever, and bibasilar interstitial infiltrates on chest radiographs. Synergistic toxicity has been described in patients receiving radiation therapy or other cytotoxic agents. [29] Cyclophosphamide-induced pulmonary fibrosis, unlike IPF, may present with bilateral pleural thickening typically without clubbing and "velcro" crackles. [27] The prognosis is generally poor; with a mortality rate approaching 50%. Most patients are treated with corticosteroids based upon anecdotal reports of benefit.

Methotrexate

Methotrexate is a folic acid antagonists that is used in the management of malignant and nonmalignant inflammatory diseases. The incidence of pulmonary toxicity is nearly 7% for high-dose methotrexate, as used to treat malignancies, but 2% to 3% with low-dose methotrexate regimens used to treat chronic inflammatory conditions such as rheumatoid arthritis. Methotrexate-induced pulmonary toxicity does not have a clear dose relationship since it occurs over a broad range of doses (40 to 6500 mg).

The clinical manifestations include: (1) hypersensitivity-type disease – the most common form, (2) chronic pneumonitis/fibrosis, (3) BOOP, (4) acute chest pain, (5) noncardiogenic pulmonary edema, (6) acute pleurisy/pleural effusions, and (7) bronchospasm. [30] Methotrexate-induced hypersensitivity-type reactions typically occur within 10 days to 4 months of initiating therapy but can occur up to 1 month after stopping methotrexate. [30] Patients may complain of fever, cough, dyspnea, arthralgias, and, less commonly, skin rash (approximately 17%). Chest radiographs reveal diffuse interstitial infiltrates with ground-glass changes on HRCT scan. Other radiographic abnormalities that are occasionally seen include nodular infiltrates, hilar/mediastinal adenopathy, and pleural effusions. Blood eosinophilia is present in nearly 40%. Bronchoalveolar lavage findings typically reveal a predominance of lymphocytes, especially T-suppressor cells characteristic of a hypersensitivity reaction. [31]

The diagnosis of methotrexate-induced pulmonary toxicity requires three major criteria: (1) hypersensitivity pneumonitis by histopathology, (2) radiographic evidence of interstitial and/or alveolar infiltrates, and (3) blood (if febrile) and sputum (if available) cultures that are negative for microbes. Patients must also have three of five minor criteria: (1) dyspnea < 8 weeks, (2) nonproductive cough, (3) room air oxygen saturation ≤ 90%, (4) D_{LCO} ≤ 70% of predicted, and (5) leukocyte count ≤ 15,000 cells/mm^3. [32]

Risk factors for the development of methotrexate-induced pulmonary toxicity include: (1) symptoms within the first 32 weeks of therapy, (2) multidrug regimens (synergy with cyclophosphamide has been reported), (3) diabetes mellitus, (4) age ≥ 50 years old, (5) rheumatoid pleuropulmonary disease, and (6) hypoalbuminemia. [33] Dose, frequency, smoking status, previous lung disease, and route of administration route (*eg*, oral, IV, intrathecal and IM) do not consistently affect the frequency of methotrexate-induced adverse pulmonary effects. Notably, PFTs have not been helpful in identifying patients with rheumatoid arthritis at risk for developing pulmonary toxicity while re-

ceiving chronic, low-dose methotrexate. [34] Chronic pneumonitis/fibrosis, which occurs less commonly due to methotrexate than other chemotherapeutic agents, typically presents 4 months to over 3 years after initiating therapy.

Management centers on drug withdrawal and administering corticosteroids. Approximately 7% of patients with methotrexate-induced hypersensitivity reactions will develop chronic fibrosis and 8% will die of progressive respiratory failure.

Mitomycin

Mitomycin is an alkylating cytotoxic antibiotic used in the treatment of breast, gastrointestinal, gynecologic and lung carcinomas. The incidence of pulmonary cytotoxicity is approximately 5% (range: 3% to 39%). [35] However, the full scope of the problem is difficult to assess because mitomycin is typically administered concurrently with other agents and is also a co-toxin with oxygen and radiation. The presenting features as well as the radiographic and physiologic changes are similar to those seen with bleomycin-induced interstitial pneumonitis/fibrosis. Of note, this reaction seems to occur most frequently after the third cycle of treatment. Although serial monitoring of the D_{LCO} to detect clinically occult disease is unproven, it is generally recommended and widely used for this purpose. Prednisone can rapidly resolve the symptoms and interstitial infiltrates. A unique reaction of mitomycin is the induction of microangiopathic hemolytic anemia concurrently with noncardiogenic pulmonary edema and renal failure. [36] The mortality rate associated with this uncommon reaction is over 90%.

The combination of mitomycin with vinca alkaloids (*eg*, vinblastine and vincristine) induces an acute onset (< 3 h of receiving the vinca alkaloid) of bronchospasm that is associated with focal or diffuse interstitial infiltrates on chest radiographs and hypoxemia. [37] Vinca alkaloids alone do not cause this adverse side effect. Approximately two thirds of the patients develop chronic respiratory symptoms that respond to corticosteroids.

Retinoic Acid

All-*trans*-retinoic acid (ATRA) is a highly effective biologic response modifier that induces clinical remission in patients with acute promyelocytic leukemia by augmenting the differentiation of malignant stem cells into mature neutrophils. Nearly 25% of patients initially treated with ATRA developed an ARDS-like picture, termed "retinoic acid syndrome". Prednisolone therapy (75 mg/day) reduces the incidence to approximately 8%. [38] The syndrome is characterized by sudden onset of fever, dyspnea, effusions (pleural and pericardial), diffuse alveolar infiltrates on chest radiographs, and hypoxemic respiratory failure. Before the efficacy of steroid therapy was recognized, more than half of the patients required mechanical ventilation and the mortality rate was 33%. The pathogenesis is not established but likely relates partly to the rapid increase in mature leukocytes. Autopsy studies reveal diffuse alveolar damage with edema and hemorrhage as well as leukemic cells in the interstitium. Mechanisms implicated in ATRA-induced capillary leak syndrome include the release of vasoactive cytokines, oxidants and lipid mediators from inflammatory cells as well as enhanced expression of leukocyte adhesion molecules that impair leukocyte transit through the pulmonary microcirculation. Some patients who develop retinoic acid syndrome while on prednisolone have responded to dexamethasone. Management is otherwise largely supportive similar to patients with ARDS.

Other Chemotherapeutic Agents

Other chemotherapeutic drugs are less commonly associated with adverse pulmonary effects but seen than the agents reviewed earlier. Chlorambucil, an alkylating agent similar to cyclophosphamide, is used in the treatment of lymphoproliferative disorders as well as nonmalignant diseases. Pulmonary toxicity is relatively rare but chronic pneumonitis/fibrosis has been reported. Cytosine arabinoside (Ara-C), an antimetabolite used to treat acute leukemia, causes noncardiogenic pulmonary edema in 13% to 20% of patients. [39,40] The mortality rate varies from 2% to 50%. Corticosteroids may improve outcome but this remains uncertain. Gemcitabine, an agent increasingly being used in the management of a variety of solid tumors, can induce an ARDS-like condition that is potentially fatal. [41] Fludarabine, an antimetabolite used in the management of patients with chronic lymphoproliferative disorders, can cause both chronic pneumonitis/fibrosis as well as a hypersensitiv-

ity-type reaction. Biologic response modifiers, such as IL-2 and TNFα, are used in experimental protocols to treat various malignancies. Each can induce noncardiogenic pulmonary edema that, in the case of IL-2, is also associated with massive fluid retention. Granulocyte-macrophage colony stimulating factor (GM-CSF) and G-CSF can cause a hypersensitivity-type pneumonitis when administered in conjunction with other cytotoxic agents. Also, G-CSF, especially in the presence of other cytotoxic agents, can induce ARDS. [42] Although beyond the scope of this review, immunosuppressive agents can promote the development of opportunistic pulmonary infections. Recently, infliximab, which is a monoclonal antibody directed against TNFα that is approved for use in rheumatoid arthritis and Crohn's disease, increases the likelihood of reactivation of tuberculosis. [43] It is recommended that all patients receiving infliximab be screened and treated for latent tuberculosis before the drug is utilized.

Nonchemotherapy-Associated Pulmonary Toxicity

Anti-inflammatory Drugs

Aspirin: Aspirin (acetylsalicylic acid), the most commonly prescribed drug worldwide, causes two forms of pulmonary toxicity: bronchospasm and noncardiogenic pulmonary edema. Aspirin-induced asthma (AIA) occurs in less than 1% of normal and up to 20% of asthmatic individuals. However, aspirin sensitivity occurs in a larger proportion of asthmatic patients with nasal polyps; a clinical triad first identified by Samter and Beers. [44] Symptoms of AIA occur within minutes to hours after ingestion and may be associated with facial flushing, rhinorrhea, angioedema, and conjunctivitis. The pathogenesis of AIA is mediated by enhanced production of cysteinyl leukotrienes via the 5-lipoxygenase pathway and, to a lesser extent, by a reduction in bronchodilating prostaglandins secondary to cyclooxygenase inhibition. Aspirin-sensitive asthmatic patients that are challenged with aspirin have increased levels of urinary leukotriene E_4, a general marker of serum leukotriene levels. This is due to increased activity of leukotriene C synthase, the rate-limiting step in leukotriene synthesis. [45] As expected, they exhibit symptomatic and spirometric improvement in the presence of 5-lipoxygenase inhibition and cysteinyl leukotriene receptor antagonism. [45] A similar syndrome occurs with other nonsteroidal anti-inflammatory drugs (NSAIDs). Agents that do not block the cyclooxygenase pathway, such as acetaminophen and salicylate, can be safely used in patients with aspirin- or NSAID-induced bronchospasm. [45]

Aspirin-induced noncardiogenic pulmonary edema occurs in 10% to 15% of patients with a severe salicylate overdose. This can occur inadvertently in chronic aspirin users, typically elderly patients with multiple medical problems, or intentionally in individuals attempting suicide. These patients will often present with dyspnea, tachypnea, altered mental status and a chest radiograph revealing diffuse alveolar infiltrates. Most patients will manifest either a simple respiratory alkalosis or a mixed anion gap metabolic acidosis plus a respiratory alkalosis. The constellation of findings can mimic a pseudosepsis syndrome. [46] The diagnosis is made by first considering aspirin ingestion in the differential diagnosis of patients presenting with noncardiogenic pulmonary edema or a sepsis-like picture and then determining the serum salicylate level. Respiratory alkalosis is typically seen with serum salicylate levels of 35 mg/dL (therapeutic range: 10 to 20 mg/dL) while noncardiogenic pulmonary edema occurs at serum levels of 45 mg/dL or higher. Although the pathogenesis of aspirin-induced noncardiogenic pulmonary edema is unclear, it likely results from increased capillary permeability from toxic levels of salicylates. Management is based upon drug withdrawal and supportive care, often in the intensive care unit with the patient on mechanical ventilation. Alkaline diuresis should be performed as soon as the diagnosis is suspected to enhance renal clearance and thereby reduce the serum salicylate level. Hemodialysis is reserved for patients with aspirin-associated seizures, refractory acidosis, coma, or very high salicylate levels (80 to 100 mg/dL). Outcome is generally favorable in young patients with an acute salicylate overdose. However, there is a high mortality in older patients with multiple medical problems who have chronically ingested salicylates and have a more subtle presentation.

Gold: Gold has been widely used for decades in the management of chronic inflammatory conditions, most notably, rheumatoid arthritis, but also pemphigus, psoriatic arthritis, bronchial asthma, and ankylosing spondylitis. Both the oral (aurano-

fin) and the IM (gold sodium thiomalate) preparations can induce chronic pneumonitis/interstitial fibrosis. Bronchiolitis obliterans, in the presence or absence of organizing pneumonia, occurs less frequently. Interstitial lung disease due to gold therapy can be distinguished from the patient's underlying rheumatoid lung disease by the following: (1) an acute onset of dyspnea and a nonproductive cough, (2) fever (> 38°C), (3) skin rash, (4) crackles on chest examination, (5) absence of finger clubbing or subcutaneous nodules, (6) presence of blood eosinophilia, proteinuria or liver dysfunction, (7) bronchoalveolar lavage fluid (BALF) lymphocytosis with a predominance of CD8 (suppressor) cells typical of a hypersensitivity-type reaction, (8) alveolar opacities in a nonbasilar distribution, and (9) HRCT scan that shows bronchovascular, rather than peripheral, infiltrates. [47] A favorable clinical response typically occurs after drug withdrawal and a course of corticosteroids. Recurrent disease has been documented following re-treatment which is not warranted.

NSAIDs: NSAIDs are among the most commonly prescribed drugs since they are widely used in the management of an array of rheumatologic disorders as well as for minor musculoskeletal pain in healthy individuals. Similar to salicylates, NSAIDs can precipitate asthma in aspirin-sensitive individuals as well as noncardiogenic pulmonary edema. Ophthalmic NSAIDs also can trigger bronchospasm. Nearly every type of NSAID can induce a hypersensitivity-type reaction that may be associated with PIE. In general, prompt resolution occurs with drug withdrawal and, rarely, a course of corticosteroids is required.

Methotrexate: (see chemotherapy section)

Penicillamine: Penicillamine is an antiinflammatory, antifibrotic, and copper-chelating agent that is used in the treatment of rheumatoid arthritis, scleroderma, primary biliary cirrhosis, and Wilson's disease. The manifestations of penicillamine-induced pulmonary toxicity include: (1) interstitial pneumonitis/fibrosis, (2) bronchiolitis obliterans, in the presence or absence of organizing pneumonia, (3) drug-induced SLE, and (4) alveolar hemorrhage due to a pulmonary-renal syndrome.

Patients with penicillamine-induced interstitial pneumonitis/fibrosis generally present with insidious onset of dyspnea and cough associated with restricted lung volumes and a reduced DLCO. A subset of patients present with a hypersensitivity-type reaction associated with peripheral blood eosinophilia and elevated serum IgE levels. As with gold therapy, it can be challenging to distinguish drug-induced pulmonary toxicity from the patient's underlying collagen vascular disorder.

The incidence of penicillamine-induced bronchiolitis obliterans is unknown but is estimated to occur in < 1% of patients with rheumatoid arthritis receiving this therapy. There are no clear risk factors. Patients present with a subacute onset of dyspnea, cough, and wheeze. The chest film reveals hyperinflation in the absence of infiltrates while PFTs confirm the presence of increased lung volumes as well as airflow limitation without a bronchodilator effect. Lung biopsies from these patients reveal bronchiolar constriction due to mononuclear inflammation and fibrosis. Management centers on drug withdrawal, supportive therapy, and consideration of a trial of corticosteroids, azathioprine or cyclophosphamide. However, there are no data demonstrating the value of immunosuppressive therapy. The prognosis from penicillamine-induced bronchiolitis obliterans is poor; nearly 50% die while the remainder have a very poor quality of life due to a severe permanent residual obstructive impairment.

Penicillamine rarely induces Goodpasture's syndrome consisting of diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis due to autoantibodies directed against components of the alveolar and glomerular basement membranes. There are case reports of this syndrome occurring after penicillamine was used to treat rheumatoid arthritis as well as Wilson's disease demonstrating that it is not simply due to the patient's underlying collagen vascular disease. Typically the serum ANA is elevated but the double-stranded DNA antibodies seen in classical SLE are negative. However, it is important to consider SLE or an ANCA-related vasculitis in the differential diagnosis since a number of these patients will not have serum and tissue anti-glomerular basement membrane antibodies. Despite drug withdrawal and corticosteroids, the mortality is nearly 50% and there is a high incidence of progression to chronic renal failure necessitating chronic dialysis.

Anti-Microbial Drugs

Antibiotic-Induced Hypersensitivity-Type Disease: The most common antibiotics causing a hypersensitivity-type lung reaction in the presence of PIE

include: β-lactam and sulfa antibiotics. Less commonly fluoroquinolones, tetracycline, erythromycin, nitrofurantoin, isoniazid, para-aminosalicylic acid and ethambutol cause this type of a reaction. There are no known risk factors and most reactions are idiosyncratic. Typically the patients present over a period of 1 to 4 weeks (can be delayed up to 1 year) with minimal, nonspecific respiratory complaints. Prompt resolution occurs with drug withdrawal perhaps with a short course of corticosteroids and antihistamines.

Nitrofurantoin: Nitrofurantoin has been used for decades in the management of acute urinary tract infections and as chronic suppressive therapy for patients with asymptomatic bacteruria. Nitrofurantoin has two main distinct adverse pulmonary manifestations: (1) acute hypersensitivity-type reaction and (2) chronic pneumonitis / fibrosis that mimics IPF. Alveolar hemorrhage and noncardiogenic pulmonary edema have also been described but are less common. The incidence of nitrofurantoin-induced adverse pulmonary effects is not firmly established. One study showed that the nitrofurantoin-induced acute hypersensitivity-type reaction that was severe enough to warrant hospitalization occurred in one in 5000 new drug administrations while the chronic form occurred in one in 50,000. [48]

Acute nitrofurantoin pulmonary toxicity very rare (< 0.1%) side effect occurs within 1 month of the first dose in 86% of the patients. Symptoms consist of dyspnea, cough, fever, chest pain, and a macular-papular skin rash. There is an elevated erythrocyte sedimentation rate (ESR) and peripheral blood eosinophilia in most patients. The chest radiograph shows a mixed alveolar / interstitial infiltrative pattern but is normal in 18% of patients. One third of patients have a small pleural effusion. PFTs typically reveal a restrictive pattern with a reduced DLCO. Although the diagnosis is generally made clinically, lung biopsy and bronchoalveolar lavage fluid (BALF) should be obtained in any patient in whom infection, metastatic tumor and / or an inflammatory condition are in the differential diagnosis. Histopathologic findings include interstitial inflammation with lymphocytes and plasma cells and, in the more severe cases, alveolar edema, hyaline membranes and hemorrhage. The prognosis is generally favorable with drug withdrawal and, occasionally, corticosteroids. Although some patients develop ARDS, the overall mortality rate is under 1%. [49]

Chronic nitrofurantoin pulmonary toxicity occurs in elderly patients treated with chronic suppressive therapy for asymptomatic bacteruria. Although much less common than the acute form, it is similar to the acute form in that patients present with dyspnea and cough but, in contrast, fever and rash are uncommon. Unlike the acute form, patients with the chronic form of disease have systemic complaints of fatigue and weight loss and infrequently have an elevated ESR and peripheral blood eosinophilia. Low-level elevations of the serum ANA and rheumatoid factor can be seen similar to patients with IPF. The chest radiograph shows a bilateral interstitial infiltrative pattern typically without pleural effusions. PFTs generally reveal a restrictive pattern with a reduced DLCO. As with the acute form, the diagnosis is usually made on clinical grounds. However, lung biopsy and BALF are indicated in any patient who might have an infection, metastatic tumor and / or an inflammatory condition. The characteristic histopathologic findings include lymphocytic interstitial inflammation along with interstitial and alveolar fibrosis that can be indistinguishable from the usual interstitial pneumonitis form of IPF. Unlike the generally reversible acute form of the disease, three quarters of patients with chronic nitrofurantoin pulmonary toxicity fail to improve at all or are left with substantial residual disease despite drug withdrawal and a trial of corticosteroids. The overall mortality rate is nearly 8%. [49]

Sulfasalazine/Mesalamine: Sulfasalazine, an antibiotic used in the management of inflammatory bowel disease, can cause BOOP, PIE, pulmonary fibrosis and bronchospasm. [50] Sulfapyridine, which is the carrier component of sulfasalazine, is responsible for the majority of the side effects. However, mesalamine, the clinically active component, can also induce pulmonary adverse side effects.

Pentamidine: Pentamidine can cause bronchospasm when given by either the IV or nebulized route. The adverse effect can be prevented by pretreatment with β-agonists or ipratropium.

Cardiovascular Drugs

Amiodarone: Amiodarone is an effective agent for treating ventricular and supraventricular arrhythmias that are refractory to other drugs. However, the utility of this drug is limited by adverse pulmonary effects that can occur in 5% to 10% of

patients as well as toxicity to the eyes, thyroid gland, liver, gastrointestinal tract, and nervous system. The adverse effects of amiodarone are typically associated with a high daily dose (> 400 mg/d) and a prolonged duration of therapy (> 12 months). A meta analysis of randomized, placebo-controlled low-dose amiodarone efficacy trials involving 1,465 patients receiving < 400 mg/d of amiodarone for a minimum of 12 months demonstrated a trend toward increased pulmonary toxicity compared to those patients receiving placebo (odds ratio: 2.0, 95% confidence interval 0.9-5.3; p = 0.07) but this difference did not reach statistical significance. [51] In contrast, compared to placebo, low-dose amiodarone did increase pulmonary toxicity (1.2% vs. 3.8%, respectively) in the Canadian Myocardial Infarction Amiodarone Trial. [52]

The mechanisms underlying amiodarone-induced pulmonary toxicity are not firmly established. As reviewed elsewhere, [53] several theories that are not mutually exclusive have been implicated including: (1) direct cellular damage in part due to alveolar epithelial cell apoptosis, (2) enhanced phospholipidosis, (3) immunologic injury, (4) ROS-induced damage, (5) alterations in membrane properties, (6) increased intracellular calcium in vascular endothelial cells, (7) activation of G proteins, and (8) inhibition of pulmonary epithelial cell sodium-potassium ATPase. Amiodarone has a large volume of distribution with a very long half-life of 30 to 60 days. Thus, the antiarrhythmic as well as the adverse effects of amiodarone will persist for weeks to months after the drug is withdrawn. Amiodarone is an iodine-containing phospholipase inhibitor that causes lipid accumulation in nearly all tissues, especially the lungs, skin and liver. This blockade results in the accumulation of undigested surfactant phospholipids in the lung, a feature seen in virtually all patients receiving the drug.

The histologic features of amiodarone-induced pulmonary toxicity include: (1) accumulation of foamy macrophages with characteristic lamellated inclusions in the interstitium and alveolar spaces, (2) hyperplasia of alveolar type II cells, and (3) widening of the alveolar septa with infiltration of lymphocytes, plasma cells, eosinophils, and neutrophils. Edema, intra-alveolar fibrin exudation, lamellar inclusions in pulmonary endothelial cells, bronchiolar epithelial cells and type II cells, and fibrosis can also occur.

The clinical and laboratory manifestations of amiodarone-induced pulmonary toxicity include: (1) interstitial pneumonitis/fibrosis, (2) ARDS, (3) BOOP, (4) mass lesions that can cavitate, (5) eosinophilic pneumonia, (6) diffuse alveolar hemorrhage, and (7) pleural effusions. Uncommon reactions include hypersensitivity pneumonitis, alveolar hypoventilation, and bronchospasm. The patients typically present with an insidious onset of a nonproductive cough and dyspnea with radiographic evidence of asymmetric chronic pneumonitis/fibrosis and an elevated ESR. Occasionally ill-defined alveolar infiltrates, a lung mass or pleural effusions may be seen. Risk factors for amiodarone-induced adverse pulmonary side effects are not firmly established but some that have been implicated include: (1) maintenance dose > 400 mg/d, (2) angiography–acute lung injury, and (3) cardiothoracic surgery–ARDS. Total cumulative dose or serum levels of amiodarone are not useful. Further, a reduction in the D_{LCO} and increased gallium uptake may support a clinical diagnosis but are not reliable predictors of pulmonary toxicity in the absence of clinical and radiographic abnormalities.

The diagnosis of amiodarone-induced pulmonary toxicity is one of exclusion, especially heart failure, pulmonary embolism, infection, and other inflammatory interstitial diseases (*eg*, BOOP, chronic eosinophilic pneumonia). Chest CT scans may reveal high attenuation areas due to the iodine present in amiodarone. However, this is a nonspecific finding that may be present in normal subjects. The typical PFT abnormalities include a reduction in the D_{LCO} and reduced lung volumes. Although a decreased D_{LCO} is a nonspecific finding seen in all patients with amiodarone-induced disease, a normal D_{LCO} suggests that heart failure, rather than amiodarone, may account for the patients respiratory symptoms. Bronchoscopy may be necessary to exclude infection. KL-6, a high molecular weight glycoprotein secreted by alveolar type II cells, is a potentially useful serum marker that is elevated (> 500 U/mL) in patients with interstitial lung disease due to IPF, radiation, as well as amiodarone. [54,55] Serum KL-6 levels are typically < 500 U/mL in patients with congestive heart failure and pneumonia. Although further studies are necessary to corroborate these small observational studies, the sensitivity and specificity of an elevated serum KL-6 in identifying interstitial disease approaches 94% and 96%, respectively. [54,55]

Management of amiodarone-induced pulmonary toxicity includes drug withdrawal and initiation of a new antiarrhythmic agent or implantation of an automatic cardioverter/defibrillator if required. A trial of corticosteroids is often used in symptomatic patients but the efficacy of steroids is not established. Radiographic resolution generally occurs over 2 months and patients are treated for at least 6 months to reduce the likelihood of relapse. [56] Recurrent amiodarone pulmonary toxicity also can occur. If amiodarone is the only effective agent in a patient with life-threatening arrhythmias, the dose must be reduced to the minimum that is effective (ideally < 400 mg/d) and corticosteroids added.

ACE Inhibitors: Cough occurs in up to 5% to 15% of patients receiving any type of ACE inhibitor. [5,57] The cough generally appears from 1 to 2 months up to 1 year after initiating therapy. Patients without asthma who develop ACE inhibitor-induced cough, as compared to those without cough, are slightly more sensitive to methacholine. However, ACE inhibitors do not consistently cause airways obstruction nor are patients with asthma at an increased risk. [58] Although the mechanism of ACE inhibitor-induced cough is not firmly established, it likely involves blocking the metabolism of cough-inducing neuropeptides such as substance P and bradykinin. [59] Before extensive testing is performed to evaluate the source of a cough in a patient taking ACE inhibitors, the drug should be discontinued. Patients with an ACE inhibitor-induced cough will generally show resolution within 1 to 4 days. Management is simple—avoid all ACE inhibitors. Patients can be switched to an angiotensin II receptor antagonist (*eg*, losartan) which can rarely induce cough. [60] However, losartan can induce angioedema in a manner similar to ACE inhibitors. [61] If ACE inhibitors are required for management of a patient's cardiovascular disease and there are no alternative agents, then the cough can be partly controlled with oral theophylline or nebulized cromolyn or lidocaine. [62,63]

Angioneurotic edema is a rare adverse effect of ACE inhibitors (0.1% to 0.2% of patients) that is potentially life-threatening. [64] It is manifest by swelling of the tongue, lips, and mucous membranes within hours or at most one week after initiating treatment and can rapidly evolve into acute respiratory distress, upper airway obstruction, and death. Patients with a history of idiopathic angioneurotic edema should avoid ACE inhibitors since they may be at increased risk. The mechanism underlying this serious adverse effect is unknown but immune pathways, increased tissue levels of bradykinin or histamine, and/or a deficiency of complement 1-esterase inactivator have all been implicated. Management of ACE inhibitor-induced angioedema includes drug withdrawal, attention to airway patency, and, if severe, subcutaneous injection of epinephrine (0.01 mL/kg body weight of 1:1000 solution) every 15 to 20 minutes along with IV saline to correct hypotension. Diphenhydramine (1-2 mg/kg up to 50 mg IV or IM) and steroids are also useful.

β-Blockers: β-Adrenergic receptor blockers administered by any route (*eg*, oral, IV, or ophthalmic solutions) can precipitate bronchospasm, especially in patients with asthma or COPD. Propranolol, a nonselective β-blocker, causes dose-dependent reductions in air flows and should be avoided in patients with asthma or COPD. [65] Timolol, a nonselective β-blocker used in ophthalmic solutions, has predictable adverse effects on these patients similar to propranolol and should also be avoided. Severe bronchospasm and sporadic deaths have been reported with nonselective β-blocker ophthalmic solutions. Physicians should specifically inquire about ophthalmic solutions in patients with glaucoma presenting with respiratory complaints since most patients do not consider these as "drugs". Selective β_1-blockers (*eg*, atenolol and betaxolol ophthalmic solution) are better tolerated in patients with airflow obstruction. However, caution is warranted since β_1 selectivity is relative since β_1-selective inhibitors, especially in high doses, can block β_2-adrenergic receptors and trigger bronchospasm. Esmolol is the drug of choice in critically ill patients with asthma or COPD that require a β-blocker (*eg*, unstable angina) because it is an IV selective β_1-blocker in doses < 300 μg/kg/min and has an extremely short half-life (approximately 9 min).

Illicit Drugs

The use of illicit drugs continues to be a significant healthcare problem of epidemic proportions worldwide. Respiratory symptoms in patients using illicit drugs may be due to a wide array of pulmonary disorders including: (1) alveolar hypoventilation (hypercarbic respiratory failure), (2) aspiration, (3) noncardiogenic pulmonary edema, (4) barotrauma (*eg*, pneumothorax, pneumomediastinum, pneu-

moperitoneum), (5) endocarditis / septic emboli, (6) foreign body granulomatosis, (7) PIE, (8) BOOP, (9) alveolar hemorrhage, (10) bronchospasm, (11) interstitial pneumonitis/fibrosis, and (12) HIV-associated infections. Knowledge about the drugs used, route of administration, and the presenting clinical syndrome helps narrow the broad differential diagnosis in these patients.

Noncardiac Pulmonary Edema: Noncardiac pulmonary edema is an infrequent complication of heroin, cocaine, or methadone abuse, but heroin is by far the most common cause. [66] Naloxone, an opiate antagonist, also causes a similar syndrome. [67] There are no known risk factors for opiate-induced pulmonary edema. Although the pathogenesis is not established, several mechanisms have been proposed including: (1) altered alveolar/capillary permeability, (2) neurogenic pulmonary edema, (3) direct opiate cytotoxicity, (4) drug hypersensitivity, and (5) hypoxemic alveolar injury. However, none of these have been adequately tested in animal models or human studies. Typically, patients present within minutes to hours (at most 24 h) of use with dyspnea, reduced respirations and mental status, miotic pupils, and a chest radiograph demonstrating perihilar alveolar infiltrates in a "batwing" distribution. Pathologic studies from autopsies reveal changes similar to ARDS such as: (1) alveolar edema and hemorrhage, (2) diffuse alveolar damage, (3) hyaline membranes, (4) interstitial inflammatory cell infiltrates, and (5) type II cell hyperplasia. Management centers on supportive care including mechanical ventilation, which is needed in 40%. [66] Unlike other causes of ARDS, the prognosis in opiate-induced noncardiogenic pulmonary edema is good, with resolution of the pulmonary edema over 48 to 72 h, and nearly all patients survive.

Cocaine: Cocaine, an alkaloid extracted from the leaves of *Erythroylon coca* sp, is a sympathomimetic agent that causes topical anesthesia and central nervous system stimulation. In 1995, an estimated 1.5 million people in the United States regularly used cocaine. [68] Cocaine hydrochloride, the salt form that can be injected IV or rapidly absorbed across the nasal mucosa, causes pulmonary manifestations similar to IV opiates (*eg*, heroin). A unique feature of cocaine is that it causes nasal mucosal vasoconstriction that can result in ischemic necrosis and perforation of the nasal septum. Free-base cocaine, which is derived from the alkaline crystallization of the salt, vaporizes when heated and is rapidly absorbed across the respiratory membranes. The term "crack" refers to the popping sound that occurs when cocaine crystals are heated.

Free-base crack cocaine smoking causes a distinct set of pulmonary abnormalities that are termed "crack lung". [69] These patients typically present with cough, chest pain, dyspnea, hemoptysis, and wheezing. Chest pain from either a pulmonary or cardiac origin occurs in approximately 20% to 40% of cocaine users. Cocaine can induce direct coronary artery vasoconstriction. [70] Unlike IV crack users, patients with crack lung from inhalation may have a cough productive of black, soot-like material (approximately 10% to 33%), bronchospasm (approximately 50%), and thermal burns to the upper and lower airways. Other pulmonary complications of crack cocaine use include PIE, BOOP, pulmonary hypertension, alveolar hemorrhage/hemoptysis, and barotrauma (*eg*, pneumothorax, pneumomediastinum, and pneumoperitoneum). Barotrauma is likely due to the Valsalva maneuver that is performed to enhance alveolar-capillary cocaine absorption. The D_{LCO} is either normal or mildly reduced within weeks to months after using crack cocaine. [70,71] The reason for the reduction in D_{LCO} is unclear, but may reflect loss of alveolar-capillary surface area. [69,70] Recent evidence demonstrate that crack users have increased lower respiratory tract iron and ferritin levels that may contribute to lung injury via oxidant-induced mechanisms. [72]

Foreign Body Granulomatosis: Foreign body granulomatosis is due to IV injection of insoluble particulate contaminants used to "cut" street heroin or from talc or cellulose in crushed tablets (*eg*, amphetamines, methadone, or hydromorphine). Initially patients may be asymptomatic despite an abnormal chest radiographs showing reticular nodular interstitial infiltrates. However, relentless progression of the infiltrates generally occurs accompanied by increasing dyspnea. The nodules may coalesce similar to silicosis resulting in progressive massive pulmonary fibrosis with surrounding cysts and bullae. Notably, PFTs reveal airways obstruction, rather than restriction, that progresses to severe disease with a reduced D_{LCO}. [73] The lungs demonstrate vascular and interstitial noncaseating giant cell granulomatous infiltrates containing birefringent talc crystals. As the disease progresses, parenchymal destruction and pulmonary hypertension occur leading to re-

spiratory failure/cor pulmonale. The poor outcome noted in most patients is generally not altered by corticosteroids.

Miscellaneous Agents

Contrast Media: Both the ionic and nonionic forms of contrast media can induce bronchospasm and a reduction in airflow. Typically this occurs within 5 minutes and resolves within 30 minutes of infusion. Contrast media rarely induces potentially fatal leukostasis in the pulmonary arterioles and capillaries. [74] This occurs within minutes to an hour after injection resulting in dyspnea and hypoxemic respiratory failure due to noncardiogenic pulmonary edema. Although the mechanism is unclear, a complement-mediated pathway has been implicated. Management centers on supportive care, high-dose corticosteroids, IV diphenhydramine, and heparin.

Tocolytic Agents: Tocolytic agents, such as albuterol, terbutaline, ritodrine, isoxuprine, and salbutamol, are β-adrenergic agents that are used to inhibit uterine contractions during premature labor. Although acute pulmonary edema reportedly occurs in 0.5% to 5% of patients, in a recent study of 8,700 patients there was an incidence of only 0.32%. [75] The mechanism of pulmonary edema is not established but is believed to be due to β-adrenergic-induced peripheral vasodilation and increased intravascular volume. After the tocolytic drug is discontinued the vascular tone normalizes, thereby promoting fluid movement into the extravascular spaces, including the alveoli. Left ventricular function and pulmonary wedge pressure are usually normal. Patients typically present during or within 12 h of delivery (rarely beyond 12 h postpartum) with acute onset of dyspnea, cough productive of pink-tinged sputum, chest pain, tachycardia, tachypnea, hypoxemic respiratory failure and diffuse alveolar infiltrates on chest radiograph. The differential diagnosis includes: gastric acid aspiration, cardiac pulmonary edema, pulmonary embolism, amniotic fluid embolism, and peripartum cardiomyopathy. The transthoracic echocardiogram is generally normal. Management involves supportive care and diuresis. The prognosis is generally favorable, with intubation/mechanical ventilation required in under 10% and a mortality rate of nearly 3%. [76]

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Annotated Bibliography

Internet Site

Foucher P, Camus P, the GEPPI. Pneumotox on line. http://www.pneumotox.com

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