Chapter e48: Drug-Induced Pulmonary Diseases

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 7, Drug-Induced Pulmonary Disease.

KEY CONCEPTS

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1. The most common drug-induced pulmonary diseases (DIPDs) are interstitial pneumonitis and pulmonary fibrosis.
2. DIPD is a diagnosis of exclusion.
3. The occurrence of DIPD is unpredictable, but there are agent- and population-specific risk factors, including extremes of age, the dose of the offending agent, and preexisting lung conditions.
4. Prevention includes avoiding causative agents in high-risk patients.
5. Early recognition of DIPD is essential to improving long-term outcomes.
6. Management of DIPD commonly involves discontinuation of the causative agent and treatment with corticosteroids.

BEYOND THE BOOK

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Watch the video entitled "Lung Disease and Double Lung Transplantation" at Stanford: "Jen Julian's Story" (https://stanfordhealthcare.org/stanford-health-care-now/2012/julian-interstitial-lung-disease.html) from Stanford Health Care. This 5-minute video shares the patient perspective of living with a severe interstitial lung disease ultimately necessitating transplantation. While the etiology of this patient's chronic hypersensitivity pneumonitis is believed to have been from an inhaled environmental exposure, certain medications can cause a similar condition. The video adds a personal connection to the impact healthcare providers can have on patients with DIILD.

INTRODUCTION

Clinicians should be familiar with drug-induced pulmonary diseases (DIPD) to promptly identify cases and manage complications to minimize potential morbidity and mortality. In the United States, over 2 million adverse drug reactions (ADRs) and 100,000 drug-associated deaths are reported annually. Pulmonary complications may represent the largest proportion of fatalities from ADRs.[1,2] Certain medications and patient-specific situations carry a greater risk for pulmonary ADRs. As an example, up to 10% of patients receiving chemotherapy and up to 40% of patients receiving chemotherapy with bleomycin may develop pulmonary toxicity.[1] The Website pneumotox.com and the companion Android and iPhone applications list over 1,500

medications reported to cause DIPD, 650 patterns of DIPD, and 10,000 references. This resource functions as a free searchable database for clinicians. The true rate of drug-induced reactions is likely underestimated because there is a challenge in reaching a definitive diagnosis of DIPD, and estimates largely rely on case reports and observational studies.

DIPD may result from direct or indirect drug effects. Direct effects may present as an idiosyncratic reaction or through direct pulmonary toxicity from a drug or its metabolites. DIPD can affect a variety of pulmonary tissues and structures. The clinical presentation and patient symptoms associated with DIPD are often nonspecific. Patients may complain of pleuritic chest pain, dyspnea, cough, wheezing, and fever. Symptoms may be present at rest or during activity. When DIPD affects the vasculature, it often presents with pulmonary hemorrhage or vasculitis, hemoptysis, hematoma, or alveolar hemorrhage. DIPD is a diagnosis of exclusion. It should be considered when a patient has had a known drug exposure and subsequently develops new signs and symptoms consistent with DIPD clinical presentation. The resolution of symptoms after drug withdrawal is particularly informative. Radiographic imaging, including X-rays and CT scans, can help rule out other potential causes of pulmonary disease and establish the diagnosis of DIPD.[3] Table e48-1 summarizes DIPD diagnostic considerations and general management strategies.

TABLE e48-1

Summary of Drug-Induced Pulmonary Disease – Presentation, Diagnosis, Causative Agents, and Management

Disease	Presentation	Key Diagnostic Components	Causative Agents	Management
Reactions involving the interstitium				
Interstitial pneumonitis and fibrosis[18,53]	Can be acute or chronic Dyspnea, cough, Clubbing, crackles	History of drug exposure Bilateral localized or diffuse opacities and reduced lung volumes on CXR "Honeycombing" on chest CT Elevated ESR with amiodarone Restrictive/normal PFTs	Amiodarone, bleomycin, gemcitabine, carmustine, cyclophosphamide, taxanes, EGFR inhibitors, dasatinib, mTORi, busulfan, sulfasalazine, methotrexate, leflunomide, phenytoin, nitrofurantoin, daptomycin	Drug discontinuation, dose reduction or interruption Corticosteroids Supplemental oxygen
Organizing pneumonia[22]	Nonproductive cough, shortness of breath, bilateral crackles Less commonly, fever	History of drug exposure Bilateral patchy infiltrates on CXR Rarely, eosinophilia present	Amiodarone, bleomycin, minocycline, nitrofurantoin, gold, sulfasalazine, interferon alpha, carbamazepine, L-tryptophan, cocaine	Drug discontinuation Corticosteroids Supplemental oxygen
Eosinophilic pneumonia[7]	Can be acute or chronic Dry cough, dyspnea, chest pain, fever	History of drug exposure Bilateral reticular ground-glass opacities on chest	Daptomycin, mesalamine, sulfasalazine, minocycline	Drug discontinuation Corticosteroids Omalizumab Supplemental

		CT Acute: elevated peripheral neutrophils with high BAL eosinophils Chronic: elevated peripheral eosinophils, elevated IgE, CRP, ESR		oxygen Acute: mechanical ventilation common
Hypersensitivity pneumonitis[15,36]	Usually, immediate Urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, and bronchospasm	History of drug exposure Based on presentation	NSAIDS (dose-dependent), methotrexate, nitrofurantoin	Drug discontinuation Corticosteroids Antihistamines Supplemental oxygen
Noncardiac pulmonary edema[35]	Dyspnea, chest discomfort, tachypnea, hypoxemia	History of drug exposure Interstitial and alveolar infiltrates Laboratory values and PFTs not helpful	Cytarabine, gemcitabine, immune globulins, interleukin, methotrexate, mitomycin muronomab-CD3, pentostatin, tretinoin, tricyclic antidepressants, aspirin (dose-dependent), methadone, morphine, oxytocin, protamine, heroin, cocaine, cytarabine, infliximab, GM-CSF, vinca alkaloids, amiodarone, nitrofurantoin, talc	Drug discontinuation Diuretics Supplemental oxygen Mechanical ventilation ? Role corticosteroids
Diffuse alveolar damage[54]	Typically acute, can be subacute Hemoptysis, cough, dyspnea, acute respiratory failure	History of drug exposure New or unexplained infiltrates on CXR Dropping hematocrit Hemorrhagic BAL	Chemotherapy, all-trans-retinoic acid, propylthiouracil, penicillin, sulfasalazine, hydralazine, leukotriene antagonists, mitomycin, amiodarone, nitrofurantoin, crack cocaine, thrombolytics, anticoagulants, antiplatelet agents, dextran 70	Drug discontinuation Reversal of coagulation Corticosteroids for chemotherapy-induced Supplemental oxygen
Reactions involving the pleura				
Nonlupus-related pleural effusion[29]	Pleuritic chest pain, pleural effusions	History of drug exposure Pleural fluid	Sclerotherapy agents (most common), amiodarone, minoxidil, methysergide, bromocriptine, bleomycin, mitomycin,	Drug discontinuation Corticosteroids

		eosinophilia (nonspecific) Elevated peripheral eosinophils	procarbazine, methotrexate, cyclophosphamide, dasatinib	Supplemental oxygen
Lupus-related pleural effusion[29]	Pleuritic chest pain, pleural effusions	History of drug exposure Similar to idiopathic lupus Pleural fluid: exudative, ANA higher than serum values, lupus erythematosus cells may be present	Procainamide (most common), hydralazine, chlorpromazine, isoniazid, D-penicillamine, methyldopa, quinidine	Drug discontinuation Supplemental oxygen
Reactions without direct toxic effect to the lung tissue				
Bronchospasm[10]	Wheezing	History of drug exposure Based on presentation	Acetaminophen, aspirin, NSAIDs, beta-blockers, iodinated radiocontrast dye	Drug discontinuation Corticosteroids Supplemental oxygen
Cough[13]	Can occur within hours to months Persistent dry cough, “tickle” in throat	History of drug exposure Based on presentation	ACE inhibitors, calcium channel blockers, fentanyl, latanoprost ophthalmic	Drug discontinuation
Pulmonary arterial hypertension[24,39]	Dyspnea	History of drug exposure mPAP ≥25 mmHg at rest during RHC	Anorectic agents, amphetamines, dasatinib, selective serotonin inhibitors (risk to the newborn if mother taking)	Drug discontinuation Pulmonary vasodilators
Thromboembolic disorders[39,42]	Dyspnea	History of drug exposure Pulmonary embolism on chest CT	Bleomycin, cyclophosphamide, alkylating/alkylating-like agents, mitomycin, high-dose combined oral contraception, immune checkpoint inhibitors	Drug discontinuation Anticoagulation Thrombolysis Supplemental oxygen
Apnea[15,18,19]	Hypoventilation	History of drug exposure	Opioids, neuromuscular blockers	Dose reduction or

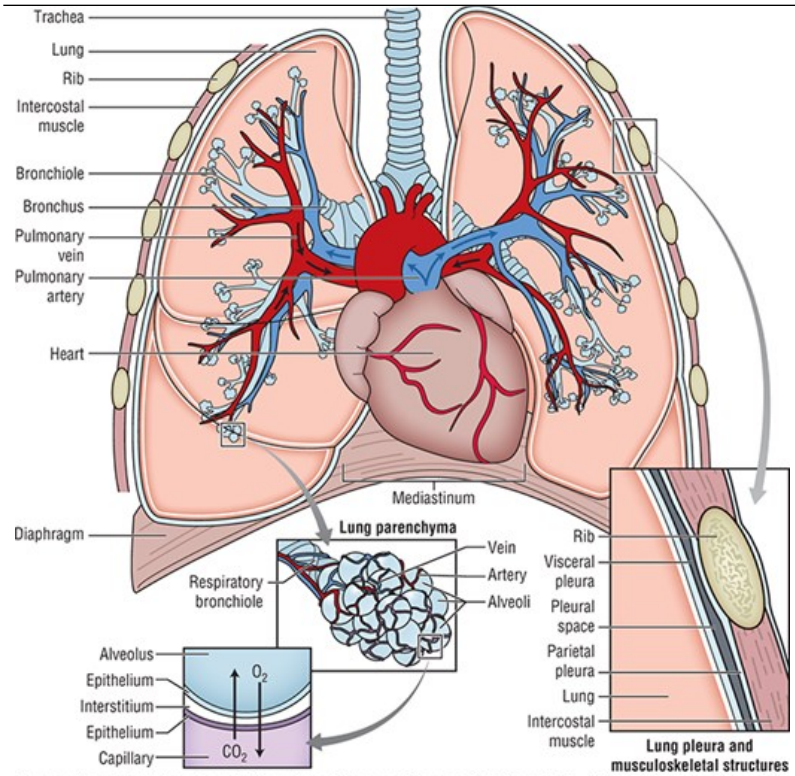
		Based on presentation		discontinuation of drug Naloxone (for opioids)
Chest wall rigidity[50]	Decreased compliance of chest wall, respiratory muscles, or laryngeal structures	History of drug exposure Based on presentation	Synthetic opioids (fentanyl, remifentanyl, methadone), also morphine	Dose reduction or discontinuation of drug

CXR, chest X-ray; CT, computerized tomography scan; ESR, erythrocyte sedimentation rate; PFTs, pulmonary function tests; EGFR, epidermal growth factor receptor; NSAIDS, nonsteroidal anti-inflammatory drugs; mTORi, mechanistic target of rapamycin inhibitors; CRP, c-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; BAL, bronchoalveolar lavage; ANA, antinuclear antibodies; mPAP, mean pulmonary arterial pressure; RHC, right heart catheterization.

The clinical spectrum of DIPD is heterogeneous; narrowing down the affected region of the lung can assist with identifying a distinct diagnosis and subsequent management approach. DIPD most frequently impacts the pulmonary parenchyma but can affect the pleura, airways, pulmonary vasculature, mediastinum, and neuromuscular respiratory system (see Fig. e48-1). Notable manifestations can include interstitial pneumonitis, fibrosis, pleural effusions, or drug-induced lupus.[3]

FIGURE e48-1

Depiction of lung anatomy involved in drug-induced reactions. The trachea and bronchi serve to transport air into the lungs. Smaller bronchioles may carry air or lead to gas exchange in alveoli. Lung parenchyma, sometimes referred to as lung interstitium, is involved in gas exchange and includes alveoli, interstitium, and capillaries. Lung pleurae are lubricated membranes that protect the lungs and aid in expansion and contraction. The inner membrane (visceral pleura) lines the lungs, the outer membrane (parietal pleura) lines the chest wall and the area in between is called the pleural space. The main muscle of breathing is the diaphragm; intercostal muscles may also contribute. The brainstem along with nerves and chemoreceptors (not shown) control breathing. Pulmonary vasculature includes veins, arteries, and capillaries which function to carry unoxygenated blood into the lungs and oxygenated blood out of the lungs. The mediastinum is the cavity containing extrapulmonary structures including the heart.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

DRUG-INDUCED REACTIONS

Reactions Involving the Interstitium

When considering ADRs with direct toxic effects on the lungs, drug-induced interstitial lung disease (DIILD) is the most common. Drugs are the primary cause of between 2.6% and 6.4% of interstitial lung disease (ILD).[20] Reactions involving the interstitium include pulmonary fibrosis, pneumonitis, organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonia, noncardiac pulmonary edema, and diffuse alveolar damage/diffuse alveolar hemorrhage (DAD/DAH). A causative agent can precipitate more than one type of interstitial reaction.

Interstitial Pneumonitis and Fibrosis

Incidence

The most common reactions involving the interstitium are interstitial pneumonitis and fibrosis. Agent-specific incidence of pneumonitis and/or fibrosis is described in "Causative Agents" section.

Presentation and Diagnosis

DIILDs are a heterogeneous set of disorders that may present acutely, subacutely, or chronically. Multiple methods of nomenclature and classification have been proposed.[21,22] Drug-induced interstitial pneumonitides commonly have histopathologic features of usual interstitial pneumonia or nonspecific interstitial pneumonia. Findings often overlap with those of drug-induced pulmonary fibrosis or idiopathic pulmonary fibrosis (IPF). Common acute signs and symptoms of interstitial pneumonitis include nonproductive cough and sudden onset dyspnea over a period of hours. Other manifestations of the acute form may include fever, rash, or eosinophilia. On the other hand, more chronic forms of the disease present as progressive breathlessness, which may lead to reduced capacity for physical activity.[1,5] During lung auscultation, most patients with interstitial pneumonitis or fibrosis will demonstrate crackles upon expiration. Digital clubbing may be detected in up to half of patients. Though not useful in making an initial diagnosis, once the disease progresses to fibrosis, cyanosis or signs of pulmonary hypertension may emerge.[1,5]

Imaging can be helpful in confirming the presence of ILD when considered in the context of other clinical features but is not useful for distinguishing the etiology of the disease. Initially, a chest radiograph may be used to exclude differential diagnoses such as infectious processes or pulmonary edema. If the disease progresses to fibrosis, radiography may show abnormalities such as decreased lung volumes or bilateral diffuse ground-glass opacities.[5] High-resolution computed tomography (HRCT) is the most sensitive imaging technique available for the detection of ILD, with up to 100% of patients showing abnormalities.[1] In an acute presentation, HRCT may reveal diffuse ground-glass opacity. In fibrosis, the hallmark pattern found on HRCT is "honeycombing," which results from the destruction of the alveolar structure, causing irregularly shaped enlarged airspaces.

Other non-imaging tests may be completed during the diagnostic workup. Pulmonary function tests (PFTs) may not be possible to obtain in patients with more progressive disease. If measured, spirometry can show a normal pattern initially or progress to a restrictive pattern. Restrictive lung disease is marked by a reduced total lung capacity and forced vital capacity on spirometry. Interstitial pneumonitis and particularly fibrosis often leads to impaired gas exchange in the pulmonary parenchyma, so the carbon monoxide diffusing capacity may also be reduced. Conventionally, arterial oxygen saturation may be easier to measure. Patients may have normal or low saturation at rest and commonly become hypoxemic upon exertion.[1,5] Laboratory tests are generally not helpful when investigating a diagnosis of DIILD though increased eosinophils or erythrocyte sedimentation rate (ESR) may be present in specific instances.[5] Bronchoscopy with bronchoalveolar lavage (BAL) can assist in ruling out malignancy or infection and can be relevant to DIILD diagnosis when used in conjunction with other presenting features. Cell differentials from BAL may point the clinician to a specific type of DIILD. For example, nonspecific interstitial pneumonia tends to have mixed cellularity on BAL, and pulmonary fibrosis may show a neutrophilic pattern.[1] There is limited evidence for the routine use of open lung biopsies in the investigation of DIILD. This procedure may be used to rule out other etiologies of disease or add valuable data when the diagnosis is uncertain but may be unsafe for patients with advanced disease.

Mechanisms of Toxicity

There are several proposed mechanisms for the pathogenesis of DIILD. While reliable evidence is lacking, the underlying pathophysiology shares a common pathway with IPF. Pathogenesis may differ across agents. Leading theories include oxidative stress and direct cellular injury, as depicted in Fig. e48-2.[5,23] Figure e48-3A visually depicts a normal alveolus and Fig. e48-3B depicts the parenchymal changes seen in fibrosis.

FIGURE e48-2

Schematic of proposed risk factors and mechanisms for the development of lung fibrosis. Risk factors may include genetic susceptibility, concomitant drugs, age, drug exposure, or preexisting lung disease. A direct toxic effect of oxidative stress causes damage to alveolar epithelial and endothelial cells. The damage leads to increased permeability, vascular leak, the release of inflammatory cells and mediators, and platelet activation with clot formation. In pneumonitis, inflammation may be temporary. In fibrosis, the damage is followed by the recruitment of fibroblasts, abnormal cellular repair, and apoptosis. Ultimately, there is an excess deposition of the extracellular matrix leading to remodeling, honeycombing, and fibrosis.

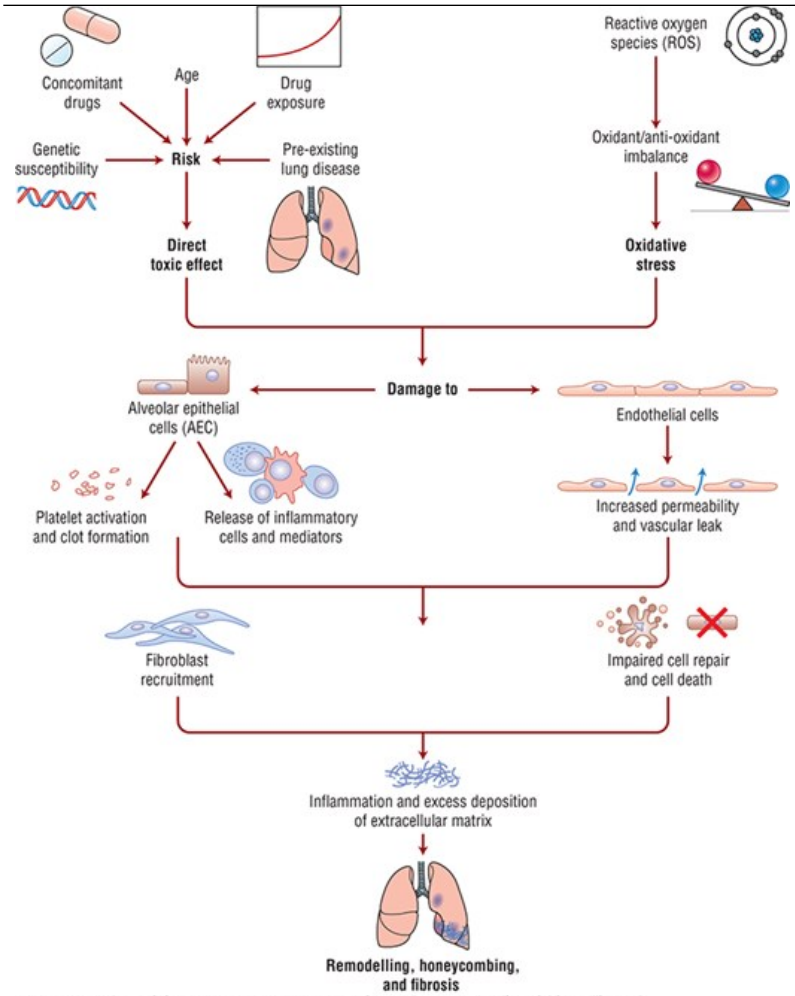
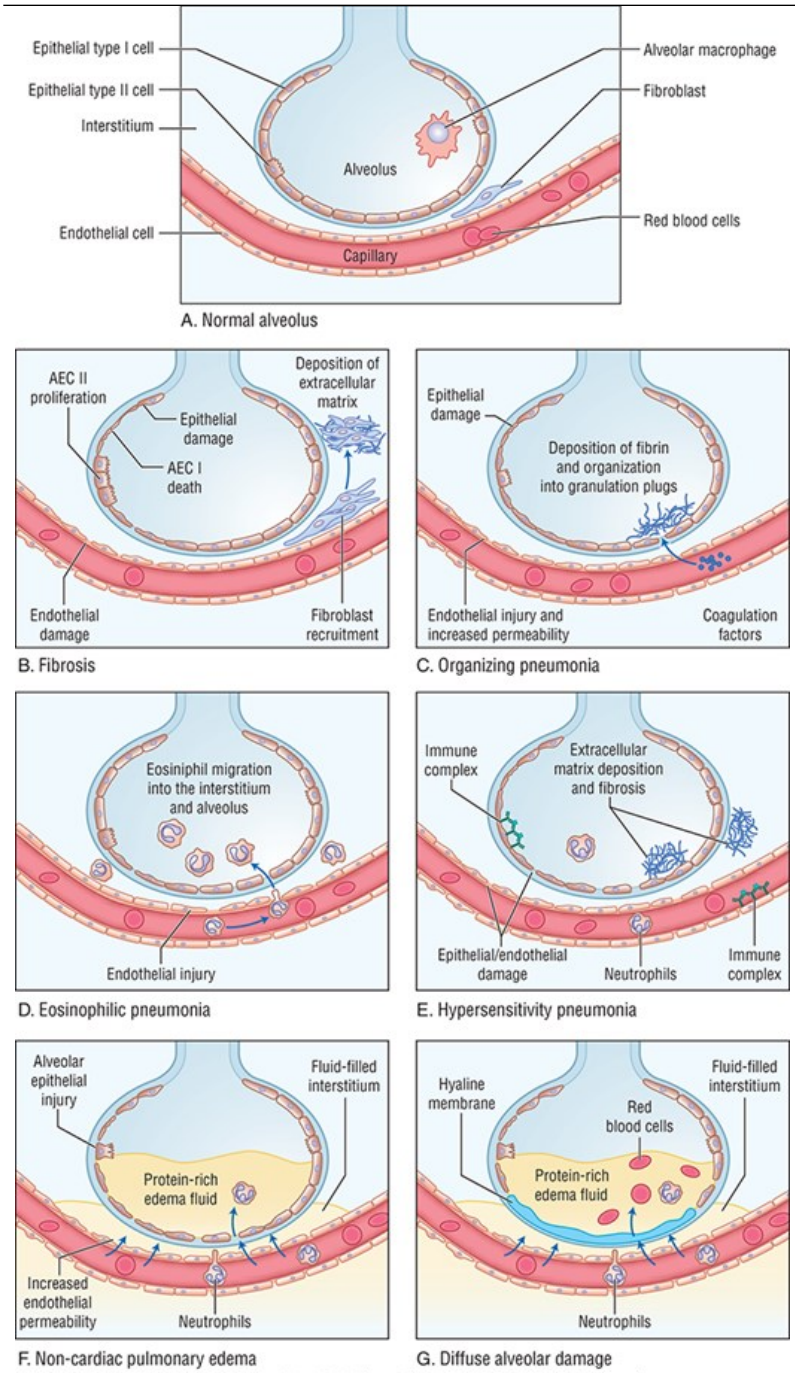


FIGURE e48-3

Visual representation of normal parenchyma and parenchymal abnormalities caused by six drug-induced lung disease processes. Panel A shows a normal alveolus with undamaged epithelium and endothelium. Panel B depicts fibrosis in which there is the deposition of extracellular matrix. Panel C depicts organizing pneumonia in which fibrin deposition is organized into granulation plugs in the alveoli. Panel D depicts eosinophilic pneumonia in which eosinophils migrate into the interstitium and alveolus. Panel E depicts hypersensitivity pneumonitis in which an agent triggers an immune-complex mediated or delayed hypersensitivity reaction leading to inflammation. Panel G depicts noncardiac pulmonary edema in which edema fills the interstitium and alveoli. Panel F depicts diffuse alveolar damage in which red blood cells and fluid fills the interstitium and alveoli; hyaline membranes, made from cellular debris, collect along the alveolar epithelium.



Causative Agents

Many medications have been implicated in interstitial pneumonitis and pulmonary fibrosis. As new drug molecules are developed, approved, and used in clinical practice, the list of causative agents will continue to grow. Conversely, the incidence of DIILD may decline for agents that are no longer favored in clinical practice. Most agents fall within one of several classes, including antimicrobial, antineoplastic, antirheumatic, and cardiovascular. While not exhaustive, the agent-specific mechanisms, presentation, incidence, and mortality rates are described for the most common causative agents.

Antimicrobial

Nitrofurantoin is an antibiotic often used to treat or prevent cystitis. This agent causes DIPD via oxidant/antioxidant imbalance.[5] The most commonly presenting reaction is acute eosinophilic pneumonia, which is described in the "Eosinophilic Pneumonia" section of this chapter. However, long-term use of nitrofurantoin can cause chronic interstitial pneumonia presenting as pulmonary fibrosis, which has been reported from 8 months to 16 years of treatment.[24] One registry showed that less than 10% of nitrofurantoin-associated DIPD present chronically but the mortality rate for this form was 8%.[25]

Antineoplastic

Bleomycin is an antibiotic and neoplastic agent used to treat several tumor types. The proposed mechanism of bleomycin-induced pneumonitis (BIP) is the induction of cytokines, inflammatory cells, and free oxygen radicals.[26] BIP is a well-known and common ADR of bleomycin therapy. It typically presents weeks to months after treatment initiation and may progress to fibrosis. The estimated incidence of BIP is 6.8% to 21%, with a reported mortality of up to 48%.[20]

Busulfan is an alkylating agent commonly used in conditioning regimens prior to hematopoietic stem cell transplantation. Pulmonary fibrosis due to busulfan, commonly referred to as "Busulfan Lung," is due to direct alveolar injury. The condition presents an average of 4 years after monotherapy use and months after high-dose use. Incidence has been reported to be approximately 6%.[27]

Carmustine is a nitrosourea used to treat certain lymphomas, myelomas, and brain tumors. Acutely presenting pneumonitis may occur months to years after initiating therapy; chronic pulmonary fibrosis may present years after therapy. Upper lung lobes tend to be most impacted. The estimated incidence of these reactions is 1.5% to 20%.[27]

Cyclophosphamide is an alkylating agent typically combined with other antineoplastic agents to treat malignancies. It is also used to treat certain inflammatory and autoimmune disorders. Early-onset pneumonitis generally presents within months of initiation and typically responds to glucocorticoids, whereas late-onset pneumonitis presents within months to years and is often progressive and permanent.[27] The cyclophosphamide-induced lung reactions are rare, with an estimated incidence of 1%.[5]

Epidermal growth factor receptor inhibitors (EGFRIs) such as erlotinib, gefitinib, mobocertinib, and osimertinib are small-molecule tyrosine kinase inhibitors used to treat non-small cell lung cancer. DIILD, which could present as pneumonitis, fibrosis, or DAD, most often develops within one month of treatment initiation. The incidence of DIILD with erlotinib and gefitinib is reported to be between 1.2% and 1.6% with a mortality rate of 22.8%.[20] The incidence of DIILD with mobocertinib and osimertinib is slightly higher at 3.3% to 4.3% though the mortality rate was significantly lower at 0.5% to 1.2%.[28,29] Monoclonal antibody EGFRIs such as cetuximab and panitumumab are primarily used to treat colorectal cancers. According to a postmarketing study in Japan, DIILD associated with these monoclonal antibodies has an incidence of around 1% and a mortality rate of up to 50%. The median onset of DIILD was reported to be about 3 to 4 months after therapy initiation.[20]

Immune checkpoint inhibitors (ICPis) target programmed cell death receptor 1 (PD-1) (eg, nivolumab, pembrolizumab), programmed cell death ligand 1 (PD-L1) (eg, avelumab, durvalumab), or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) (eg, ipilimumab) and are used to treat a wide array of malignancies. Pneumonitis occurred in less than 1% of trial participants receiving the anti-CTLA-4 drug ipilimumab whereas the incidence of this reaction in patients treated with anti-PD-1 or anti-PD-L1 therapy ranged from 0% to 10%. The median time to onset is reported to be about 3 months, though the use of ICPis in combination therapy may trigger earlier onset.[30]

Gemcitabine is a pyrimidine analog used alone or in combination with other agents to treat malignancies, including pancreatic, breast, ovarian, and non-small cell lung cancers. The mechanism of toxicity is from endothelial dysfunction after cytokine release. Gemcitabine is also a radiosensitizer. The onset of symptoms occurs an average of about two months after initiation of therapy. The incidence of DIILD was reported to be 1.1% to 1.9% in a retrospective study in Japan, but other studies found an incidence of up to 20% when used as part of a combination regimen. Mortality is generally low but may reach up to 22% in patients requiring hospitalization.[20,31]

Mechanistic targets of rapamycin inhibitors (mTORis) such as everolimus, sirolimus, and temsirolimus are used as rejection prophylaxis in solid organ transplantation as well as to treat certain tumors. The pathogenesis of mTORi-induced pneumonitis is hypothesized to be due to DAD from an autoimmune response or delayed hypersensitivity reaction. In phase II and III trials of patients treated with a mTORi for breast cancer, the incidence

of pneumonitis ranged from <0.5% to 42% and grade 3 or 4 pneumonitis ranged from 0% to 9%. In one trial, the median time to onset was 51 days in patients treated with daily everolimus and 104 days in patients treated with weekly everolimus. The patients treated with daily everolimus were about twice as likely to develop mTORi-associated pneumonitis than those treated with weekly regimens. Most cases resolve with discontinuation of the mTORi and/or treatment with corticosteroids.[4]

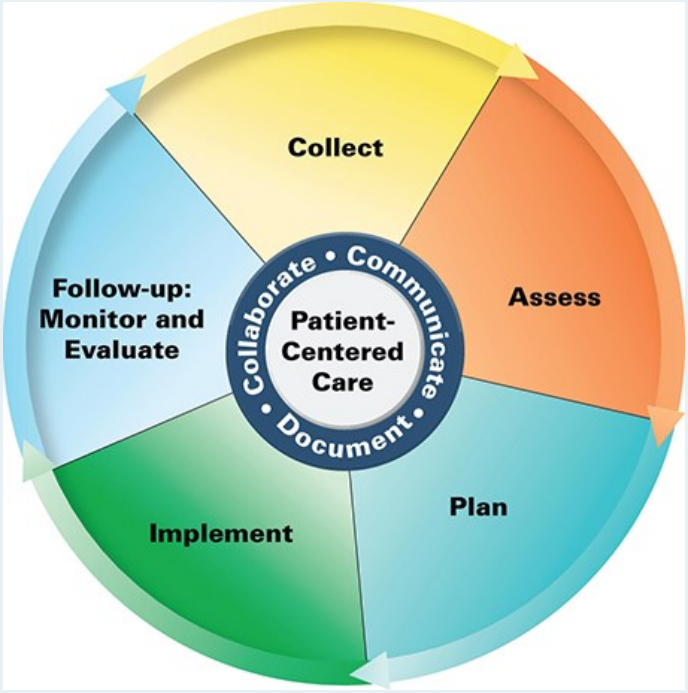
Taxanes such as paclitaxel, nanoparticle albumin-bound paclitaxel, and docetaxel are antimicrotubular agents used to treat a variety of malignancies. They cause interstitial pneumonia via delayed hypersensitivity mechanism or direct toxic effect but are also reported to cause organizing pneumonia or DAD.[32,33] In one case series of patients with non-small cell lung cancer treated with docetaxel, the incidence of interstitial pneumonitis was 4.6%.[33] Onset was acute or subacute in nature and most frequently occurred during cycle 2 of therapy with a median onset of 18 days after the last administration. The incidence of paclitaxel-induced ILD has been reported to be from 0.7% to 12%.[34]

Antirheumatic

Leflunomide is used in the treatment of rheumatoid arthritis and exhibits antiproliferative, anti-inflammatory, and immune-modulating properties. In a Japanese study, the incidence of leflunomide-associated ILD reportedly declined from 1.46% to 0.63% after a risk advisory was issued.[20]

Methotrexate is a folate antimetabolite with antineoplastic, antiproliferative, anti-inflammatory, and immune-modulating properties used to treat certain malignancies, psoriasis, and connective tissue diseases such as rheumatoid arthritis. The mechanism of DIILD remains unclear but is proposed to be hypersensitivity or a direct toxic effect.[5,35] The incidence of methotrexate-induced ILD is reported to range from 0.06% to 15% with mortality ranging from 10% to 33%. The onset of the reaction can vary from days to years.[20] For patients treated with low-dose methotrexate for rheumatoid arthritis, a published literature review found the incidence of methotrexate pneumonitis to be 0.43%.[36] Interestingly, though folic acid may be used to mitigate some methotrexate ADRs, it does not reduce the risk of pneumonitis.[37]

Patient Care Process: Amiodarone-Induced Interstitial Pulmonary Fibrosis



Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (eg, preexisting lung disease, radiation)

- Social history (eg, smoking)
- Current medications (eg, amiodarone duration of therapy and daily dose, interacting medications)
- Objective data
  - Vitals (eg, pulse oximetry)
  - Physical exam (eg, lung auscultation, inspection of extremities)
  - Imaging (eg, chest radiograph, HRCT)
  - PFTs (eg, spirometry, diffusing capacity of carbon dioxide [DLCO])

Assess

- Likelihood of drug-induced adverse reaction
  - Clinical presentation consistent with pulmonary fibrosis
  - Presence of risk factors for amiodarone-induced pulmonary fibrosis (eg, advanced age, daily dose > 400 mg, long-term use, preexisting lung conditions)
  - Absence of alternative cause of pulmonary fibrosis
  - Improvement following discontinuation of amiodarone
- Need for alternative antiarrhythmic therapy or implantation of an automatic defibrillator

Plan*

- Discontinue amiodarone
- Establish alternate antiarrhythmic therapy
- Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day for 6 to 12 months and ensure the dose is tapered gradually upon completion of therapy
- Patient education (eg, the purpose of treatment, corticosteroid-specific information)
- Self-monitoring for improvement in shortness of breath and exercise tolerance
- Referrals to other providers when appropriate (eg, pulmonology, transplant)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, spirometry, DLCO, HRCT, ADR assessment, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, shortness of breath, improved exercise tolerance)
- Improvement of objective measures (eg, pulse oximetry, spirometry, DLCO, HRCT)

- Presence of adverse effects of corticosteroids (eg, hyperglycemia, hypertension, gastrointestinal upset, weight gain, edema, mood changes, decreased bone density, cataracts, Cushing's Syndrome)
- Patient's adherence to the treatment plan

Collaborate with patient, caregivers, and other healthcare professionals

Cardiovascular

Amiodarone is a class III antiarrhythmic agent used to treat atrial and ventricular arrhythmias. It exerts an adverse effect via phospholipidosis, or excessive accumulation of lipids and drug, in the lung as well as through a direct toxic effect.[38] The most commonly presenting reaction is a subacute or chronic interstitial disease occurring months after the initiation of the agent. Amiodarone-associated ILD occurs at a rate of 1.2% to 8.8%, with a reported mortality of 3% to 37%.[20]

Risk Factors

Multiple risk factors for DIILD have been identified. However, the occurrence of DIILD remains unpredictable, and risk factors vary across patient populations and inciting agents.[5] Though not applicable to all situations, some risk factors may include age extremes, concomitant use of radiation, oxygen, or other inciting medications, the dose of the causative agent, presence of underlying lung conditions and tobacco smoking.

Advanced age is a well-recognized risk for DIILD in certain agents (eg, amiodarone, bleomycin, EGFRIs, gemcitabine, methotrexate, and nitrofurantoin). Impaired renal clearance and oxidant/antioxidant imbalance in patients of advanced age contribute to this effect. On the other hand, the risk of DIILD with carmustine is highest in patients under 7 years of age. Extremes of age do not seem to be a risk factor for disease with other agents, such as mTORis.[5]

Thoracic and total body radiation cause radiation pneumonitis and concomitant or sequential use of certain chemotherapies (eg, bleomycin, cyclophosphamide, gemcitabine, taxanes) may compound risk.[39] Both radiation and chemotherapy can exert direct toxic effects on the lungs and the generation of free radicals. Exposure to high oxygen concentrations can also increase the formation of reactive oxygen species. Theoretically, concomitant oxygen supplementation and bleomycin use can raise the chance of DIILD. While data in animals identify high concentration oxygen as a risk factor, high-quality evidence in humans is lacking.[26]

Cumulative drug exposure increases the likelihood of DIILD with amiodarone, bleomycin, and carmustine. In amiodarone use, both maintenance daily doses greater than 400 mg and cumulative dose are well-established risk factors for DIILD.[40] Increased risk of toxicity is seen with cumulative doses greater than 300 units of bleomycin and 1,400 mg/m^2 of carmustine.[41,42]

The presence of preexisting lung diseases including IPF, chronic obstructive pulmonary disease, and asbestos-induced disease, are recognized risk factors for DIILD.[20] Genetic susceptibility (eg, altered enzyme activity, presence of variant alleles) can impact the likelihood of DIILD.[43] Another predisposing factor may be tobacco smoking, specifically with the use of EGFRIs, gemcitabine, and methotrexate.[20]

Prevention

Two general DIILD prevention strategies exist: avoid causative agents in high-risk patients and limit exposure in patients who must receive treatment with causative agents.[5] Risk factors are agent- and patient-specific and are detailed in the "Risk Factors" section. There is limited guidance for specific DIILD prevention strategies. For example, the National Comprehensive Cancer Network (NCCN) Guideline for Testicular Cancer recommends avoiding bleomycin-containing regimens for certain seminomas in patients who are over 50 years of age, are at increased risk for pulmonary complications, or have underlying lung disease.[44] There are also recommendations related to the use of oxygen in the perioperative period.[45]

Monitoring, Recognition, and Assessment

Early recognition of DIILD is essential but inherently difficult as DIILD is a diagnosis of exclusion. Monitoring protocols for the identification of DIILD

have not been well established and are often clinician-dependent. It is good practice to obtain baseline spirometry, DLCO, and chest radiograph with the use of high-risk agents. The patient should be monitored for symptoms at each follow-up. Spirometry and DLCO should be performed frequently, though a decrease in these indices may not occur until a more advanced disease occurs. A chest radiograph should also be performed at frequent intervals. The frequency of monitoring typically ranges from every 2 weeks to every 4 months, depending on the patient, agent, and clinician-specific factors.[5] Specific monitoring guidelines exist for several causative agents, including bleomycin and amiodarone. When using amiodarone, monitoring of chest radiographs and PFTs including DLCO should be conducted. The chest radiograph along with signs and symptoms should be monitored every 3 to 6 months or if clinically warranted.[46] When using bleomycin, a chest radiograph should be monitored every 1 to 2 weeks, and DLCO should be performed monthly. A decline in DLCO of 30% to 35% from baseline is clinically relevant and warrants intervention.[45]

For high-risk drugs, clinicians should educate patients on self-monitoring of symptoms and consider frequent follow-up to monitor symptoms, PFTs, and imaging. Acutely presenting disease may be more easily identifiable than chronic forms. Careful consideration of patient history, risk factors, and drug exposure must be made. Table e48-2 summarizes diagnostic criteria to consider. The Naranjo Adverse Drug Reaction Probability Scale outlines similar criteria broadly used to identify adverse drug effects.[47]

TABLE e48-2

Diagnostic Criteria for the Presence of Drug-Induced Pulmonary Diseases (DIPD)

History
Known or suspected exposure to a drug known to cause DIPD
Current
Clinical and histopathological findings correlate with previous reports of DIPD
Other causes of clinical and histopathological findings can be ruled out
Future
Clinical manifestations improve after withdrawal of the drug
Clinical manifestations recur after rechallenge

Data from References 21,48.

The severity of cancer therapy-related ADRs is clearly classified in the Common Terminology Criteria for Adverse Events (CTCAE) document published by the National Cancer Institute.[49] The document is organized by organ system class and includes severity grades 1 through 5 for each ADR. For example, the ADR "pneumonitis" is categorized under "respiratory, thoracic, and mediastinal disorders." Drug information databases typically use grades to provide recommendations on management. Conversely, the assessment of the severity and predicted mortality from non-cancer therapy DIILDs have not been well described. The American Thoracic Society/European Respiratory Society issued an update on the classification of idiopathic interstitial pneumonia, but this does not extend to drug-induced causes.[22] Predictive mortality models that exist for IPF and idiopathic interstitial pneumonia have been applied to other forms of the disease, but not specifically to DIILD. The ILD-GAP Index is one such model which incorporates factors like gender, age, and physiology (ie, % predicted FVC and % predicted DLCO) to determine the probability of survival.[50] The intention behind such tools is to provide information to patients, set goals, inform the need for referrals, and determine prognosis.

Management and Treatment

Treatment of DIILD often involves withdrawal of the offending agent, may include corticosteroids or supportive measures, and in extreme cases may require lung transplantation. Early detection of disease and discontinuation of the suspected causative agent is essential.

Corticosteroids are commonly initiated in clinical practice, but high-quality evidence to support the dose, duration, or efficacy of this approach is often lacking. Studies assessing the impact of corticosteroids have been summarized previously, but lack of randomization, incomplete information on dosing or duration, and heterogeneity of the population limit conclusions.[20] Despite weak evidence, corticosteroid dosing recommendations exist for the treatment of DIILD associated with some agents such as ICPis, mTORis, bleomycin, carmustine, and amiodarone.[4,5,30,38,51,52] The NCCN Guidelines for the Management of immunotherapy-related toxicities recommend that moderate (grade 2) pneumonitis be managed with prednisone or methylprednisolone 1 to 2 mg/kg/day until improvement and taper over 4 to 6 weeks. If there is no improvement in 48 to 72 hours or if severe (grades 3-4) pneumonitis is present, give methylprednisolone 1 to 2 mg/kg/day and taper over at least 6 weeks. If there is no improvement, infliximab, intravenous immune globuline, or mycophenolate mofetil can be considered.[52] For DIILD associated with mTORis, a dose reduction or interruption is suggested for grade 2, dose interruption is suggested for grade 3, and permanent discontinuation is suggested for grade 4. Corticosteroids at an equivalent oral prednisone dose of 0.75 to 1 mg/kg are suggested in grades 2 to 4 until pneumonitis improves to grade 1.[4] For DIILD associated with bleomycin, prednisone 0.75 mg/kg/day for a minimum of 4 to 6 weeks followed by a taper has been suggested.[5] For DIILD associated with carmustine, an initial regimen of prednisone 60 mg by mouth twice daily followed by 30 mg by mouth daily and tapered by 5 to 10 mg weekly until discontinuation showed success in breast cancer patients.[51] For DIILD associated with amiodarone, treatment with prednisone 0.5 to 1 mg/kg/day has been suggested. Given the long half-life of amiodarone, it is imperative to continue corticosteroids for several months and often up to 1 year. Cases of relapse have been described in corticosteroid treatment duration under 6 months.[38]

In addition to discontinuing the causative agent and initiating corticosteroids, supportive measures may be required. Patients with hypoxemia may be treated with supplemental oxygen therapy.[1] Mechanical ventilatory support may be needed in acutely severe cases. A referral for lung transplantation may be considered in some patients who have not shown improvement with other measures.[5]

Monitoring

Once the presence of DIILD has been identified, and management has commenced, monitoring for disease improvement should occur. An improvement (downgrading) of the CTCAE grade suggests there has been a favorable response to the treatment of cancer therapy-associated ILD.[49] Criteria defining a favorable response is lacking, but such criteria have been described in the treatment of IPF.[53] Positive response in IPF consists of improvement in symptoms, imaging, and physiologic parameters such as the increase in total lung capacity or vital capacity by ≥ 10% or 200 mL, improvement in DLCO by ≥ 15% or 3 mL/min/mmHg, or normalization or improvement of oxygen saturation by 4%. The goal of management should be to resolve symptoms and prevent progression to fibrosis. The time course to a resolution of acutely presenting interstitial pneumonitis may be days to weeks. Fibrosing disease may take months to improve or may be permanent.[5]

If patients were managed with corticosteroids or other treatments, ADRs should be monitored. For corticosteroids, this may include hyperglycemia, hypertension, gastrointestinal upset, weight gain, edema, mood changes, decreased bone density, and cataracts.

Organizing Pneumonia

Organizing pneumonia, otherwise known as bronchiolitis obliterans organizing pneumonia (BOOP) results from an inflammatory response localized in the lung parenchyma. Figure e48-3A visually depicts a normal alveolus, and Fig. e48-3C depicts the parenchymal changes seen in organizing pneumonia.

Patients with BOOP can present with nonproductive cough, dyspnea, and bilateral crackles, with occasional fever and rash, and rarely, eosinophilia. Radiographic imaging of the lung often shows bilateral, patchy infiltrates.

Causative agents are typically antimicrobials (eg, minocycline, nitrofurantoin), chemotherapeutic agents (eg, bleomycin), cardiac agents (eg, amiodarone), anti-inflammatory agents (eg, gold, sulfasalazine), and other miscellaneous agents such as interferon-alpha, carbamazepine, L-tryptophan, and cocaine.[6]

BOOP-related interstitial inflammation is generally reversed by discontinuation of the offending agent or treatment with corticosteroids.

Eosinophilic Pneumonia

Pulmonary infiltrates with eosinophilic pneumonia involve infiltration of the pulmonary parenchyma/interstitium with eosinophils.[7] Figure e48-3A visually depicts a normal alveolus and Fig. e48-3D depicts the parenchymal changes seen in eosinophilic pneumonia.

It can be a primary idiopathic process or secondary to a variety of etiologies but is most commonly drug- or toxin-mediated. A potential drug-related mechanism includes eosinophil-specific chemoattractants such as eotaxin, T-cell-expressed chemokines, or IL-5 release from T2 lymphocytes. Other proposed mechanisms are through 5HT2A (in response to antipsychotics or antiepileptic agents) or oxidant injury (in response to daptomycin or nitrofurantoin).[7]

Eosinophilic pneumonia symptoms can include dry cough, dyspnea, chest pain, and fever. BAL typically shows >25% eosinophils as a proportion of all white blood cells present. A lung biopsy is not typically recommended for diagnosis. On imaging, eosinophilic pneumonia involves bilateral reticular ground-glass opacities that expand with disease progression. It is further classified based on chronicity, and questions have been raised about whether acute and chronic eosinophilic pneumonia should actually be considered two entirely separate entities. The disease is classified as acute eosinophilic pneumonia (AEP) if symptoms have been presented shorter than one month (typically less than one week). The chief contrast between AEP and chronic eosinophilic pneumonia (CEP) is that AEP is usually fulminant, and patients have severe hypoxemia, with more than half requiring mechanical ventilation. AEP includes bilateral peripheral or pleural-based nonsegmental consolidations, and ground-glass opacities are less commonly seen as compared with chronic disease. AEP often presents with peripheral blood neutrophilic leukocytosis without an elevation in the eosinophilic fraction, although there are conflicting data on this observation. In contrast, BAL fluid in acute disease is almost always >25% and frequently reported as >40% eosinophilic fraction. In comparison, CEP is diagnosed 5 months from the onset of symptoms. Patients with CEP commonly present with a productive cough (42%), fever (67%), and dyspnea (80%), but they also have B-type symptoms, including weight loss (60%) and night sweats (47%). Peripheral blood eosinophilia is commonly present with CEP (eosinophil count > 1,000 cells/μL [1.0 ~10^9/L]). Total immunoglobulin E (IgE) levels are also high in half of these patients, along with elevated markers of chronic inflammation such as thrombocytosis, c-reactive protein, or ESR.[7]

Causative agents implicated in secondary eosinophilic pneumonia include antibiotics such as daptomycin, nitrofurantoin, and minocycline, and anti-inflammatory agents such as mesalamine and sulfasalazine. All drug classes have been implicated, but these classes carry a higher risk.[5,7,35]

Eosinophilic pneumonia is treated based on the severity of symptoms. As previously mentioned, patients with severe hypoxemia in AEP will require mechanical ventilation. AEP is commonly (82%) treated with steroids, but the recurrence rate with just discontinuing the offending agent is only 3.7%, and there is no difference in the recurrence rate between AEP treated with steroids versus no steroids. CEP is also often treated with steroids but not as commonly (65%), and the recurrence rate with just discontinuing the offending agent is 3.3%. Notably, patients with CEP treated with steroids have a higher rate of recurrence (6.5%). The optimal duration of steroids, when used, is unknown, but clinicians commonly provide a slow taper over 2 to 3 months. A steroid-sparing regimen with omalizumab can be considered if IgE levels are high, although evidence supporting this approach is weak.[7]

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis typically occurs as an immediate, immunologically mediated reaction after drug exposure but can also present chronically.[3] Figure e48-3A visually depicts a normal alveolus, and Fig. e48-3E depicts the parenchymal changes seen in hypersensitivity pneumonitis.

Patients presenting with urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, and bronchospasm after administration of a new drug should raise suspicion for hypersensitivity pneumonitis. Diagnosis is made based on a detailed history of drug exposure and the timing of symptom onset. Pneumonitis can precipitate severe asthma exacerbations requiring urgent intervention to avoid respiratory failure and the need for mechanical ventilation.[3]

Causative agents classically include nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate.[3,8]

Hypersensitivity pneumonitis is managed by discontinuing the suspected precipitating drug. Supportive care includes the administration of corticosteroids and antihistamines to blunt the immune-mediated and allergic response.[3]

Noncardiac Pulmonary Edema

Although the pathogenesis of noncardiac pulmonary edema is generally unknown, it may result from capillary leak syndrome, hypervolemia, or as a consequence of anaphylaxis.[9] Figure e48-3A visually depicts a normal alveolus, and Fig. e48-3F depicts the parenchymal changes seen in noncardiac pulmonary edema.

The clinical presentation is similar to pulmonary edema from acute respiratory distress syndrome and cardiogenic etiologies. Patients present with chest discomfort, dyspnea, tachypnea, and hypoxemia, sometimes requiring urgent mechanical ventilatory support. Diagnosis is made by ruling out cardiac causes, pulmonary hemorrhage, and infectious etiologies. Cardiomegaly or pulmonary vascular changes suggest cardiac involvement. Pulmonary infiltrates on chest X-ray reveal interstitial and alveolar filling. Laboratory monitoring and PFTs do not help establish this diagnosis.[9]

The drug-induced pulmonary edema of a noncardiac origin is uncommon; however, it has been reported more with certain classes of drugs. Chemotherapy (cytarabine, gemcitabine), immunosuppressants (immune globulins, methotrexate, muronomab-CD3), calcium channel blockers, pulmonary vasodilators (epoprostenol, nitric oxide), tricyclic antidepressants, opioids (methadone, morphine), amiodarone, nitrofurantoin, talc, protamine, heroin, cocaine, and radiocontrast dyes have been implicated. Counterintuitively, diuretics such as acetazolamide and hydrochlorothiazide can cause severe idiosyncratic pulmonary edema. Obstetric agents such as oxytocin and selective beta-2-adrenergic receptor agonists have also been implicated with noncardiac pulmonary edema, although this may be more related to fluid overload, underlying cardiac issues, steroid use, or multiple gestations.[9] Opioid analgesics such as morphine and methadone can cause noncardiac pulmonary edema. The mu-antagonist naloxone may also be a culprit. Pulmonary edema is precipitated by a catecholamine surge.[9,54]

Management of noncardiac pulmonary edema is usually conservative; most reactions are mild and self-limiting, with symptoms improving rapidly within 1 to -2 days after stopping the implicated drug. Supportive care with supplemental oxygen and diuretics can be necessary to manage pulmonary edema. The role of corticosteroids has been proposed, but evidence supporting its use is questionable. In rare, severe cases leading to respiratory failure, patients may require urgent mechanical ventilation.[9]

Diffuse Alveolar Damage/Diffuse Alveolar Hemorrhage

DAD or DAH involves the accumulation of red blood cells in the alveolar space. DAD may be caused by direct toxicity or may be immune-mediated since systemic manifestations of hypersensitivity (dermatitis, vasculitis) have been observed. Destruction of the alveolar-capillary basement membrane leads to loss of structural integrity in alveolar capillaries, and, less commonly, precapillary arterioles or postcapillary venules. DAH can be induced through coagulation defects.[10] Figure e48-3A visually depicts a normal alveolus, and Fig. e48-3G depicts the parenchymal changes seen in DAD.

The clinical presentation is usually acute, with rapid onset of respiratory failure requiring mechanical ventilation. Some cases may be subacute, with slowly progressing symptoms. The cardinal symptom of hemoptysis is present in most cases, along with cough, and progressive dyspnea. Patients may have decreased hematocrit and have red blood cells present on BAL. If hemoptysis is not present (occurs in 33% of cases), diagnosis can be confirmed with a chest X-ray of new or unexplained infiltrates, decreased hematocrit, and hemorrhagic BAL.[10]

Immune/hypersensitivity-mediated DAD can be caused by chemotherapy, all-trans-retinoic acid, propylthiouracil, penicillin, sulfasalazine, hydralazine, leukotriene antagonists, and mitomycin. DAD caused by direct toxicity to the alveolar basement membrane has also been seen with chemotherapy/bone marrow transplant, as well as amiodarone, nitrofurantoin, and crack cocaine. DAH related to coagulation defects can be seen with thrombolytics, anticoagulants, platelet glycoprotein Ib/IIIa inhibitors, platelet aggregation inhibitors, dextran 70, and drug-induced thrombocytopenia.[10]

Management of DAD and DAH depends on the underlying etiology, but always involves discontinuation of the offending agent. In DAH, treatment may include the reversal of the coagulation defect. Chemotherapy-induced DAD has been reportedly treated with high-dose corticosteroids, although data on the effectiveness of this approach is questionable.[10]

Reactions Involving the Pleura

Pleural reactions are an uncommon manifestation of DIPD. Proposed mechanisms of pathogenesis include hypersensitivity/allergic reaction, direct

toxic effect, increased oxygen free radical production, suppression of antioxidant mechanisms, and inflammation resulting from drug exposure.[11]

The presentation consists of pleural effusions, pleural thickening, and pleuritic chest pain, with or without parenchymal involvement. Pleural fluid with >10% nucleated cells (eosinophilia) raises suspicion for a drug-induced etiology. Peripheral eosinophilia sometimes occurs as well but is not present in all cases.[11]

Pleural reactions can be classified broadly as non-lupus-related and lupus-related pleural effusions.

Non-Lupus-Related Pleural Effusion

Sclerotherapy agents, including sodium morrhuate and absolute alcohol are most often implicated with non-lupus-related pleural effusions. In this case, pathogenesis involves inflammation spreading from the esophageal varices injection site to the mediastinal pleura. Effusions present on chest X-ray rapidly within 1 day but also typically resolve spontaneously within one week. Empyema rarely occurs but has been reported.[11]

Otherwise, non-lupus-related pleural effusions can be caused by cardiovascular agents (amiodarone, minoxidil), ergoline agents (methysergide, bromocriptine), chemotherapy (bleomycin, mitomycin, procarbazine, methotrexate, cyclophosphamide, dasatinib), and nitrofurantoin. Management involves the discontinuation of the offending agent. Corticosteroids are often utilized despite the absence of robust data supporting their use. With amiodarone-induced reactions, corticosteroids have been recommended in patients with severe hypoxemia and a significant decrease in diffusion capacity.[11,55]

Cyclophosphamide can cause pleural effusions early (1-6 months after exposure) or late (as late as 6 years after drug discontinuation). Patients present with fever, cough, dyspnea, and fatigue. Early onset pleural effusions may respond to corticosteroids, whereas late-onset is less likely to improve symptoms. The presence of pleural thickening on imaging is a sign of late-onset reaction.[11]

Nitrofurantoin can cause pleural effusions in 5% to 25% of patients within one month of therapy. Clinical presentation includes fever, dyspnea, and cough, with bibasilar alveolar or interstitial infiltrates. More chronic presentation results in permanent compromise of lung function and potentially progressive decompensation despite cessation of nitrofurantoin. This is hypothesized to be a consequence of pleural thickening and fibrosis.[11]

Lupus-Related Pleural Effusion

Lupus-related pleural effusions encompass reports of lupus-like reactions and lupus flares. More than 80 drugs have been implicated in this type of reaction since the first description of this in 1945, after the administration of sulfadiazine.[11]

The clinical presentation is similar to idiopathic lupus, which is described in Chapter 107 (Systemic Lupus Erythematosus). This is characterized by exudative effusions, with cell counts of 200 to 15,000 cells/mL ($0.2 \sim 10^6$/L to $15 \sim 10^6$/L), glucose typically in the normal to low range, antinuclear antibodies (ANA) higher than serum values (frequently > 1:250), and presence of lupus erythematosus cells.[11]

Procainamide is the most common causative agent. Ninety percent of patients taking procainamide will have a positive ANA after one year of therapy, and one-third develop a lupus-like syndrome. Onset can occur between 1 month and 12 years from the start of therapy. Importantly, slow acetylators of the drug are at risk for developing the ADR at lower doses and earlier after starting therapy. Hydralazine also carries a relatively high risk for drug-induced lupus, at a rate of 2% to 21%. One-third of patients present with pleural effusions, with once again greater risk for slow acetylator phenotypes, patients receiving higher doses, and longer durations of therapy. Other drugs that have been implicated include chlorpromazine, isoniazid, D-penicillamine, methyldopa, and quinidine.[11]

Reactions Without Direct Toxic Effect on the Lung Tissue

While DIPD caused by direct damage to lung tissue is relatively rare, pulmonary diseases from indirect effects of medication are much more common. Such indirect effects may include aspirin-induced bronchospasm, angiotensin-converting enzyme (ACE) inhibitor-induced cough, and opioid-induced respiratory depression.

Drug-Induced Asthma/Bronchospasm

Rarely, drugs can induce bronchospasm and asthma. The proposed pathogenesis involves the inhibition of cyclooxygenase, forcing the metabolism of arachidonic acid through the lipogenesis pathway. This increases the resulting concentration of leukotrienes. The greatest risk factor is preexisting asthma, but older patients, smokers, and those with other preexisting airway diseases are also at risk for developing drug-induced bronchospasm. Causative agents include acetaminophen, aspirin, NSAIDs, and iodinated radiocontrast dyes. About 50% to 100% of patients with asthma develop symptoms of bronchospasm after one dose of a non-selective beta-adrenergic receptor antagonist.[12] Systemic N-acetylcysteine (intravenous in particular) rarely causes bronchoconstriction due to an anaphylactoid reaction.[56] When administered by inhalation, it can also cause direct irritation to the airway, leading to increased airway resistance and bronchoconstriction.[12,57]

Drug-Induced Cough

Angiotensin inhibitor-induced cough occurs in about 10% of patients, with a greater risk for females and non-smokers. Patients present with a persistent, dry cough and "tickle" sensation in the throat. This ADR can occur within hours to months of starting therapy. The pathogenesis is proposed to be related to the accumulation of bradykinin or substance P. Patients are managed by discontinuation of the drug, with improvement typically observed over the course of 1 to 4 weeks.[13]

Calcium channel blockers can also cause cough through relaxation of the lower esophageal sphincter, thereby leading to reflux of gastric contents. Fentanyl intravenous bolus has been hypothesized to cause cough by increasing vagal tone by decreasing central sympathetic outflow or induction of pulmonary chemoreflex. Cough with fentanyl has been reported at rates of 18% to 65%. Latanoprost ophthalmic drops have been hypothesized to upregulate the cough reflex systemically.[13]

Drug-Induced Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) (see Chapter 46) and the comprehensive clinical presentation and diagnostic criteria are included there. Drug-induced PAH has been observed with anorectic agents, amphetamines, and dasatinib. Newborns of mothers taking selective serotonin reuptake inhibitors during pregnancy are at risk for developing PAH.[14,15]

Drug-Induced Thromboembolic Disorders

It is often challenging to distinguish between PAH and pulmonary veno-occlusive disease, but drug-induced thromboembolic disorders are important to consider in the clinical differential. Refer to Chapter 38 (Venous Thromboembolism) for a comprehensive review of venous thromboembolism (VTE) and pulmonary embolism (PE). Drug-induced causes of thromboembolic disease include chemotherapy (bleomycin, cyclophosphamide, alkylating agents, and mitomycin).[15] High-dose combined oral contraception (>50 mg ethinyl estradiol) is no longer available in the United States due to the increased risk for VTE and PE.[58] A VTE incidence of 10% shows with immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab), likely due to effects related to autoimmunity.[16]

Drug-Induced Respiratory Depression or Apnea

Drug-induced respiratory depression or apnea can be unintentional or intentional, such as the facilitation of patient-ventilator synchrony. This can occur via central nervous system (CNS) depression leading to hypoventilation, or neuromuscular blockade, completely blunting patient-initiated respirations.[3]

Opioids for the treatment of pain or in abuse scenarios are often implicated in CNS depression-mediated respiratory depression and/or apnea. Opioids cause respiratory depression by decreasing the sensitivity of peripheral chemoreceptors to carbon dioxide and by decreasing neuronal activity in central respiratory centers.[19] Concomitant administration of other CNS depressants increases the risk for respiratory depression. Other important risks noted in hospitalized patients include renal failure, advanced age, and patients within the first 24 hours of opioid initiation.[18]

Chemical paralysis with a neuromuscular blocking agent blunts respiratory function through skeletal muscle relaxation by stopping the transmission of neuronal impulses at the neuromuscular junction.[17] These agents are used intentionally to facilitate endotracheal intubation and promote patient-ventilator synchrony in patients. However, an important consideration is that the use of neuromuscular blocking agents has been associated with an

increased risk for postoperative weakness and difficulty weaning off the ventilator.[59]

Drug-Induced Chest Wall Rigidity

Muscle rigidity and decreased compliance have been observed as an ADR with opioid administration. Although this can occur with any muscle group, when it involves respiratory muscles, laryngeal structures, or chest wall, it can lead to severe complications and require endotracheal intubation for mechanical ventilatory support. The mechanism is related to the stimulation of alpha-2 adrenergic receptors and serotonin receptors. Accordingly, synthetic opioids with greater serotonin activity (fentanyl, remifentanyl, methadone) have been implicated with chest wall rigidity, although it has been seen with other opioids, such as morphine. An incidence of 50% has been reported in healthy male volunteers receiving a 15 mcg/kg dose of fentanyl infused at 150 mcg/min. Drug-induced rigidity is believed to be dose-related, although it can also be seen at lower doses.[19]

CONCLUSIONS

DIPD is an uncommon complication of drug therapy that can lead to significant symptoms, including acute respiratory failure. Many drugs have an indirect effect on lung function, such as respiratory depression associated with opioids, bronchospasm associated with aspirin, or cough associated with ACE inhibitors. Direct toxicity is less common. DIILD, specifically pneumonitis and fibrosis, is the most common manifestation of DIPD with direct lung injury.

DIPD is a diagnosis of exclusion. Many drugs have been reported to cause pulmonary complications. A detailed drug history and documentation of the temporal relationship between exposure and clinical presentation are key to either identifying or ruling out an offending agent. Risk factors for DIPD based on the suspected etiology can also point to the potential likelihood of DIPD. Preventative strategies include avoiding causative agents in high-risk patients and limiting the duration of exposure. Early identification of DIPD is crucial. Management involves the discontinuation of the offending agent. The data for corticosteroids for most DIPD scenarios are weak, although they are commonly used in practice. Supplemental oxygen and mechanical ventilation are supportive therapies used in severe cases.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AEP	acute eosinophilic pneumonia
ANA	antinuclear antibodies
BAL	bronchoalveolar lavage
BIP	bleomycin-induced pneumonitis
BOOP	bronchiolitis obliterans organizing pneumonia
CEP	chronic eosinophilic pneumonia
CNS	central nervous system
CRP	c-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CT scan	computerized tomography scan

DAD	diffuse alveolar damage
DAH	diffuse alveolar hemorrhage
DIILD	drug-induced interstitial lung disease
DIPD	drug-induced pulmonary diseases
DLCO	diffusing capacity of carbon dioxide
EGFRI	epidermal growth factor receptor inhibitor
ESR	erythrocyte sedimentation rate
HRCT	high-resolution computed tomography
ICPi	immune checkpoint inhibitor
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
mTORi	mechanistic target of rapamycin inhibitor
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory drug
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PFT	pulmonary function test
VTE	venous thromboembolism

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SELF-ASSESSMENT QUESTIONS

1. Which of the following factors is associated with an increased risk of amiodarone-induced lung disease?
   A. Concomitant oxygen supplementation
   B. History of current tobacco smoking
   C. Age less than 40 years
   D. A maintenance daily dose greater than 400 mg
2. Which of the following is the most appropriate strategy to monitor for the onset of bleomycin-induced lung disease?
   A. High-resolution computed tomography (HRCT) twice per month
   B. Carbon monoxide diffusing capacity (DLCO) monthly
   C. Bronchial alveolar lavage (BAL) after three months
   D. Physical exam to inspect for cyanosis weekly
3. Which of the following is the most appropriate initial treatment for drug-induced interstitial lung disease?
   A. Discontinue the suspected offending agent
   B. Refer for lung transplantation consult
   C. Initiate a low-dose course of steroids
   D. Provide supplemental oxygen therapy
4. Which of the following is the most appropriate strategy for the early identification of drug-induced interstitial lung disease?
   A. Perform imaging in high-risk patients only if symptoms are present
   B. Educate patients on common symptoms of DIILD before initiation of therapy
   C. Measure eosinophils and erythrocyte sedimentation rate monthly while on therapy
   D. Obtain baseline bronchial alveolar lavage (BAL) with biopsy
5. Which of the following patients is *least likely* to meet the diagnostic criteria for DIILD?
   A. Prescribed everolimus for breast cancer; presents with “ground glass” opacities on HRCT, which resolve after discontinuation of everolimus
   B. Prescribed methotrexate for psoriasis; presents with cough and expiratory crackles 6 months after initiating methotrexate
   C. Prescribed docetaxel for prostate cancer; presents with reduced DLCO from baseline
   D. Prescribed ipratropium for COPD; presents with chronic dyspnea and cough

6. Which of the following drug-induced pulmonary diseases can have both an acute and chronic presentation?

   A. Bronchospasm

   B. Chest wall rigidity

   C. Eosinophilic pneumonia

   D. Apnea

7. Which of the following is the most appropriate strategy for *immediate* treatment of drug-induced pulmonary diseases in a patient who is oxygenating well and being managed as an outpatient?

   A. Initiate supplemental oxygen

   B. Investigate drug causes

   C. Initiate dexamethasone

   D. Discontinue new medications

8. Which of the following patients is most likely to develop drug-induced bronchospasm?

   A. 89-year-old with asthma receiving intravenous carvedilol

   B. 26-year-old with acute liver failure receiving intravenous N-acetylcysteine

   C. 68-year-old with chronic myeloid leukemia receiving oral dasatinib

   D. 56-year-old with chronic obstructive pulmonary disease receiving furosemide

9. Nitrofurantoin-induced chronic eosinophilic pneumonia (CEP) with low IgE levels would be most appropriately managed using which of the following strategies?

   A. Discontinue nitrofurantoin and initiate prednisone

   B. Discontinue nitrofurantoin and initiate albuterol

   C. Decrease the dose of nitrofurantoin, initiate dexamethasone and omalizumab

   D. Decrease the dose of nitrofurantoin and initiate dexamethasone

SELF-ASSESSMENT QUESTIONS-ANSWERS

1. **D.** Daily and cumulative drug exposure are risk factors for amiodarone-induced DIPD. See "Risk Factors" section for more information. While smoking and oxygen use increase the risk of DIILD for certain agents, they are not correlated with amiodarone toxicity. Advanced age is a risk factor for amiodarone-related pulmonary toxicity—not age under 40 years.

2. **B.** The manufacturer of bleomycin recommends monitoring DLCO monthly to assess the efficiency of lung gas transfer. See the "Prevention and Monitoring" sections for further details. Plain film imaging is preferred over HRCT for routine monitoring. BAL is typically only performed to rule out other causes of pulmonary disease or differentiate between types of interstitial lung disease. Cyanosis typically is not present at disease onset as it develops after disease progression.

3. **A.** The first step in treating DIILD is to remove the offending agent. See the "Management and Treatment" section for more information.

4. **B.** Patients should be informed of the signs and symptoms of DIILD before starting high-risk therapy so that they may self-monitor in between

clinician visits. See the "Monitoring, Recognition, and Assessment" section for further details.

5. **D.** The likelihood of DIILD is increased if the patient has been exposed to an agent known to cause the disease. Ipratropium does not cause DIILD. Diagnosis is also more likely if other causes of lung disease can be excluded. COPD is a lung disease that may present similarly to certain DIILD.

6. **C.** Bronchospasm, chest wall rigidity, and apnea present as acute reactions, whereas eosinophilic pneumonia can present acutely or chronically after drug exposure. See Table e48-1 for more information.

7. **B.** The most appropriate strategy for managing drug-induced pulmonary diseases is to review the patient's medication list and identify the most likely inciting drug based on history and presentation. Discontinuing all new medications without regard to the likelihood of causing the pulmonary disease can have unintended adverse consequences related to drug withdrawal. Although supplemental oxygen and corticosteroids may be required for management, they would typically not be needed for immediate treatment in a stable outpatient.

8. **A.** More than 50% of patients with asthma develop bronchospasm after one dose of a non-selective beta-adrenergic receptor antagonist such as carvedilol. Advanced age is also another risk factor for drug-induced bronchospasm. N-acetylcysteine is most likely to cause bronchoconstriction when inhaled, and even then, the risk is relatively low. Dasatinib and furosemide have not caused bronchospasm. Although chronic obstructive pulmonary disease can increase the risk for bronchospasm, this risk would be higher in a patient with asthma.

9. **A.** CEP is best treated by discontinuing the inciting agent, in this case, nitrofurantoin. Corticosteroids are commonly used in conjunction with both CEP and acute eosinophilic pneumonia. When IgE levels are high, omalizumab can also be considered. Bronchodilators have no specific role in CEP.