EDUCATIONAL OBJECTIVES

Goal: To review the common medications associated with pulmonary toxicity and how to recognize and treat idiopathic pulmonary fibrosis

After participating in this activity, pharmacists will be able to:

- Identify the major drugs and drug classes that can cause pulmonary disease
- Identify risk factors and monitoring plans for the commonly prescribed medications that can induce pulmonary reactions
- Describe the pathophysiology and clinical presentation of idiopathic pulmonary fibrosis
- Discuss new and emerging drug therapies for idiopathic pulmonary fibrosis

Recognition of drug-induced pulmonary disease and management of idiopathic pulmonary fibrosis

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Abstract

Drug-induced pulmonary disease is a potential adverse effect associated with a number of medications, most notably amiodarone and bleomycin. Management of this condition generally includes immediate cessation of the offending agent and treatment with systemic corticosteroids. Idiopathic pulmonary fibrosis (IPF), a form of interstitial lung disease, has been plagued by a lack of effective pharmacotherapeutic management options. In 2014, pirfenidone and nintedanib were approved by the FDA, making these agents the first treatments to be approved for the treatment of mild-to-moderate IPF in the United States. New guidelines for the management of IPF were released in 2015, with a conditional recommendation for pharmacological management of IPF with pirfenidone and nintedanib.
CPE SERIES: MTM FOR THE PATIENT WITH RESPIRATORY DISEASE

Welcome to the CPE series, Medication Therapy Management for the Patient with Respiratory Disease, which was designed for pharmacists who take care of patients with respiratory disease. Beginning in April 2015 and continuing through December 2015, pharmacists can earn up to 18 hours of CPE credit with 9 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and Drug Topics.

This series kicked off in April and May with MTM essentials for asthma management—Part 1 and Part 2. In June and July, the focus shifts to MTM essentials for chronic obstructive pulmonary disease (COPD) management. The August CE activity is a primer on inhalers and nebulizers. In September, pharmacists have the opportunity to learn about allergic rhinitis management. In October, the CE activity covers MTM essentials for cold, flu, and sinusitis management. The November CE activity includes drug-induced pulmonary disease recognition and management of idiopathic pulmonary fibrosis. The series concludes in December with a focus on MTM essentials for cough management. The series also offers application-based and practice-based activities in 2016.

Background
Drug-induced pulmonary disease (DIPD) has been attributed to a multitude of medications and may present in a variety of clinical syndromes depending on the pulmonary tissue affected. Chemotherapeutic agents, cardiovascular medications, antimicrobial agents, and anti-inflammatory medications are some of the most common causes of DIPD. This article seeks to familiarize pharmacists with commonly prescribed medications that are implicated in DIPD, along with associated risk factors and monitoring parameters when available.

Idiopathic pulmonary fibrosis (IPF) is an interstitial pneumonia of unknown origin that typically occurs in older adults and manifests with progressive worsening of lung function and dyspnea. This chronic fibrosing pneumonia is limited to pulmonary manifestations and is accompanied by histopathologic or radiologic changes consistent with interstitial pneumonia. For IPF to be diagnosed, the exclusion of other causes of lung disease, including the medications listed below, and imaging or biopsy results indicative of IPF are required. The median survival for this disease is approximately two to three years, making effective therapy of great interest. This article will review the most recent information on IPF.

Drugs/Drug classes that can cause DIPD
Amiodarone
Amiodarone-induced pulmonary toxicity may occur in up to 17% of patients treated with this agent. Toxicity will typically present within the first year of therapy but may appear as late as two years into treatment. Amiodarone-induced toxicity is believed to be caused by dose-related direct cellular toxicity via oxygen free radicals and an abnormally high concentration of phospholipids. Additionally, some patients may display immune-mediated and inflammatory reactions. Although toxicity is believed to be more likely at higher doses (specifically doses greater than 400 mg daily), toxicity is possible at any dose. As such, patients should be prescribed the lowest effective dose, and monitoring should be conducted for all patients taking amiodarone.

Patients with hypersensitivity pneumonitis will typically present with cough, shortness of breath, and fever within weeks of amiodarone initiation. In a small subset of patients (5%-7%), this condition may progress to fibrosis. Patients presenting with symptoms of pleuritic chest pain, shortness of breath, cough, and fever that have instead developed over months to years of treatment may have pulmonary alveolitis. Reduced diffusing capacity of the lung for carbon monoxide (DLCO) is commonly seen on pulmonary function testing (PFT) in patients with amiodarone-induced pulmonary toxicity. Rarely, amiodarone may cause bronchiolitis obliterans with organizing pneumonia (BOOP) or alveolar hemorrhage, a rare life-threatening condition precipitated by direct injury to the basement membrane of alveolar capillaries.

Amiodarone-induced pulmonary toxicity should be treated with immediate withdrawal of amiodarone and initiation of oral corticosteroids. Because of amiodarone’s long half-life, resolution of symptoms may be delayed and treatment may be needed for up to 12 months.

Angiotensin-converting enzyme inhibitors
Dry cough may occur in up to 19% of patients treated with angiotensin-converting enzyme inhibitors (ACE-Is). While more recent evidence suggests the true incidence may be far less, perhaps as low as 3%, it is nonetheless an important adverse effect. This cough is believed to be related to bronchoconstriction caused by a substance known as bradykinin. Normally, bradykinin is degraded by ACE. With the addition of an ACE-I, bradykinin accumulates, stimulating bronchoconstriction and associated cough. The appearance of this adverse effect may

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be immediate, within hours of ACE-I initiation, or delayed, occurring several months after initiation. It is not related to dose. Preexisting asthma and cigarette smoking do not appear to be risk factors, however those of the female sex and Chinese heritage are at increased risk. Antitussives are ineffective in the treatment of ACE-I-induced cough. The only effective management is to discontinue the ACE-I, after which cough typically resolves in a matter of four weeks. To replace ACE-I treatment, an angiotensin receptor blocker (ARB) may be initiated, as this class of medications does not affect bradykinin degradation.

**Aspirin**

Aspirin-induced asthma (AIA), also known as aspirin-exacerbated respiratory disease (AERD), is a clinical syndrome composed of asthma, sinusitis with nasal polyps, and bronchospasm that is exacerbated after ingestion of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). This condition is preceded by viral upper respiratory tract infection and may result in a loss of smell. Between 4% and 10% of adults with asthma and 20% of adults with both asthma and nasal polyps are believed to have AIA. AIA is most commonly seen in female patients aged 30 to 50 years. Patients with this condition typically experience symptoms of bronchospasm and congestion and/or rhinorrhea approximately two hours after taking aspirin. However, it is important to note that symptoms continue after the offending agent is withdrawn, and AIA is believed to be a lifelong condition.

AIA is presumed to be caused by an alteration in the metabolism of arachidonic acid. Cyclooxygenase (COX), the enzyme inhibited by aspirin, is a crucial component of arachidonic acid metabolism. By inhibiting COX, aspirin is believed to decrease the production of protective prostaglandins and increase the production of bronchoconstrictive and inflammatory leukotrienes via the enzyme 5-lipoxygenase. This mechanism is supported by the fact that selective COX-2 inhibitors do not cause bronchospasm in patients with AIA.

Inhaled corticosteroids, as recommended in the Guidelines for Diagnosis and Management of Asthma (EPR-3), are the cornerstone of AIA treatment. Leukotriene modifiers have an adjunctive role in therapy and have been shown to decrease exacerbations, and salmeterol appears to have a protective effect beyond its bronchodilatory activity. Patients with AIA should be counseled to avoid aspirin and all forms of NSAIDs. Alternatively, some patients may undergo aspirin desensitization.

**Beta-blockers**

Stimulation of beta-1 receptors in the heart increases cardiac output, while stimulation of beta-2 receptors in the lungs dilates the bronchi. Consequently, while beta-blockade is of benefit for several cardiovascular indications, it may induce bronchospasm in patients with asthma and chronic obstructive pulmonary disease (COPD). However, avoidance of beta-blockers may not be an appropriate solution for patients with concomitant cardiovascular disease such as acute myocardial infarction or congestive heart failure. In patients with bronchospastic disease who are eligible for beta-blocker treatment, metoprolol and atenolol may be preferred, depending on indication, because of their beta-1 selectivity, generic availability, and inexpensive cost. At higher doses, these agents may lose beta-1 selectivity, and thus the total daily dose should not exceed 200 mg for metoprolol and 100 mg for atenolol. All noncardioselective beta-blockers should be avoided, including ophthalmic formulations of timolol, which may have sufficient systemic absorption to cause bronchospasm. Patients with bronchospastic disease who are treated with beta-blockers should be prescribed a short-acting inhaled agent for the treatment of beta-blocker-induced bronchospasm. While patients taking cardioselective beta-blockers may respond to short-acting inhaled beta-agonists, ipratropium bromide is the preferred treatment.

**Bleomycin**

Bleomycin’s cytotoxic effect is attributed to the generation of free radicals resulting from oxidation of bleomycin-iron complexes. These reactive species bind to and subsequently break DNA strands in cancerous cells, eventually culminating in cell death. Bleomycin is predominately excreted unchanged through the kidneys; however, it is also metabolized by bleomycin hydrolase. This enzyme is absent from the lungs and skin. Consequently, these tissues are at the highest risk for bleomycin toxicity. Endothelial cell damage results from the aforementioned free radicals, as well as stimulation of the release of cytokines, particularly tumor necrosis factor-α (TNF-α), from macrophages. This leads to an inflammatory process in the interstitium with increased fibroblast activity that may potentially progress to fibrosis.

The most common pulmonary toxicity associated with bleomycin is interstitial pneumonitis; however, bleomycin may also cause eosinophilic hypersensitivity and BOOP. Pneumonitis is a serious and dose-limiting concern, with an incidence as high as 46% and death occurring in up to 3% of patients. This condition typically manifests during the course of bleomycin treatment but may occur up to six months after treatment cessation. Patients typically present with reduced exercise tolerance, dry cough, and, less commonly, fever.

Treatment of bleomycin-induced pulmonary toxicity includes immediate withholding of further bleomycin doses and, in some cases, treatment with high-dose systemic corticosteroids. Unfortunately, neither the optimal dose and duration of corticosteroid treatment nor the efficacy of these agents in the treatment of bleomycin-induced pneumonitis has been fully determined. Improvement may be seen after several weeks of treatment, but full resolution can take over a year.

**Cyclophosphamide**

Cyclophosphamide-induced pulmonary toxicity is rare, occurring in less than 1% of patients. Pulmonary reactions occurring within the first few months of cyclophosphamide therapy are attributed to interstitial inflammation and can generally be treated with corticosteroids. Conversely, pulmonary fibrosis occurring several years after therapy, defined as a late-onset reaction, is irreversible and has poor outcomes, with a mortality rate as high as 60%. PFT in patients with late-onset reaction shows a decreased DL_{CO} and vital capacity.

**Methotrexate**

Methotrexate-induced interstitial lung disease, particularly interstitial pneumonitis, may occur in up to 11.6% of patients with rheumatoid arthritis (RA) who are treated with this agent. Potential risk factors include advanced age, Japanese ethnicity, past medical history of pulmonary disease, prior use of disease-modifying antirheumatic drugs, and presence of the
Drugs/Drug Classes Associated with Pulmonary Toxicity

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>Most Commonly Occurring Type(s) of Pulmonary Toxicity</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Hypersensitivity pneumonitis</td>
<td>Cough, shortness of breath, fever; occurs within weeks of starting amiodarone treatment</td>
</tr>
<tr>
<td></td>
<td>Pulmonary alveolitis</td>
<td>Pleuritic chest pain, shortness of breath, cough, fever; develops slowly months to years after starting amiodarone treatment</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Bronchoconstriction</td>
<td>Dry cough; may occur months after starting ACE-I treatment</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin-induced asthma</td>
<td>Bronchospasm, congestion/rhinorrhea; occurs 2 hours after taking aspirin/nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Bronchospasm in patients with asthma/COPD</td>
<td>Cough, wheezing, shortness of breath shortly after administration of beta-blocker</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Interstitial pneumonitis</td>
<td>Reduced exercise tolerance, dry cough, sometimes fever; may occur during treatment or up to 6 months after stopping bleomycin treatment</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Pulmonary fibrosis</td>
<td>Shortness of breath, cough; progresses over several years after completion of cyclophosphamide treatment</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Interstitial pneumonitis</td>
<td>Nonproductive cough, shortness of breath; occurs within months to years after starting methotrexate treatment</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Acute hypersensitivity</td>
<td>Cough, shortness of breath, fever; occurs within a month of starting nitrofurantoin treatment</td>
</tr>
<tr>
<td></td>
<td>Chronic toxicity</td>
<td>Cough, shortness of breath; worsens over several months to years after nitrofurantoin treatment</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Eosinophilic hypersensitivity</td>
<td>Shortness of breath, fever, cough; occurs within first 6 months after starting sulfasalazine treatment</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease.

Source: Ref 3-9, 12, 14, 15, 16, 25-27

HLA-A*31:01 allele. However, it is difficult to ascertain the true potential for methotrexate to cause pulmonary toxicity, as RA itself may manifest in pulmonary disease in 40% to 70% of patients, and the cause of pulmonary disease is difficult to determine based on clinical presentation. Methotrexate-induced interstitial pneumonitis is not believed to be dose related and has been seen in patients using daily low-dose methotrexate. The proposed etiology for this condition suggests the involvement of reactive oxygen species and cytokines, including nitrous oxide (NO), interleukin-1 beta (IL-1β), TNF-α, and tumor growth factor-beta (TGF-β).

Symptoms of methotrexate-induced toxicity may present within months to years of treatment initiation. The clinical presentation consists of nonproductive cough and shortness of breath, and PFT shows a reduced DLCO. Additionally, case reports have suggested that methotrexate may increase the risk of opportunistic pulmonary infections, such as Pneumocystis carinii pneumonia, because of its immunosuppressive effects. However, a recent meta-analysis did not find an increased risk of infections or noninfectious pulmonary adverse events in patients with inflammatory bowel disease, psoriatic arthritis, or psoriasis treated with methotrexate. Further research is needed to determine the true risk of opportunistic pulmonary infections occurring in patients treated with this agent.

**Nitrofurantoin**

Nitrofurantoin has been reported to cause acute pulmonary toxicity in one of 5000 first-time users and fibrosis leading to hospitalization in one of 750 patients who use this agent over the long term. The risk of nitrofurantoin-induced pulmonary toxicity is highest in elderly female patients with recurrent urinary tract infections. DIPD related to nitrofurantoin may manifest in several forms, including inflammation of the alveoli or pulmonary vasculature, hemorrhage, fibrosis, or BOOP. Toxicity may be mediated by an immunologic response and/or the release of reactive oxygen species. Some studies have demonstrated that the incidence of DIPD may be decreased by antioxidants such as vitamin C.

Acute pulmonary reactions (those occurring with one month of initiation) are often attributed to hypersensitivity; these patients may present with cough, shortness of breath, and fever. Patients with chronic reactions present with increasing shortness of breath and cough over several months or years, and these conditions are believed to have a toxic etiology. The presentation of chronic nitrofurantoin toxicity may resemble that of IPF.

Treatment of nitrofurantoin-induced toxicity includes immediate discontinuation of nitrofurantoin. In acute cases, clinical improvement is generally seen within one day, and the risk of mortality is minimal at 0.5%. Steroids may be used for patients whose condition does not improve as expected.

**Sulfasalazine**

The most common manifestations of sulfasalazine-induced pulmonary toxicity are pneumonitis and eosinophilic pneumonia secondary to hypersensitivity to the sulfa moiety. Patients with this condition may present with shortness of breath, fever, cough, and eosinophilia. Decreased DLCO is the most frequently seen abnormality on PFT. This reaction tends to occur within the first...
six months of sulfasalazine use. Treatment consists of withdrawal of sulfasalazine. The role of corticosteroids in treating these conditions is controversial; the use of these agents should generally not be recommended.

Less commonly, patients treated with sulfasalazine may develop fibrosing alveolitis, a chronic interstitial pneumonitis with fibrosis, which has poorer outcomes and can be life threatening.26,27 If fibrosing alveolitis is suspected, systemic corticosteroids should be recommended.

Table 1 summarizes the common clinical presentations of the various DIPDs.3-9,12,14,18,25-27

**Risk factors and monitoring plans for medications that can cause DIPD**

Unfortunately, out of the aforementioned medications, only amiodarone and bleomycin have well-described risk factors and monitoring parameters with respect to DIPD.

**Amiodarone**

PFT may not be a reliable monitoring parameter because patients taking amiodarone are almost certain to display some type of abnormality even in the absence of toxicity.3 However, PFT (specifically DLCO) should be performed and a chest x-ray should be obtained at baseline.3,4 Chest x-rays should be repeated yearly while the patient is taking amiodarone. If pulmonary toxicity is suspected, PFT should be performed and a chest x-ray should be obtained as soon as possible.

**Bleomycin**

Bleomycin toxicity appears to be related to dose and duration of therapy. As such, patients should not receive a total cumulative dose greater than 400 units.13 However, toxicity is possible at any dose. Pneumonitis fatalities have been reported in patients receiving a cumulative dose of less than 100 units.

Because bleomycin is primarily renally excreted, individuals with impaired renal function, defined as creatinine clearance lower than 80 mL/min, may be at increased risk for toxicity.28 Cigarette smoking also increases the risk, as does increased age, with the risk potentially increased in patients aged as young as 30 to 40 years.15,28 The use of supplemental oxygen, including that used while scuba diving, may increase the risk of death in patients who have received bleomycin.28 Patients should avoid scuba diving for at least one year after completion of treatment. Patients who have received radiation to the chest may have increased free radicals, and those who have received granulocyte colony-stimulating factor (G-CSF) may have increased cytokines, both of which may increase the risk of toxicity.15,28

Appropriate monitoring for bleomycin toxicity should consist of baseline PFT followed by PFT every three weeks during bleomycin treatment.28 Specifically, decreasing DLCO appears to be predictive of toxicity; bleomycin should be withheld if a 40% to 60% decrease in DLCO from baseline is observed.

**Pathophysiology of IPF**

Although by definition the etiology of IPF is unknown, the current school of thought suggests that the fibrotic process originates in an inappropriate immune system response to alveolar epithelial cell (AEC) injury.29 Potential sources of AEC injury include gastroesophageal reflux disease (GERD), viral respiratory tract infection, and exposure to inhaled irritants, including cigarette smoke. Rather than a normal cellular repair response to this injury, excessive amounts of matrix and collagen are produced, leading to thickening and stiffening of the interstitium and alveoli. Surviving AECs appear to be permanently altered such that they are at increased risk for future damage. Patients who develop IPF are thought to be susceptible because of a number of genetic factors, including malformations of surfactant proteins A2 and C and mutations in telomerase genes. These malformed proteins may increase the vulnerability of AECs to damage from the aforementioned sources, whereas malfunctioning telomerase may accelerate cellular death. Mediators that have been implicated in this fibrotic process include but are not limited to fibroblast growth factor (FGF), insulin-like growth factor-binding protein-5, platelet-derived growth factor (PDGF), TGF-β, TNF-α, and vascular endothelial growth factor (VEGF).

**Clinical presentation and progression of IPF**

IPF is a form of interstitial lung disease, and the most common of the idiopathic interstitial pneumonias.30 This disease affects approximately 150,000 to 200,000 people in the United States alone.31 Patients with IPF manifest with nonspecific pulmonary symptomatology including a nonproductive cough, shortness of breath on exertion, biphasical crackles, and clubbing of the fingers.1 IPF is most commonly seen in patients aged 60 to 80 years who have a history of smoking. Once diagnosed with IPF, the majority of patients have a median survival time of 3.8 years from time of diagnosis,32 with a 20% survival rate at 5 years.30,32

**Pharmacologic treatment options for IPF**

Understanding the planned pathophysiology of IPF has changed over the years, with theories shifting from chronic inflammation to abnormal repair mechanisms of the lungs leading to fibrosis.30 This alteration in the understanding of the pathophysiology of IPF has led to new agents being studied for the management of the disease. At present, there is no cure for IPF; treatment options demonstrating benefit have been studied to hinder disease progression only. As there are a number of new potential targets of therapy and a multitude of studies have recently been published or are ongoing, the focus of this section will be on the updates addressed in the most recent treatment guidelines. A more complete review of new agents can be found elsewhere.29

In 2011, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (LAT) produced guidelines for the management of IPF; the first update since the original consensus statement was released in 2000.33 In this joint 2011 guideline, no pharmacologic agents were specifically recommended for the management of IPF because of a lack of proven benefit. As such, management...
options were to be selected from those given a conditional recommendation against use. This weak recommendation against use reflected the need for higher-quality data before more routine use of the medication could be recommended for IPF.

An update to this guideline was released in July 2015 because of the availability of new trial data and FDA approval of two medications for IPF with an estimated cost of over $100,000/year for their use in the United States (Table 2).1,2,32

On October 15, 2014, the FDA approved pirfenidone and nintedanib for the management of mild-to-moderate IPF. These two agents come with a conditional, or weak, recommendation for use in the management of IPF in the most recent guideline update (Table 2).1,2

The mechanism of pirfenidone in the treatment of IPF has not been established, but this agent has been shown to inhibit the actions of factors associated with the pathophysiologic changes of IPF, such as TGF-β.34

Pirfenidone requires a dosage titration on initiation of treatment, and retreatment should occur in patients who have missed 14 or more days of the medication (Table 3).35 A temporary reduction or cessation in medication therapy may be appropriate for patients experiencing severe side effects of the medication, most notably photosensitivity and diarrhea. Photosensitivity occurs most commonly within the first six months of therapy, and patients should be counseled on proper sun protection. Nausea, vomiting, diarrhea, and dyspepsia are the most common adverse effects occurring within the first three months of therapy; these side effects decrease over time. Elevated liver function tests (LFTs) were seen in clinical studies of pirfenidone, leading to requirements for regular LFT monitoring. LFTs should be assessed before therapy initiation, then monthly for six months, and then every three months. Pirfenidone is a substrate of the cytochrome P (CYP) 450 system, primarily by CYP1A2, and therefore a dose adjustment is required when this agent is used concomitantly with strong and moderate CYP1A2 inhibitors: one pirfenidone capsule three times daily with strong CYP1A2 inhibitors and two capsules three times daily with moderate CYP1A2 inhibitors.35

Phase 2 trials suggested a benefit with pirfenidone,34,36 and multiple phase 3 trials then confirmed this benefit. Two studies (CAPACITY 004 and 006) assessed the effect of pirfenidone compared to placebo in patients with IPF. Study 004 showed that statistically fewer patients taking pirfenidone had a change in forced vital capacity (FVC) of at least 10% versus those taking placebo, with patients taking pirfenidone demonstrating a reduction in disease progression over the 72-week period.37 This outcome did not meet significance in Study 006, but significant improvements in patients with a change in FVC of at least 10% with pirfenidone were demonstrated in a pooled analysis.37 Patients treated with pirfenidone in the pooled analysis also had significant improvements in six-minute walk distance, and progression-free survival with numerical improvements in all-cause mortality, and mortality related to IPF in the pooled analysis.37 Similar to the CAPACITY trials, the ASCEND study demonstrated improvements with pirfenidone in the rate of decline of lung function as assessed by FVC and in six-minute walk distance. However, no significant improvements in dyspnea or mortality were observed.38 Based on the reduction in the rate of pulmonary decline, pirfenidone was given a conditional recommendation for use in the 2015 guidelines.2

Nintedanib is a tyrosine kinase inhibitor that antagonizes the receptors of several inflammatory mediators, including but not limited to FGF, PDGF, and VEGF. This agent is approved for the treatment of IPF at a dose of 150 mg twice daily taken with food. The most common adverse effect associated with nintedanib is diarrhea, which is most likely to occur within the first three months of treatment. Other notable adverse effects include nausea, vomiting, and abdominal pain. For patients experiencing adverse effects, a temporary reduction in the dose to 100 mg daily or cessation of the medication may be needed. As elevated LFTs were noted in clinical trials, LFTs must be assessed before the initiation of treatment, then monthly for three months, and then every three months. Nintedanib should not be used in pregnant women because of the risk for fetal harm, and women should be counseled on appropriate use of contraception during nintedanib treatment. Other precautions for the use of nintedanib include an increased risk of bleeding, gastrointestinal perforation, and arterial thromboembolic events. Nintedanib is a substrate of P-glycoprotein and CYP3A4, and coadministration of medications affecting these pathways may cause elevations in nintedanib exposure.39
Nintedanib has been found to be effective at reducing disease progression and improving lung function. In TOMORROW, a phase 2 trial over a 12-month period, patients were randomized to receive placebo or nintedanib dosed at 50 mg daily, 50 mg twice daily, 100 mg twice daily, or 150 mg twice daily.\(^4^6\) Compared to placebo, nintedanib 150 mg twice daily demonstrated improved outcomes pertaining to lung function. Secondary outcomes such as exacerbations and respiratory quality of life scores were also significantly improved in the nintedanib groups. However, nintedanib 150 mg twice daily was also associated with a higher number of patients discontinuing treatment because of adverse effects, the most common of which were gastrointestinal in nature. In two phase 3 trials, INPULSIS-1 and INPULSIS-2, nintedanib 150 mg twice daily was compared to placebo for a 52-week period.\(^4^7\) Treatment with nintedanib was associated with improvements in the rates of decline of pulmonary function over time as measured by FVC. As in the phase 2 trial, nintedanib was associated with higher rates of gastrointestinal side effects, leading to more discontinuations of the study drug. Based on the results of these trials, the 2015 guideline conditionally recommends the use of nintedanib for patients with IPF.\(^2\)

With the most recent guideline update, four medications were given the designation of conditional recommendation against use in IPF, which is similar to the previous guideline designation of weak recommendation against use (Table 2).\(^1,^2\) One such agent, N-acetylcysteine, maintained its designation from the 2011 guidelines. As a free radical scavenger, N-acetylcysteine may be of benefit for patients with IPF, as an imbalance of oxidants and antioxidants may play a role in disease progression.\(^5^2\) When studied as monotherapy, this agent was associated with no statistical difference in FVC versus placebo\(^6^3,^4^4\) and demonstrated no benefit on mortality or exacerbation outcomes.\(^4^4\)

Sildenafil, a phosphodiesterase-5 inhibitor, has also been studied for use in the IPF population. STEP-IPF, a phase 3 trial comparing sildenafil to placebo over a 12-week treatment period followed by a 12-week open-label assessment of sildenafil in all patients, found no significant difference between sildenafil and placebo in the primary outcome (improvement of ≥20% in six-minute walk distance at 12 weeks).\(^4^5\) Statistically significant improvements with sildenafil were observed for some secondary outcomes, including the University of California, San Diego Shortness of Breath Questionnaire; the St George’s Respiratory Questionnaire; and the carbon monoxide diffusion capacity. The two groups demonstrated no difference in adverse event rates. A similar lack of benefit with sildenafil for the six-minute walk distance was observed in another small trial conducted over a six-month period.\(^4^6\) The 2011 guidelines did not make recommendations regarding the use of sildenafil. However, sildenafil was given the designation of conditional recommendation against use for IPF in the 2015 guidelines because of the lack of clinical benefit in pertinent outcomes and cost of therapy (Table 2).\(^1,^2\)

Bosentan and macitentan, dual endothelin receptor A and B antagonists used in the treatment of pulmonary hypertension, have also been studied in patients with IPF.\(^2,^4^7\) These agents were thought to benefit patients with IPF by blocking the effects of endothelin-1, a growth factor and vasoconstrictor thought to be involved in the pathophysiology of both IPF and pulmonary hypertension. Macitentan was not addressed in the 2011 guideline, but bosentan was given a strong recommendation against use because of the cost of therapy and quality of evidence. Since the 2011 guidelines were released, newer evidence regarding both agents has become available.\(^1\) The BUILD-1 and BUILD-3 trials assessed bosentan versus placebo in the IPF population.\(^4^8,^4^9\) BUILD-1 occurred over 12 months and found no difference between bosentan and placebo in improvement of the six-minute walk distance. Bosentan was more effective than placebo in secondary outcomes of the trial including quality of life scales and time to disease progression or death, although these differences were not significant.\(^4^8\) BUILD-3 similarly found a nonsignificant improvement in the primary outcome of time to death or IPF progression in the bosentan group versus placebo, with no significant improvements in quality of life questionnaires.\(^4^9\) Similarly, the MUSIC study, a phase 2 trial comparing macitentan to placebo, did not demonstrate a significant difference with macitentan in the primary outcome of change in FVC or in the secondary outcome of mortality at 12 months.\(^3^0\) As such, both agents were given a conditional recommendation against use in the 2015 guidelines because of lack of mortality benefit and high cost of therapy (Table 2).\(^1,^2\)

Unlike other pulmonary hypertension medications shown to have some benefit in secondary outcomes such as dyspnea in the IPF population, ambrisentan has been found to be potentially detrimental to patients with IPF. Similar to bosentan and macitentan, ambrisentan works through
The use of imatinib, a tyrosine kinase inhibitor similar to nintedanib, was not addressed in the 2011 guidelines, but the 2015 update strongly recommends against the use of this agent in patients with IPF. This trial failed to demonstrate benefit for imatinib versus placebo in the outcomes of disease progression or death, and imatinib was associated with an increased risk of adverse events over a 96-week period.

Before the release of the 2011 guidelines, one study evaluated the use of anticoagulants plus corticosteroids versus corticosteroids alone in patients with IPF and found that the addition led to preservation of FVC at 12 months. Based on the data available, the 2011 guidelines made a weak recommendation against the use of this combination. Because of the methodological issues with INFIGENIA, another study, PANTHER-IPF, was conducted to assess the effect of the three-drug regimen on patients with IPF. This trial was stopped early at a planned interim analysis because of an increased risk of death and hospitalization in the triple-therapy group. Based on these results, the 2015 guideline recommends strongly against the use of this combination therapy because of the potential for harm.

IPF is associated with a number of comorbid conditions. Two such disease states are GERD and pulmonary hypertension, both of which occur in patients with IPF to significant degrees. GERD has been suggested as a risk factor for IPF due to microaspiration leading to AEC injury. In addition, GERD is common in patients with IPF. As such, management of this comorbid condition is a focus to prevent worsening of disease. Both the 2011 and 2015 guidelines provided a conditional recommendation for the use of acid suppression therapy in patients with IPF due to the potential for improvements in survival and lung function. Similar to GERD, pulmonary hypertension is a common comorbid condition found in patients with IPF that impact the disease prognosis.

Current guidelines make no specific recommendations regarding the effective management of pulmonary hypertension in patients with IPF; however, consideration should be given to the worsened outcomes seen in patients with IPF who were treated with ambrisentan, as such it should be avoided in IPF with a strong recommendation against use regardless of pulmonary hypertension diagnosis. Other treatment considerations for patients with IPF should include the use of long-term oxygen therapy in patients with resting hypoxemia, pulmonary rehabilitation, vaccinations, lung transplantation, and palliative care as appropriate.

Conclusion

DIPD is a potential adverse effect of many commonly prescribed medications, including but not limited to amiodarone, ACE-Is, aspirin, beta-blockers, bleomycin, cyclophosphamide, methotrexate, nitrofurantoin, and sulfasalazine. Before initiation of treatment with these medications, pharmacists should counsel patients about potential symptoms that may indicate pulmonary toxicity. Specifically, patients taking amiodarone should undergo chest x-ray and PFT, including DLCO, at baseline, with chest x-ray repeated annually. Patients taking bleomycin should undergo baseline PFT with PFT repeated every three weeks until the end of treatment. Although management of DIPD is specific to the offending medication, in all cases, the primary intervention is immediate cessation of the injurious agent.

With new information and updated ATS/ERS/JRS/ALAT guidelines available for the management of IPF, change to current practices will need to occur. Agents previously used, such as N-acetylcysteine and anticoagulation, have not been found to be helpful and may in some cases be harmful in this patient population. In patients with IPF, initial therapy should include either pirfenidone or nintedanib. The currently available clinical data and guidelines do not preferentially select one agent over another. Future research should evaluate the potential for combination or sequential therapy with these agents to allow for better care. With improved understanding of the pathophysiology of IPF, new trials are ongoing, which could potentially lead to more effective therapy over the longer term.

References are available online at www.drugtopics.com/cpe.
1. Which of the following statements about nintedanib is most correct?
   a. Nintedanib has been shown to reduce mortality in IPF compared to placebo.
   b. Nintedanib has been shown to worsen six-minute walk distance in patients with IPF.
   c. Nintedanib has been shown to decrease exacerbation rates in patients with IPF.
   d. Nintedanib has been shown to worsen pulmonary function in patients with IPF.

2. Which of the following statements about pirfenidone is most correct?
   a. Pirfenidone has been shown to reduce mortality in IPF compared to placebo.
   b. Pirfenidone has been shown to worsen six-minute walk distance in patients with IPF.
   c. Pirfenidone has been shown to improve six-minute walk distance in patients with IPF.
   d. Pirfenidone has been shown to worsen pulmonary function in patients with IPF.

3. Which of the following statements about N-acetylcysteine is most correct?
   a. N-acetylcysteine is conditionally recommended for use in IPF.
   b. N-acetylcysteine as monotherapy has been shown to improve mortality outcomes in IPF.
   c. Guidelines have conditionally recommended against use of N-acetylcysteine in IPF.
   d. N-acetylcysteine as monotherapy has been shown to worsen mortality outcomes in IPF.

4. Which of the following statements best describes the appropriate use of the combination N-acetylcysteine/azathioprine/prednisone for the treatment of IPF?
   a. This combination should be recommended in all patients, as it has been shown to reduce mortality in patients with IPF.
   b. This combination should not be recommended, as it has been shown to increase hospitalization and mortality in patients with IPF.
   c. This combination should be recommended in all patients, as it has been shown to reduce hospitalizations in patients with IPF.
   d. This combination should not be recommended, as it has not been shown to preserve FVC in patients with IPF.

5. Which of the following statements best describes the relationship of GERD to IPF?
   a. GERD is independent of IPF.
   b. GERD is a potential source of alveolar epithelial cell injury.
   c. Patients with IPF do not require therapy for GERD.
   d. IPF causes GERD.

6. Which of the following statements best reflects the current guideline recommendations for the treatment of pulmonary hypertension in patients with IPF?
   a. Ambrisentan is the drug of choice.
   b. Pirfenidone is the drug of choice.
   c. Sildenafil is the drug of choice.
   d. There are no specific recommendations at this time.

7. Which of the following patients is most likely to have IPF?
   a. A 7-year-old boy with exercise-induced wheezing and nonproductive cough.
   b. A 27-year-old woman with dyspnea while running and no significant past medical history.
   c. A 47-year-old man with a productive cough and a significant smoking history.
   d. A 77-year-old man with a nonproductive cough and clubbing of the fingers.

8. Which of the following statements best reflects the current thought process regarding IPF pathophysiology?
   a. A disease of chronic inflammation leading to scarring of the lungs.
   b. A disease of allergic inflammation leading to improper repair of the lungs.
   c. An inappropriate immune response to alveolar epithelial cell injury leading to fibrosis.
   d. Alveolar epithelial cell injury leading to an appropriate immune response and fibrosis.

9. Which of the following LFT monitoring recommendations matches the medication listed?
   a. Pirfenidone: before initiation and monthly thereafter.
   b. Nintedanib: before initiation and every three months thereafter.
   c. Pirfenidone: before initiation, then monthly for three months, and then every three months thereafter.
   d. Nintedanib: before initiation, then monthly for three months, and then every three months thereafter.

10. Which of the following best matches the mechanism of action to the agent?
    a. Sildenafil: unknown.
    c. Pirfenidone: tyrosine kinase inhibitor.
    d. Nintedanib: tyrosine kinase inhibitor.

11. Which of the following is true regarding pulmonary function testing in patients taking bleomycin?
    a. Pulmonary function testing should be conducted at baseline and at the first sign of toxicity.
    b. Pulmonary function testing should be conducted at baseline and every three months thereafter.
    c. Pulmonary function testing should be conducted at baseline and every three months thereafter.
    d. Pulmonary function testing should be conducted at baseline and every three months thereafter.

12. Which of the following statements describes an appropriate monitoring plan for a patient taking adalimumab?
    a. Chest x-ray and pulmonary function testing should be conducted at baseline only.
    b. Chest x-ray and pulmonary function testing should be conducted at baseline and annually.
    c. Chest x-ray and pulmonary function testing should be conducted at baseline and chest x-ray should be repeated annually.
    d. Chest x-ray and pulmonary function testing should be conducted at baseline, and pulmonary function testing should be repeated annually.

13. Which of the following patients is most likely to present with AIA?
    a. A 35-year-old woman with asthma and nasal polyps.
    b. A 42-year-old man with asthma.
    c. A 21-year-old woman with nasal polyps.
    d. A 28-year-old man with allergic rhinitis.

14. Which of the following is true regarding amiodarone-induced pulmonary toxicity?
    a. Pulmonary toxicity only occurs at doses greater than 400 mg.
    b. Hypersensitivity pneumonitis typically presents months to years after starting amiodarone.
    c. Pulmonary alveolitis typically presents within weeks of starting amiodarone.
    d. Pulmonary toxicity may occur at any dose.

15. Which of the following is the most common type of pulmonary toxicity associated with bleomycin?
    a. Intestinal pneumonitis.
    b. Bronchiolitis obliterans with organizing pneumonia.
    c. Alveolar hemorrhage.
    d. Eosinophilic hypersensitivity.

16. Which of the following best explains why it is difficult to determine the true risk of methotrexate-induced pulmonary disease?
    a. Methotrexate-induced pulmonary disease is extremely rare.
    b. Methotrexate-induced pulmonary disease only occurs at high doses.
    c. Methotrexate-induced pulmonary disease is difficult to distinguish from pulmonary manifestations of rheumatoid arthritis.
    d. Methotrexate-induced pulmonary disease is difficult to distinguish from viral upper respiratory tract infections.

17. The risk of pulmonary toxicity among first-time users of nitrofurantoin is approximately:
    a. One in five.
    b. One in 50.
    c. One in 500.
    d. One in 5000.

18. The most common etiology for pulmonary toxicity associated with sulfasalazine is:
    a. Unknown.
    b. Hypersensitivity.
    c. Direct cellular toxicity.
    d. Reactive oxygen species.

19. Which of the following is true of ACE-I-induced cough?
    a. Patients present with a productive cough.
    b. Antifungals are an effective treatment for ACE-I-induced cough.
    c. Cough typically resolves within 4 weeks of ACE-I discontinuation.
    d. Cough is caused by increased breakdown of bradykinin.

20. Which of the following beta-blockers is least likely to induce bronchospasm in a patient with preexisting asthma/COPD?
    a. Propranolol.
    b. Metoprolol.
    c. Timolol.
    d. Nadolol.
References


