<table>
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<tr>
<th>Program Name:</th>
<th>Idiopathic pulmonary fibrosis: an approach to early recognition and referral</th>
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</table>
| Planning Committee: | Dr. Gerard Cox  
Dr. Alan Kaplan  
Dr. Suzanne Levitz  
Dr. Robert Woodland |
| Accreditation Information: | This version of the program is unaccredited and intended for informational purposes only. An accredited version is available online at [www.mdBriefCase.com](http://www.mdBriefCase.com) / [www.AdvancingIn.com](http://www.AdvancingIn.com) until Monday December 8, 2014 |
| Sponsor: | This case study is supported by an educational grant from Boehringer Ingelheim |
LEARNING OBJECTIVES

- Review the epidemiology of IPF
- Describe the diagnostic assessment for IPF

PRE-/POST-COURSE SURVEY

1. How likely are you to consider a diagnosis of idiopathic pulmonary fibrosis (IPF) in an elderly patient with chronic unexplained dyspnea on exertion? (1 = very unlikely; 5 = very likely)
2. How would you rate your familiarity with the clinical features of IPF (1 = not at all familiar; 5 = very familiar)
3. How confident are you about monitoring and following patients with IPF (1 = not at all confident; 5 = very confident)

PRE-/POST-TEST

1. Which age group is most likely to be affected by IPF?
   a) Children aged <12 years
   b) Adolescents
   c) Adults aged <50 years
   d) Individuals aged >50 years

2. The median survival of patients following a diagnosis of IPF is
   a) <1 year.
   b) 2-3 years.
   c) 5-10 years.
   d) similar to the general population.

3. Common findings on pulmonary function testing (PFT) in IPF include all of the following, EXCEPT:
   a) Reduction in total lung capacity
   b) Decreased forced vital capacity (FVC)
   c) Reversible airflow obstruction
   d) Reduced diffusing capacity of carbon monoxide (DL_{CO}).

4. In most cases, the diagnosis of IPF can be made with
   a) clinical examination alone.
   b) chest X-ray.
   c) high resolution computed tomography (HRCT).
   d) 6-minute walk test (6MWT).
5. True or false: Breathlessness can be a feature of chronic obstructive pulmonary disease (COPD), but as chest X-rays are largely normal in COPD patients, even subtle radiographic abnormalities such as increased interstitial markings or nodular opacities should warrant further investigation.

   a) True  
   b) False

BACKGROUND INFORMATION

Idiopathic pulmonary fibrosis (IPF) is the most common and deadly of the interstitial lung diseases (ILDs), which are a group of diffuse parenchymal lung disorders that share similar clinical, radiographic, physiologic or pathologic features. [1, 2] Most ILDs are "restrictive" disorders in which the lungs have a reduced ability to expand on inhalation. This is in contrast to "obstructive" disorders such as asthma, chronic obstructive pulmonary disease (COPD) and emphysema, in which the airways are narrowed so that the patient cannot exhale completely. [3] ILDs may be associated with environmental or occupational exposures (e.g., asbestosis, silicosis), the use of certain drugs (e.g., chemotherapeutic agents, biologic therapies, and cardiovascular drugs), or with connective tissue disorders (e.g., systemic sclerosis, polymyositis/dermatomyositis and rheumatoid arthritis). [3-5]

Unlike other ILDs for which a cause may be identified, IPF is a disease of unknown cause. It is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs. [6]

Epidemiology

IPF is a rare disease, so it is difficult to study its epidemiology. In published studies, the prevalence of IPF has varied from 0.7 to 63.0 per 100,000, and the incidence has ranged from 0.6 to 17.4 per 100,000 person-years. [2] No accurate prevalence data are available for Canada; but it is estimated that there are approximately 5,000-10,000 patients with IPF in Canada, with 3,000-4,000 new cases each year. [7] The incidence and prevalence of IPF appear to be increasing, and may be higher than reported in the literature because of reporting and recognition bias. [2]

Ask the expert question (for video)

• How common is IPF in Canada?

Risk factors

Although IPF is a disease of unknown etiology, various risk factors have been described. The identification of risk factors is important because it can facilitate prevention strategies, early diagnosis, and management. Risk factors for IPF include cigarette smoking, environmental exposures, microbial agents, and gastro esophageal reflux. Smoking is strongly associated with IPF, particularly for individuals with a smoking history of more than 20 pack-years. However, IPF should be suspected even in the absence of a smoking history when a patient presents with dyspnea (especially exertional dyspnea) with/without persistent dry cough. [6, 8] Environmental exposures implicated in the etiology of IPF include farming, livestock, raising birds, vegetable dust/animal dust, metal dust, stone cutting/polishing,
and hairdressing. [9] Among microbial agents, viruses are believed to play a role in the initiation and progression of IPF, and viral infection may contribute to a proportion of acute exacerbations, while the role played by bacteria in the pathogenesis of IPF is less clear. [10] Gastroesophageal reflux leads to microaspiration of gastric contents, causing repetitive lung injury and resulting pulmonary fibrosis in susceptible individuals. [2, 11]

Genes associated with familial IPF include telomerase-related genes (TERT and TERC), surfactant proteins C (SPC) and A2 (SPA2), and ELMOD2. [2] Mutations in the TERC and TERT genes have been found in about 15% of all cases of familial pulmonary fibrosis and a smaller percentage of cases of sporadic idiopathic pulmonary fibrosis. [12] A polymorphism in the promoter of MUC5B is associated with IPF. [13]

Ask the expert question (for video)

- What are the risk factors for IPF?

Clinical presentation

IPF typically presents in the sixth and seventh decades; it is rare in individuals aged <50 years. More males than females are affected; most patients have a history of cigarette smoking. A diagnosis of IPF should be considered in all adult patients with unexplained chronic exertional dyspnea. [6, 14]

The clinical manifestations of IPF are nonspecific. The disease commonly presents with exertional dyspnea, cough, bibasilar inspiratory crackles, and finger clubbing. Dyspnea tends to develop insidiously, often over ≥6 months, and to progress steadily, and is an important factor contributing to impairment in the patient’s health-related quality of life. Over 80% of patients report a non-productive, and often intractable, cough refractory to antitussive medications. Fine, or Velcro-like crackles may be the earliest clinical finding, and are reported in over 90% of patients with IPF. About 25-50% of patients display finger clubbing. [6, 14]

Signs of connective tissue disease including joint deformity, synovitis, muscle weakness and rash make IPF unlikely and should prompt further investigation into rheumatologic disease. [14]

A minority of patients experience acute exacerbations of IPF, characterized by worsening of respiratory symptoms over ≤30 days accompanied by hypoxemia and appearance of new radiographic infiltrates, for which no cause (e.g., pneumonia, pulmonary embolism, pneumothorax, or cardiac failure) can be identified. Acute exacerbations can occur in patients with known IPF, but may also be the initial manifestation of IPF. [15-17]

Ask the expert question (for video)

- What are the clinical manifestations of IPF?

Natural history

IPF follows a course of progressive decline in pulmonary function, eventually resulting in death from respiratory failure or complicating comorbidity. Most patients experience slow and gradual progression
over many years. In other patients, progression may be rapid, or may be marked by periods of relative stability interposed with periods of acute respiratory decline. [18]

The median survival of patients following a diagnosis of IPF is 2-3 years, but some patients may live much longer. The most frequent cause of death is respiratory failure. Factors associated with a shorter survival time include older age, smoking history, lower body mass index (BMI), more severe physiologic impairment, greater radiologic extent of disease, and other complications or conditions, particularly pulmonary hypertension, emphysema, and malignancy. [18]

Investigations

**Chest X-ray:** The chest X-ray may usually shows a symmetric peripheral, basilar reticular opacity with lower lobe volume loss (Figure 1). About 10% of patients have normal chest X-rays. [14, 19]

![Chest X-ray](image)

Figure 1. (Left) Chest X-ray of a patient with IPF, showing bilateral reticular infiltrates with lower lobe predominance, [19] compared with (Right) normal chest X-ray

**Pulmonary function testing:** Usual findings include a reduction in total lung capacity. Most patients with IPF also exhibit decreased forced vital capacity (FVC), but the FVC may be normal early in the course of the disease. Other findings may include normal-to-increased forced expiratory volume in 1 second to FVC ratio (FEV1/FVC), and reduced diffusing capacity of carbon monoxide (DLco). Low baseline FVC, decline in FVC and low DLco are associated with decreased survival in IPF. [14]

**6-minute walk test (6MWt):** The 6MWt is a reliable, valid, and responsive measure of disease status in IPF. A decline in the 6-minute walk distance (6MWD) is associated with decreased survival in IPF. [14, 20]

**High resolution computed tomography (HRCT) scan:** HRCT has good specificity for IPF, and in most cases, can be used to diagnose the disease. HRCT generally shows a pattern of usual interstitial pneumonia (UIP), characterized by reticular opacities, often associated with honeycombing and traction bronchiectasis (Table 1). Honeycombing manifests as clustered cystic airspaces, which are usually subpleural, and characterized by well-defined walls. Ground glass opacities may be present, but are usually less extensive than the reticulation (Figure 2). [6]

Table 1. **HRCT criteria for UIP pattern** [6]
<table>
<thead>
<tr>
<th>UIP pattern (all 4 features)</th>
<th>Possible UIP pattern (all 3 features)</th>
<th>Inconsistent with UIP pattern (any of the 7 features)</th>
</tr>
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</table>
| • Subpleural, basal predominance  
  • Reticular abnormality  
  • Honeycombing with/without traction bronchiectasis  
  • Absence of features listed as inconsistent with UIP pattern (see third column) | • Subpleural, basal predominance  
  • Reticular abnormality  
  • Absence of features listed as inconsistent with UIP pattern (see third column) | • Upper or mid-lung predominance  
  • Peribronchovascular predominance  
  • Extensive ground glass abnormality (extent > reticular abnormality)  
  • Profuse micronodules (bilateral, predominantly upper lobes)  
  • Discrete cysts (multiple, bilateral, away from areas of honeycombing)  
  • Diffuse mosaic attenuation/air-trapping (bilateral, in ≥3 lobes)  
  • Consolidation in bronchopulmonary segment(s)/lobe(s) |

Figure 2. **HRCT images showing UIP pattern and possible UIP pattern** [6]
(A and B) UIP pattern, with extensive honeycombing: axial and coronal HRCT images show basal predominant, peripheral predominant reticular abnormality with multiple layers of honeycombing (arrows).
(C and D) UIP pattern, with less severe honeycombing: axial and coronal CT images show basal predominant, peripheral predominant reticular abnormality with subpleural honeycombing (arrows).
(E and F) Possible UIP pattern: axial and coronal images show peripheral predominant, basal predominant reticular abnormality with a moderate amount of ground glass abnormality, but without honeycombing.

**Surgical lung biopsy:** IPF is characterized by a histopathologic pattern of UIP (Figure 3 and Table 2), in which areas of fibrotic and normal alveolar tissue occur adjacent to each other. [21]
Figure 3. **UIP pattern of fibrosis** [21]

A. Geographic (or spatial) heterogeneity, with areas of pulmonary fibrosis (at the pleural surface and lower right) alternating with areas of uninvolved parenchyma (lower left).

B. Higher magnification shows the temporal heterogeneity of the fibrosing process. Arrow points to immature fibrosis in the form of fibroblast foci.

### Table 2. **Histopathological criteria for UIP pattern** [6]

<table>
<thead>
<tr>
<th>UIP pattern (all 4 criteria)</th>
<th>Probable UIP pattern</th>
<th>Possible UIP pattern (all 3 criteria)</th>
<th>Not UIP pattern</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hyaline membranes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Organizing pneumonia</td>
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<tr>
<td>Evidence of marked fibrosis/architectural distortion, ± honeycombing in a predominantly subpleural/paraseptal distribution</td>
<td>Evidence of marked fibrosis/architectural distortion, ± honeycombing</td>
<td>Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
<td></td>
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<tr>
<td>Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>Absence of either patchy involvement or fibroblastic foci, but not both</td>
<td>Absence of other criteria for UIP (see UIP pattern column)</td>
<td></td>
</tr>
<tr>
<td>Presence of fibroblast foci</td>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td></td>
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<tr>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) OR Honeycomb changes only</td>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Other features suggestive of an alternate diagnosis</td>
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Surgical lung biopsy may be considered for patients whose HRCT findings may be described as possible UIP pattern, or inconsistent with UIP pattern. This procedure is known to be associated with several complications, and the decision requires a thorough consideration of its risks and benefits. [21]

Performing a surgical lung biopsy is becoming more difficult due to an increasingly ageing population, leaving patients without a clear diagnosis, and posing treatment challenges. [22]

**Ask the expert question (for video)**

- How is IPF diagnosed?
Diagnosis and referral

Breathlessness and cough are common symptoms in elderly patients, most notably due to COPD and heart failure. ILD should be suspected in patients presumed to have COPD or heart failure (early pulmonary function testing can facilitate detection), who fail to benefit from treatment for these conditions. Patients with COPD have largely normal chest radiographs, and even subtle abnormalities such as increased interstitial markings or nodular opacities should warrant further investigation. ILD should also be considered in middle-aged or elderly patients presenting with unexplained chronic dyspnoea on exertion, or cough of several months’ duration. [3]

Patients with evidence of ILD should be evaluated for an identifiable cause. If no cause can be identified, the finding of a UIP pattern on HRCT is diagnostic of IPF. If HRCT does not show a UIP pattern, IPF is diagnosed with specific combinations of HRCT and histopathological patterns. Requirements for a diagnosis of IPF are as follows [6]:

1. Exclusion of other known causes of ILD (e.g., environmental exposures, connective tissue disease, drug toxicity)
2. UIP pattern on HRCT in patients not subjected to surgical lung biopsy
3. Specific combinations of HRCT and histopathological patterns in patients subjected to surgical lung biopsy (for details, [click here])

A diagnostic algorithm for IPF is provided in Figure 4.

Figure 4. [Diagnostic algorithm for IPF] [6] (MDD = multidisciplinary discussion)

Making a diagnosis of IPF can be difficult. Isolated radiographic or histopathologic findings suggestive of UIP can be due to conditions other than IPF, and on the other hand, radiographic or histopathologic UIP may not always be found in IPF. The accuracy of IPF diagnosis can be increased by adopting a
multidisciplinary approach which involves the clinician, radiologist, and pathologist. [6, 23] If multidisciplinary evaluation cannot be done locally or if diagnostic doubt remains following multidisciplinary evaluation, early referral to a centre specializing in ILD/IPF is recommended. [14] For a list of ILD/IPF clinics in Canada, click here.

Primary care physicians play a key role in facilitating the diagnosis of ILD by referring patients with relevant symptoms to a respirologist and, in some cases, by ordering HRCT. [3] In practice, the diagnosis of IPF is commonly delayed, and greater awareness of IPF amongst primary care providers is needed for improving IPF diagnosis. A patient survey, [24] the first of its kind in Canada, found that 97% of patients see a primary care provider before diagnosis, but in only 15% of cases did the provider suggest IPF as the cause of their symptoms. On average, patients wait 20 months to receive a confirmed diagnosis of IPF from onset of their symptoms, and 11 months from first presentation of symptoms to a health care provider. On average, 32% of respondents reported receiving one diagnosis other than IPF, and 15% of patients reported receiving ≥3 diagnoses.

Ask the expert question (for video)

• How can primary care providers facilitate early diagnosis of IPF?

Treatment

New guidelines for the management of IPF are expected in 2015. For current treatment recommendations as per joint guidelines from American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT), click here.

CASE STUDY 1

Josh, a 65-year old male, presents to his primary care physician with a 1-year history of dyspnoea on exertion and cough. He feels that the dyspnea has been gradually becoming worse. His cough is non-productive, and cough medications do not appear to provide much relief.

Josh is a current smoker, and has been smoking approximately one pack of cigarettes a day for approximately 35 years. He also has a history of gastroesophageal reflux disease (GERD).

Auscultation reveals basal inspiratory crackles. Physical examination is otherwise unremarkable.

The chest X-ray appears largely normal, except for the presence of bilateral, peripheral opacities.

Chronic obstructive pulmonary disease (COPD) is suspected. Josh is advised to stop smoking, and is prescribed a short-acting bronchodilator for use as needed.

A month later, Josh complains of worsening dyspnea. He says that the bronchodilator is not useful.
1. Idiopathic pulmonary fibrosis (IPF) most commonly presents as
   a) Dyspnea at rest and productive cough.
   b) Exertional dyspnea, cough, bibasilar inspiratory crackles, and finger clubbing.
   c) An acute exacerbation, associated with marked worsening of lung function in a patient previously experiencing mild respiratory symptoms.
   d) Manifestations of right heart failure.

2. Regarding risk factors for IPF:
   a) Smoking is not a risk factor for IPF.
   b) Bacterial infections are strongly implicated in the pathogenesis of IPF.
   c) Gastroesophageal reflux disease (GERD) is a known risk factor for IPF.
   d) No risk factors for IPF have been identified to date.

Josh is referred to a pulmonologist, who orders pulmonary function testing (PFT) and high resolution computed tomography (HRCT). PFT shows decreased total lung capacity and reduced diffusing capacity of carbon monoxide (DLco). HRCT shows a pattern of usual interstitial pneumonia (UIP). No cause for interstitial lung disease (ILD) can be identified. A diagnosis of IPF is made, and treatment is initiated.

3. A usual interstitial pneumonia (UIP) pattern on HRCT includes:
   a) Reticular opacities with basal and subpleural predominance, associated with a honeycombing appearance.
   b) Opacities with upper or mid-lung predominance.
   c) Reticular opacities together with extensive ground glass abnormality (ground glass abnormality > reticular abnormality)
   d) Bilateral peribronchial opacities.

4. Which of the following statements regarding the treatment of IPF is correct?
   a) IPF is an inflammatory disease which responds to treatment with anti-inflammatory drugs.
   b) Several randomized controlled trials have documented the efficacy of high dose corticosteroid therapy for managing acute exacerbations of IPF.
   c) IPF does not respond to, and should not be treated with, corticosteroid or immunosuppressant therapy.
   d) Anticoagulation is a mainstay of IPF management.
CASE STUDY 2

Joan is a 55-year old female with a 6-month history of dyspnea and cough, diagnosed as asthma. She is being treated with antiasthmatic medications. Joan is a past smoker, having smoked 5-10 cigarettes a day for approximately 20 years.

Joan now complains of malaise, fatigue, and worsening of her respiratory symptoms. She has also complains of joint pains.

A physical examination reveals inspiratory crackles. PFT results demonstrate restrictive physiology with reduced diffusing capacity, and HRCT scanning confirms a diagnosis of ILD. A diagnosis of IPF is considered.

1. How can Joan's joint pains influence a possible diagnosis of IPF?

   a) Joint pains are a feature of IPF, which increases the likelihood that Joan has this disease.
   b) Joan's joint pains may be caused by a rheumatologic disease, which would make a diagnosis of IPF unlikely, and should prompt rheumatologic investigation.
   c) Joan's joint pains may be caused by a rheumatologic disease, which is a cause of IPF, and therefore increases the likelihood of a diagnosis of IPF.
   d) Joan's joint pains are not relevant to making a diagnosis of IPF.

Joan is investigated for rheumatologic disease, and is found to have rheumatoid arthritis (RA), which is now considered to be the cause of her ILD. Hence Joan does not have IPF.

2. Which of the following statements is correct?

   a) Like IPF, other ILDs should not be treated with corticosteroids or immunosuppressants.
   b) ILD associated with RA has a better prognosis than IPF.
   c) Differentiating between IPF and other ILDs is not important because the treatment remains the same.
CASE STUDY 3

Adam, a 76-year old male, with diabetes mellitus and coronary heart disease, presents to his primary care provider with chronic dyspnea. Possible causes for this patient’s dyspnea, including asthma, COPD, and heart failure are ruled out.

The patient is referred to a respiratory diseases specialist, who orders HRCT. HRCT of the lung fields shows subpleural reticular opacities predominantly involving the lung bases. Ground glass opacities, less extensive than the reticulation, are also present. Honeycomb appearance is not present. In view of its risks, surgical lung biopsy is not done.

1. In the absence of features inconsistent with the UIP pattern, HRCT findings of reticular opacities with subpleural, basal predominance, associated with honeycombing, would represent
   a) definite IPF.
   b) possible IPF.
   c) not IPF

KEY LEARNING POINTS

- IPF is a fibrotic lung disease of unknown cause, and is the most common and deadly of the ILDs.
- Risk factors for IPF include cigarette smoking, environmental exposures, microbial agents, and gastroesophageal reflux.
- IPF typically presents in the sixth and seventh decades; it is rare in individuals aged <50 years.
- IPF commonly presents with exertional dyspnea, cough, bibasilar inspiratory crackles, and finger clubbing. IPF follows a course of progressive decline in pulmonary function, eventually resulting in death from respiratory failure or complicating comorbidity.
- ILD/IPF should be suspected in patients presumed to have COPD or heart failure, who fail to benefit from treatment for these conditions. Primary care physicians can facilitate the diagnosis of ILD by referring patients with relevant symptoms to a pulmonologist.
- Signs of connective tissue disease including make IPF unlikely and should prompt further investigation into rheumatologic disease.
- HRCT has good specificity for IPF, and in most cases, can be used to diagnose the disease.
- Patients with IPF should be monitored every 4-6 months, or sooner as clinically indicated, for signs of disease progression and for disease- or treatment-related complications.
DISCUSSION FORUM

- What are your suggestions for earlier diagnosis of IPF?
- In your opinion, what are the barriers to the optimal care of IPF patients and how can they be overcome?

RESOURCES

- ATS/ERS/JRS/ALAT Guidelines
- Canadian Pulmonary Fibrosis Foundation
- Canadian Lung Association

REFERENCES


