Clinico Radiological Series
IMAGING OF
INTERSTITIAL LUNG DISEASES
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The concept of multidisciplinary teams working together to care for patients and to find solutions
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Interstitial lung disease, the very phrase sends many a shivers down the spines of young radiologists. And truly so, interstitial lung diseases (ILDs) in itself remain an enigma; only to be decoded with an in-depth knowledge of the pathophysiology, imaging and clinical manifestations. The range of ILDs is wide, and with advances in knowledge, everyday a new entity is being added to the list! A thorough knowledge of the newer classification and terminology is crucial in order to identify, and describes the imaging abnormalities. In addition, there are several diseases that can simulate ILDs radiologically, and hence preference of the term, Diffuse Lung Diseases (DLDs) by many. Even a trained eye may miss significant yet subtle findings unless a systematic approach is adopted for reporting.

Pulmonary medicine is a rapidly expanding medical specialty which relies heavily on imaging. Practicing physicians need to be aware of the basics of imaging, as that will affect the management of a critically ill patient. Similarly, radiologists in practice need to be aware of the imaging patterns and their differential diagnoses. This book is not intended to be a detailed text on ILDs, but we hope that it will help the busy radiologists and physicians in their daily practice. The pattern approach at the end of each section is aimed at this.

We wish to thank all the contributors, for their efforts in compiling the text. We sincerely thank Professor Randeep Guleria and Professor GC Khilnani for guiding us in this new endeavor. We are also obliged to Professor Sushil K Kabra and Professor Rakesh Lodha for their valuable contributions on ILD in children.

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We welcome any feedback on enhancing the content of the book, which can be incorporated in the subsequent editions.

Ashu Seith Bhalla
Manisha Jana
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Clinical and Management Issues

Pawan Tiwari, GC Khilnani

TERMINOLOGY

- Acute onset of respiratory symptoms, in conjunction with diffuse bilateral pulmonary infiltrates can result from a variety of causes.
- While the milder forms may only have shortness of breath or chest tightness; severe forms can lead to respiratory failure.
- Hypoxemic respiratory failure is most common; hypercarbia may be an indicator of advanced disease or respiratory muscle fatigue.

EVALUATION

- History of pre-existing connective tissue disorder or interstitial lung disease
- Immune status and use of immunosuppressant drugs or drugs known to cause lung toxicity
- History of occupational exposure and risk factors for hypersensitivity pneumonitis
- Clinical features suggesting acute infective process (e.g. antecedent upper respiratory tract infection, concurrent viral illness, history of contact with patient with active tuberculosis).

PHYSICAL EXAMINATION

- Nonspecific
- General physical examination:
  - Assessment of hemodynamic stability and sensorium
  - Presence of tachypnea (>30/min), tachycardia (>110/min); use of accessory muscles of respiration.
  - Pandigital clubbing; may point towards pre-existing disease.
  - Pedal edema, elevated jugular venous pressure, tender hepatomegaly, or other signs of fluid overload or cor pulmonale
  - Assessment for mucocutaneous manifestations of connective tissue disorders
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- **Chest examination:** Inspiratory crackles on auscultation, inspiratory squeaks in patients with bronchiolitis, or traction bronchiectasis associated with pulmonary fibrosis.
- **Cardiac examination:** S₃ gallop to rule out cardiogenic pulmonary edema; murmurs to rule out valvular diseases. Loud and palpable P₂, findings of tricuspid regurgitation may indicate associated pulmonary hypertension.

**ANCILLARY INVESTIGATIONS**

Important for diagnosis and monitoring of patients.

**PULSE OXIMETRY**

- Provides non-invasive measurement of peripheral arterial oxygen saturation (SpO₂) using spectrophotometry
- May be used for continuous non-invasive titration of oxygenation and prevention of hypoxemia
- May not be reliable in patients with shock and reduced peripheral tissue perfusion
- Cannot measure oxygen tension or ventilation.

**ARTERIAL BLOOD GAS ANALYSIS**

- Common sites for arterial blood gas (ABG) sampling include radial, brachial or occasionally axillary artery in the upper limb, and femoral or dorsalis pedis in the lower limb. Radial artery remains the most commonly used site.
- Taking sterile precautions, two fingers of one hand should be used to palpate the artery while holding the needle in the other hand. Both fingers should be proximal to the desired puncture site. The artery should be punctured with the needle at a 30–45° angle (radial, brachial, axillary, dorsalis pedis) or at a 90° angle (femoral artery) relative to the skin. Around 2–3 mL of blood should be removed.
- Normal values are: pH 7.35–7.45, PaCO₂ 35–45 mm Hg (4.7–6 kPa), HCO₃⁻ 24 (22–26) mEq/L. For PaO₂, generally resting PaO₂ >80 mm Hg (10.7 kPa) and SaO₂ >95% are considered normal, unless the new values are substantially different than prior values.
- In acute hypoxemic respiratory failure, patients commonly have respiratory alkalosis with hypoxemia. Hypercarbia and respiratory acidosis are features of advanced disease or respiratory muscle fatigue. Patients with shock, lactic acidosis, renal involvement or acute kidney injury may have concomitant metabolic acidosis.

**INTRAVASCULAR PRESSURE MEASUREMENTS**

- May be utilized in patients with shock, or those with acute respiratory failure, on ventilatory support. May also be used to take frequent samples for ABG analysis. Should not be placed routinely in all patients, and should be removed once the patients improve.
PULMONARY ARTERY OCCLUSION PRESSURE

Not routinely used. These may be used in cases of pulmonary edema when
diagnosis is not clear using transthoracic 2D echocardiography. It can also be
used for the diagnosis of pulmonary hypertension and response to vasodilator
therapy.

MONITORING OXYGENATION

- $\text{SpO}_2$: Noninvasive measure of oxyhemoglobin in peripheral tissue
- $\text{PaO}_2$: Partial pressure of oxygen in arterial blood; measures the portion of
  $\text{O}_2$ dissolved in plasma
- $\text{FiO}_2$: Fractionated inspired $\text{O}_2$; on the basis of oxygen delivery devices or
  ventilatory settings
- In general, $\text{SpO}_2$ of > 90% implies a $\text{PaO}_2$ of 60 mm Hg or more.
- $\text{PaO}_2/\text{FiO}_2$ ratio is used to classify the severity of hypoxemic respiratory
  failure and to monitor improvement.

TRACHEAL ASPIRATE, BRONCHOSCOPY, BRONCHOALVEOLAR LAVAGE

- Used for diagnosis of specific disorders (like acute eosinophilic pneumonia
  or diffuse alveolar hemorrhage), or as an indicator for possible etiology
  (lymphocytosis in hypersensitivity pneumonitis or cellular NSIP).
- Exclusion of infective etiology or malignancy.
- Bronchoalveolar lavage (BAL) may be done with supplemental oxygen or
  noninvasive ventilation in patients who have hypoxemic respiratory failure
- BAL samples are usually sent for cell counts, cultures (e.g. bacterial, myco-
  bacterial, fungal, viral), enzyme immunoassay, direct immunofluorescence,
  and cytologic analysis (e.g. viral inclusion bodies, malignant cells).

RADIOLOGY

- Chest radiograph is the mainstay
- Risks of transporting patient to CT suite

MANAGEMENT

Oxygen

- Oxygen supplementation using nasal cannula or venturi masks may suffice
  for patients with mild hypoxemia.
- Patients with high $\text{FiO}_2$ requirement and high minute ventilation may benefit
  from non-rebreathing masks with reservoir.
- High flow nasal cannula provides heated humidified high flow oxygen
  up to $\text{FiO}_2$ of 1.0 with some positive end inspiratory pressure, and has shown
  efficacy in hypoxemic respiratory failure.
Mechanical Ventilation

- The term refers to a form of assisted ventilation where mechanical means are used to assist or replace spontaneous respiration.
- **Indications:** Poor sensorium, hemodynamic instability, unable to handle respiratory secretions, respiratory rate >30/min, unable to maintain PaO₂ >90% and FiO₂ >0.60, PaCO₂ >50 mmHg and pH <7.25
- **Non-invasive:** In conscious and hemodynamically stable patients, or those with “do not intubate” status. Provided through facemasks or helmet
- **Invasive:** Through endotracheal intubation
- Lung protective ventilation, with optimal FiO₂ and PEEP should be utilized.
- Adequacy of mechanical ventilation should be assessed on the basis of clinical parameters, SpO₂, ABG parameters and plateau and peak pressures.

Drugs

- High dose systemic corticosteroids, typically 500 mg to 1 g of methylprednisolone pulse for 1–3 days is given in patients with acute hypoxemic respiratory failure. Subsequently, oral prednisone (daily 0.5–1 mg/kg) is started, which is then gradually tapered.
- Other immunosuppressants may include cyclophosphamide (pulse or oral), rituximab, azathioprine or mycophenolate mofetil, according to primary disease.
- Patients should receive intravenous antibiotics including treatment for pneumocystis in suspected infective exacerbations. In cases of suspected or proven CMV or fungal pneumonia, appropriate antivirals or antifungals may be added.
- Other supportive treatment includes prevention of complications (e.g. venous thromboembolism, gastrointestinal bleeding, nosocomial pneumonia).

SPECIFIC ENTITIES

Acute Respiratory Distress Syndrome (ARDS)

- **Definition/diagnostic criteria:** Revised Berlin definition given in 2012. Following components:
  - Acute onset of respiratory distress
  - Develops within one week of the clinical insult or new/worsening respiratory symptoms
  - Chest X ray showing bilateral lung infiltrates (Fig. 22.1)
  - Respiratory failure which is not fully explained by cardiac failure or fluid overload
- **Categories of severity (based on PaO₂/FiO₂ ratio at PEEP or CPAP ≥ 5 cm H₂O)**
  - **Mild:** PaO₂/FiO₂ ratio 200 to 300 mm Hg
  - **Moderate:** PaO₂/FiO₂ ratio between 100 to < 200 mm Hg
  - **Severe:** PaO₂/FiO₂ ratio < 100 mm Hg
Section 7: Acute Diffuse Lung Diseases

Fig. 22.1: Acute respiratory distress syndrome, with bilateral air bronchograms, on mechanical ventilation. Also seen is jugular venous access for venovenous extracorporeal membrane oxygenation.

- Causes
  - Pulmonary/direct injury: Pneumonia, aspiration
  - Extrapulmonary/indirect injury: Sepsis, pancreatitis, major trauma, multiple transfusions.

  Pathogenic mechanisms depend on inciting insult; common features include increased permeability due to epithelial and endothelial damage, and neutrophilic infiltration in early ARDS.

- Management
  - Ventilatory management includes lung protective ventilation (i.e., low tidal volume < 6 mg/kg of calculated ideal body weight), along with adequate positive end expiratory pressure (PEEP).
  - Early recognition and management of refractory hypoxemia (defined as \( \text{PaO}_2 < 100 \text{ mm Hg} \), inability to keep plateau pressure \( P_{\text{plat}} \) below 30 cm \( H_2O \) despite tidal volume < 4 mL/kg of ideal body weight, occurrence of barotrauma or oxygenation index of < 30)
  - Prone positioning and early institution of extracorporeal membrane oxygenation have been shown to improve outcome.
  - Cautious use of noninvasive ventilation in mild ARDS under close observation.
  - Use of newer interfaces such as helmet for NIV in ARDS has shown some benefit in recent studies.
  - Non-ventilatory management includes antimicrobials, fluid conservative strategy, optimal use of sedation and neuromuscular blockade and regular sedation free intervals.
Prognosis
- Hospital mortality of 35–46% has been reported.
- In most patients, spirometry values normalise within 6 months, though diffusion capacity (Dlco) may normalize by 5 years.
- A high proportion of survivors have cognitive dysfunction (>40%) and impaired physical function (66%) persisting after 12 months.

Pulmonary Edema
- May be cardiogenic or non-cardiogenic.
- Common causes of cardiogenic pulmonary edema include decompensation of heart failure, valvular dysfunction, ischemia, or volume overload.
- Non-cardiogenic pulmonary edema may be associated with pneumonia, sepsis, aspiration or drowning.
- Up to 10% patients with pulmonary edema may have multiple causes, e.g. ARDS with concomitant fluid overload, or acute decompensated cardiac failure with associated lung injury.
- Paroxysmal nocturnal dyspnea or orthopnea point towards a cardiac cause of cardiogenic pulmonary edema. Signs and symptoms of infection, altered sensorium, witnessed aspiration, drowning or multiple blood transfusions may indicate non-cardiogenic cause.
- Engorged neck veins, and peripheral edema may indicate fluid overload. \( S_3 \) gallop is highly specific for left ventricular dysfunction. Other specific findings include murmurs of valvular stenosis or regurgitation.
- Laboratory testing:
  - ECG findings, troponin levels and serum brain natriuretic peptide (BNP) levels may be useful in differentiating cardiogenic pulmonary edema.
  - Two-dimensional transthoracic echocardiogram is useful, if cause of pulmonary edema cannot be found on history, physical examination, ECG and chest X-ray.
  - Pulmonary artery catheterization determines pulmonary artery occlusion pressure. This is considered as gold standard to establish cause of acute pulmonary edema, but is not required in most cases.
- Management includes treatment of primary cause, management of hypoxemic respiratory failure and supportive treatment. Non-invasive ventilation (using continuous positive pressure ventilation) is efficacious of management of respiratory failure in cardiogenic pulmonary edema along with diuretics and vasodilators. Non-cardiogenic pulmonary edema management should managed like ARDS.

Infections
- Infections such as pneumocystis, cytomegalovirus, influenza, atypical organisms (mycoplasma or chlamydia) or mycobacteria may have presentations similar to acute ILDs, or may cause acute exacerbations of pre-existing ILDs (Fig. 22.2)
Ruling out infectious etiology, with use of BAL should be a part of work-up of acute ILD.

**Acute Interstitial Pneumonia**

- Usually affects previously healthy middle-aged persons
- Not associated with smoking; no gender predilection
- Respiratory picture similar to ARDS but no known predisposing cause (Fig. 22.3)
Rapid onset of symptoms with 7–14 days of prodromal illness
Fever, cough, progressive dyspnea and respiratory failure are usual presenting complaints. Clubbing is not commonly seen.
Needs to be differentiated from AE-IPF (older age, diagnosed IPF, pan-digital clubbing, UIP pattern on HRCT)
Histology shows diffuse alveolar damage (DAD), either organizing or proliferative phase.
Diagnosis is based upon clinicoradiologic features and lung biopsy showing DAD.
If lung biopsy is not feasible, presumptive diagnosis of AIP should be made when there is presence of a compatible clinical syndrome and radiology, after ruling out alternate causes.
Poor prognosis with >50% in hospital mortality; may progress to chronic ILD in significant proportion of patients.
Treatment is primarily supportive
Mechanical ventilation may be required
High-dose systemic corticosteroids have shown benefit in small case series.
Lung transplantation has been reported in a few cases of AIP.

Acute Exacerbation of IPF (AE-IPF)
Causes of acute deterioration in patients with IPF include pneumonia, pulmonary embolism and acute worsening of ILD.
Incidence 4.8–14% in placebo arms of various randomized controlled trials
Risk factors for AE-IPF include younger age, higher body mass index, coronary artery disease, lower FVC, pulmonary hypertension, prior surgery and prior use of immunosuppressants.
It is defined as an acute and clinically significant respiratory deterioration which is characterized by new widespread alveolar abnormality in patients with concurrent or previous diagnosis of IPF
Diagnostic criteria:
• Acute worsening or development of dyspnea typically < 1 month duration
• CT with new bilateral ground-glass opacity with or without consolidation, which is superimposed on a background pattern consistent with usual interstitial pneumonia
• Deterioration not fully explained by fluid overload or cardiac failure
• Lower PaO$_2$/FiO$_2$ ratio (<100), elevated lactate dehydrogenase (LDH) or Krebs von den Lungen-6 (KL-6) levels, and high ground-glass opacity or consolidation scores have been associated with high mortality in AE-IPF.
• Histopathology shows underlying fibrotic interstitial pneumonia with superimposed DAD.
Treatment:
• High-dose corticosteroids, typically methylprednisolone pulse for 3 days, followed by high-dose oral steroids. Other drugs including silvestat, cyclosporine or cyclophosphamide have shown some benefit in small case series.
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- Patients receive antimicrobials including cotrimoxazole irrespective of definitive evidence of infections, due to high mortality of AE-IPF.
- Hypoxemic respiratory failure is managed with non-invasive or mechanical ventilation.
- Preventive therapies include nintedanib and antacid therapies.

**Prognosis:** Overall mortality rate of 70% have been reported. Systematic reviews have reported high one month (67%) and three month (67%) mortality.

### Acute Hypersensitivity Pneumonitis

- Hypersensitivity pneumonitis (HP) is a syndrome caused by repeated exposure to various organic particles.
- Classical acute form is associated with exposure to thermophilic actinomycetes, fungi or other bacteria (e.g. farmer’s lung, hot tub lung).
- All chronic HP cases need not have a preceding acute disease. Also, the terms acute and chronic only imply presentation, but not the underlying pathogenesis.
- The acute form of HP usually presents as a “flu-like” illness, and has a self-limiting course.
- Only occasionally can it have a severe presentation leading to respiratory failure.
- Often follows a sudden, intense exposure to the offending agent. History of previous such episodes may be present.
- Symptoms include fever, myalgias and sweating, apart from dyspnea and chest tightness.
- Onset of symptoms occurs usually 6–24 hours following the acute exposure.
- May have associated wheezing and bronchial hyperresponsiveness.
- Acute episodes may be indistinguishable from acute viral or mycoplasma infections.
- **Physical examination:** Inspiratory crackles; short-high pitched end-inspiratory sound (also called “sqwaks”).
- **PFT:** Seldom performed. Restrictive pattern commoner, though obstructive or mixed may also be seen.
- **Diagnosis:**
  - Based on high index of suspicion, recognition of antecedent antigen exposure, along with clinical, radiologic or histopathologic findings.
  - Elevated serum levels of specific circulating antibodies may be taken as a marker of exposure. However, these may be false negative in acute HP.
  - BAL cytology shows neutrophilia and lymphocytosis (>50%), along with CD4/CD8 ratio of less than 1.
  - Lung biopsy is less commonly performed. It demonstrates shows peribroncholar small ill-formed noncaseating granulomas. Peripheral airways may show features of proliferative bronchiolitis obliteratorans.
- **Differential diagnosis:** Asthma, obliterative bronchiolitis
Management:
- Avoidance of antigen exposure is the most important step. Patients who are unable or unwilling to avoid exposure to antigens may benefit from air-purifying respirators.
- Corticosteroids may be required in severe or progressive disease.
- Mostly self-limiting, with the symptoms resolving within hours or days.
- Recurrent exposures may lead to obstructive lung disease (with or without emphysema, commonly centrilobular) instead of fibrosis.

Diffuse Alveolar Hemorrhage
- Diffuse alveolar hemorrhage (DAH) refers to diffuse bleeding from pulmonary arterioles, alveolar capillaries and pulmonary venules (i.e. pulmonary microcirculation) due to microvascular damage.
- Often a catastrophic clinical syndrome presenting with hemoptysis and dyspnea, which may progress to hypoxemic respiratory failure (Fig. 22.4)
- Extrapulmonary symptoms are those related to underlying systemic disease.

Causes: Broadly classified as immune and non-immune causes.
- Nonimmune causes include endobronchial tumors, arteriovenous malformations or aneurysms, hemorrhagic pneumonia, infections, mitral valve disease, congestive cardiac failure, uremia, coagulopathies or thrombocytopenia, pulmonary veno-occlusive disease or massive pulmonary embolism.
- Autoimmune DAH is due to capillaritis or endotheliitis; common etiologies being ANCA-associated vasculitides, Goodpasture’s syndrome,

Fig. 22.4: Diffuse alveolar hemorrhage. Bilateral lower zone interstitial infiltrates; patient had recurrent hemoptysis with anemia; bronchoalveolar lavage showed progressive hemorrhagic return; BAL and TBLB showed DAH
systemic lupus erythematosus (SLE) or drugs (D-penicillamine, trimellitic anhydride).

Other causes include immunocompromised status (post-bone marrow transplant or AIDS) or idiopathic pulmonary hemosiderosis (unknown cause, sometimes associated with celiac disease).

Diagnosis:
- BAL fluid shows blood, with progressively more blood with serial aliquots. DAH should be considered, if BAL cytology shows > 20% hemosiderin-laden macrophages (on Prussian blue staining).
- Presumptive diagnosis of DAH can be made on the basis of compatible clinical and radiologic picture, along with serologic and BAL findings.
- BAL can also be utilized to rule out alternate infective etiology.
- Transbronchial lung biopsy may be used to diagnose pulmonary capillaritis, presence of granulomatous vasculitis and immunofluorescent staining.
- Kidney biopsy can be done, if required in patients with pulmonary renal syndromes.
- Thoracoscopic or surgical lung biopsy may be required for diagnosis, if rest of the work-up is non-diagnostic.
- Elevated serum creatinine or presence of active sediments in urine point towards pulmonary-renal syndromes.
- Markers of connective tissue disease such as ANA, ANCA (either antiproteinase or antimyeloperoxidase), anti-glomerular basement membrane antibodies (anti-GBM antibodies) may point towards specific diagnosis. Investigations should include antibodies against anti-tissue transglutaminase, IGA (anti-tTG), and work-up for celiac disease.

Management:
- Management of respiratory failure, hemodynamic status and correction of coagulation parameters
- Prompt work-up for the cause and its treatment
- High-dose corticosteroids are useful in immune-mediated causes; cyclophosphamide or rituximab have demonstrated benefit, especially in ANCA-associated vasculitis
- Other drugs include hydroxychloroquine and azathioprine.
- Plasmapheresis in anti-GBM disease or ANCA-associated vasculitis with severe renal insufficiency
- Gluten-free diet, if associated celiac disease

Prognosis: Untreated DAH has very high mortality, and thus requires aggressive treatment. Long-term prognosis depends on the underlying etiology.

Less Common Causes

Cryptogenic organizing pneumonia (COP) usually presents with subacute respiratory symptoms (less than 3 months) along with constitutional symptoms like fever, and may have neutrophilic leukocytosis. Organizing pneumonia (OP) may be idiopathic or secondary to autoimmune causes or infections. Diagnosis
Fig. 22.5: Cryptogenic organizing pneumonia. Bilateral multilobar infiltrates; CT showed reverse halo sign; TBLB showed organizing pneumonia

is based upon predisposing factors. Characteristic HRCT findings, exclusion of alternate etiology and histopathology (Fig. 22.5). Typical histopathologic features include patchy involvement, organizing pneumonia involving alveolar ducts and alveoli; bronchiolar intraluminal polyps may also be seen. Majority of patients respond to oral corticosteroids.

Nonspecific interstitial pneumonia (NSIP), related to collagen vascular diseases, antisynthetase syndrome or idiopathic may present with acute onset, or more commonly, acute worsening with hypoxemic respiratory failure. Management remains similar to acute exacerbation of IPF.

Acute Eosinophilic pneumonia (AEP) is a rare disorder. It usually presents with fever and acute respiratory failure along with diffuse infiltrates on chest radiology (Fig. 22.6); pulmonary eosinophilia is present. Causes include infections (more commonly parasitic), hypersensitivity to drugs or inhaled agents, systemic idiopathic-eosinophilic disorders or idiopathic. As presentation mimics ARDS or AIP, it is confused with these more common entities. BAL is the key to diagnosis of AEP, showing eosinophilic alveolitis along with increased neutrophils and lymphocytes. BAL can also exclude infectious etiology. TBLB or open lung biopsy, if performed, shows eosinophilic infiltration of alveoli, interstitial edema with or without organizing diffuse alveolar damage. Work-up should include ruling out infective etiology, vasculitis or drug exposure. High-dose systemic corticosteroids are frequently utilized, along with supportive treatment. With prompt management, outcome is usually favorable; relapse is uncommon.

Drug-induced ILDs, may have clinical presentation ranging from no symptoms to acute respiratory failure. Pathogenesis includes direct, dose-dependent toxicity or immune-mediated. Most reactions are immune-mediated. Diagnosis is based on high index of suspicion, exposure to known
offending drug and exclusion of alternate causes. Treatment includes withdrawal of offending agent and supportive treatment with or without corticosteroids.

BIBLIOGRAPHY