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Abstract
Aspergillus is ubiquitous, occurring in mycelial form and grows at 15–53°C and humid conditions. Pulmonary aspergillosis is a clinical spectrum of lung disease caused by the fungus Aspergillus. ABPA is the commonest disease among allergic bronchopulmonary mycosis. The exact prevalence of ABPA is not known but contemporary estimates suggested that ABPA complicates 1–11% of all chronic cases of bronchial asthma. The basic underlying immuno-pathophysiologic process in ABPA is a hypersensitivity reaction to fungus in the bronchial tree. Patients are usually atopic with previous history of bronchial asthma. The onset is insidious with constitutional symptoms like anorexia, fatigue, weight loss, headache, generalized aches and pains, and low-grade fever. It is characterized by repeated episodes of exacerbation with periods of remission, if untreated may progress to fibrotic lung disease. Patients with chronic fibrotic disease may present with cyanosis, cor pulmonale, and respiratory failure. Radiologically fleeting shadows are characteristic of ABPA. Bronchiectasis, centrilobular nodules and mucoid impaction are main features of ABPA seen in CT scan thorax. Oral corticosteroid remains the cornerstone for the treatment of ABPA. Optimization of baseline asthma therapy is essential. Early diagnosis and proper treatment may alter the prognosis of disease and further prevent end stage lung fibrosis.

Introduction
Aspergillus is a ubiquitous fungi, which most commonly occurs in mycelial form, is thermo tolerant and grows at 15–53°C, the optimum being 37–40°C, and favoring humid conditions. Pulmonary aspergillosis is a clinical spectrum of lung disease caused by the fungus Aspergillus. The classification of pulmonary aspergillosis includes saprophytic aspergillosis in the form of pulmonary aspergilloma, immune disease in the form of allergic bronchopulmonary aspergillosis (ABPA), IgE mediated asthma, hypersensitivity pneumonitis, allergic Aspergillus sinusitis (AAS), and infectious disease in the form of invasive and semi-invasive pulmonary aspergillosis. ABPA is considered to be the commonest manifestation amongst allergic bronchopulmonary mycosis. ABPA is characterized by a hypersensitivity immunological reaction which is most commonly caused by Aspergillus fumigatus in about 95% of the cases and rarely by Aspergillus flavus, Aspergillus niger, Aspergillus oryzae, Aspergillus sydowi, Aspergillus terreus, Aspergillus glaucus, Aspergillus nidulans, and Aspergillus clavatus. Other fungi such as Candida, Helminthosporium, Curvularia, Drechslera, Pseudallescheria boydii, and Fusarium vasinfectum have also been found to cause an identical syndrome. ABPA clinically manifests as chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis. The condition has immunologic features of immediate hypersensitivity (Type I), antigen-antibody complexes (Type III), and eosinophil-rich inflammatory cell responses (Type IVb), based on the revised Gel and Coombs classification of immunologic hypersensitivity. ABPA was first reported in England in 1952 and in India in 1971. Since then, a
large number of cases have been reported from various parts of the world. Concomitant occurrence of ABPA and AAS is now being increasingly recognized which is also called as “sinobronchial allergic mycosis” syndrome. ABPA is commonly associated in patients with chronic bronchial asthma and cystic fibrosis but can also occur in non-asthmatics. The aim of the present write-up is to discuss the prevalence, clinical presentation, diagnosis, and treatment of ABPA.

Prevalence of Allergic Bronchopulmonary Aspergillosis

The prevalence of ABPA is highly variable complicating 1–11% of all chronic cases of bronchial asthma. A very recent study from India, however, found a higher prevalence of Aspergillus sensitization (39.5%) and ABPA (27%) in 564 patients with asthma. A study by Alok Nath et al. on 350 patients found the prevalence of Aspergillus hypersensitivity (AH) and ABPA to be 35.1% and 21.7%, respectively. The condition is being increasingly recognized and the estimated prevalence rates in recent publications have been reported ranging from 5.9% to 20.5% for ABPA and 38% to 43% for AH. A study in northern India was conducted to determine the prevalence of ABPA in patients of bronchial asthma where 244 patients were recruited consecutively over a period of 3 years and were analyzed prospectively by clinical evaluation, chest radiography, skin test, sputum culture for fungus, and serum precipitin test. Those patients with further suspicion of ABPA were further investigated by serum titers of specific IgG and IgE against *A. fumigatus*. The diagnosis of ABPA was made on predetermined major and minor criteria, where at least five major criteria had to be present. ABPA was seen in 7.4% patients with bronchial asthma.

Immunopathology of Allergic Bronchopulmonary Aspergillosis

Majority of patients with ABPA are atopic with history of bronchial asthma. The pathogenesis of ABPA circles around a hypersensitivity reaction to the fungal spores and mycelial fragments of *A. fumigatus* present in the bronchial tree. Atopic individuals after inhalation of fungal spores in the bronchi result in the fungi to germinate and form vegetative elements (hyphae). Local immunologic reactions and stagnation of tenacious sputum in bronchial Airways favor the trapping of fungal spores and further colonization. Antigenic substance of the fungus stimulates formation of IgE, IgG, and IgA antibodies. ABPA is immunologically classified as it gives both Type I (immediate) and Type III (Arthus, antigen-antibody immune complex) hypersensitivity reactions. Type I reaction is IgE mediated and responsible for accumulation of eosinophils, bronchospasm, edema leading to acute symptoms of diseases. Type III reaction results in polymorph aggregation, inflammation of bronchial, and peribronchial tissues and is responsible for the radiological features of ABPA. Recently, possible role of Type IVb hypersensitivity reaction has also been observed in patients with ABPA and the presence of parenchymal granuloma and mononuclear cell infiltration seen on histopathology. Long-standing involvement of the bronchial tree leads to bronchiectasis, fibrosis, lung contraction, and lobar shrinkage.

Clinical Presentation

The clinical picture of ABPA is dominated by asthma and recurrent exacerbations. The onset is insidious with constitutional symptoms like anorexia, fatigue, weight loss, headache, generalized aches and pains, and low-grade fever. Asthma is generally uncontrolled with usual anti-asthmatic therapy. It is characterized by repeated episodes of exacerbation with periods of remission in between and if untreated may progress to end stage fibrotic lung disease. It may occur at any age but is usually more prevalent in the age group of 20–40 years. Patients with chronic fibrotic disease may present with cyanosis, cor pulmonale, and respiratory failure. However, symptoms have little or no relationship to severity or chronicity of the disease, as one-third patients may be relatively asymptomatic in spite of extensive radiological shadows. Expectoration of brownish mucus plugs is characteristic and has been reported in 5–54% of cases. These plugs consist of fungal hyphae with eosinophils and mucous. Cough, breathlessness, and wheezing are common symptoms seen in ABPA. Hemoptysis has been reported in approximately 34–85% of cases, while pleuritic chest pain may be present in 50% of cases. In one of his study author found that hemoptysis was found in 28.6% of patients. Chronic cases of ABPA may rarely present with symptoms of bronchiectasis.
On clinical examination of chest, wheezing and diffuse crepitations are the common findings but tachypnea, cyanosis, features of cor pulmonale, and sometimes hypertrophic osteoarthropathy may be seen. The disease is often misdiagnosed as tuberculosis, bronchiectasis, and bacterial pneumonia. Almost half of the ABPA patients are initially misdiagnosed as pulmonary tuberculosis.27

### Diagnostic Approach

ABPA should be suspected in any patient with asthma and parenchymal infiltrates on chest radiograph accompanied with peripheral blood eosinophilia. Not all features are required in order to diagnose ABPA. The important diagnostic criteria are the presence of recurrent pulmonary infiltrates, peripheral blood eosinophilia and positive skin test to Aspergillus antigen or positive specific IgE against *A. fumigatus*.

### Radiological Features

#### Chest X-ray

Radiological features in patients of ABPA may be transient (acute) or permanent (chronic). Transient shadows may clear with or without steroid therapy and are mainly due to pulmonary infiltrates and stagnation of mucus in damaged bronchi.33,34 Transient shadows are perihilar infiltrates mimicking adenopathy, air fluid levels from dilated central bronchi filled with fluid and debris. Parenchymal abnormalities are more common and present in 80–90% patients of ABPA as ill-defined homogenous shadows without evidence of loss of volume which may be of 5–15 mm in size or more as massive/lobar in extent, may be unilateral or bilateral, more in upper lobes, resolve (fleeting/migratory shadows) often after expectoration of bronchial plugs but tends to recur in same/other places. Sometimes pulmonary shadows may mimic carcinoma. Fleeting opacities are characteristic of ABPA. Author in one of his studies found that 66.7% patients had fleeting shadows. Author described “walking pneumonia” as a clue to diagnosis of ABPA.35 Bronchial abnormalities occur in 50–70% of episodes of acute ABPA consists of tramline, parallel lines, ring shadows, and toothpaste shadows which represent normal or abnormal bronchial wall. The impacted bronchus may appear as full wine glass having an open upper end with tapering lower end, gloved finger 2–3 centimeter long and 5–8 mm wide, and inverted V, Y, or toothpaste shadows. Gloved-finger shadows are due to distally occluded bronchi filled with secretions. Tram line shadows are the thickened walls of undilated bronchi, so the distance between lines is that of a normal bronchus while parallel lines shadows represent walls of bronchiectatic bronchi, the distance between walls is greater than normal. Permanent (chronic) changes reflect histological abnormalities secondary to repeated acute episodes of ABPA, and are often associated with physiologic abnormalities. Rarely cavitations, local emphysema, pulmonary fibrosis or contracted upper lobe, honeycombing, collapse due to mucous impaction, and spontaneous pneumothorax.

#### Computed Tomography

High resolution computed tomography (HRCT) has been shown to be more sensitive than the plain chest radiograph and might be useful in the assessment of extent of disease. It is a sensitive noninvasive technique for the recognition of ABPA. Central bronchiectasis occurs due to the deposition of immune complex in proximal airways. Bronchiectasis, centrilobular nodules and mucoid impaction are main features of ABPA.37 Central bronchiectasis with ABPA may be seen in 40% patients38 and is characterized by string of pearls and signet ring appearance as described by Webb et al.39 Central bronchiectasis (in 2nd, 3rd, 4th order large bronchi) is an important diagnostic feature of ABPA with normal small bronchi and bronchioles.40 Because of the lack of specificity of central bronchiectasis in diagnosis of ABPA and the fact that a significant proportion of patients with ABPA have “peripheral” bronchiectasis, the term central has been suggested to be removed by the recent expert group.38 An important HRCT finding, considered pathognomonic for ABPA, is airway plugging with high attenuation mucus (HAM).41-45 HRCT of the chest is found to be normal in a third of the patients; in that case they are labeled as ABPA-S.27

### Radiological Classification of Allergic Bronchopulmonary Aspergillosis

Serological ABPA (ABPA-S) (mild), ABPA-central bronchiectasis (ABPA-CB) (moderate), and ABPA-CB-other radiologic findings (ORF).46 In ABPA-S all the diagnostic features of ABPA are present except evidence of central bronchiectasis on HRCT. It is believed that patients with ABPA-S have milder clinical course and
less severe immunological findings when compared to ABPA-CB. In ABPA-CB all findings of ABPA including central bronchiectasis on HRCT present however in ABPA-CB-ORF all findings of ABPA and CB along with other radiological features such as pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibrocavitary lesions, Aspergilloma, ground glass appearance, collapse, mediastinal lymph node, pleural effusion, and pleural thickening. Newly proposed radiological classification of ABPA based on computed tomography chest findings, categorizes ABPA as ABPA-S, ABPA with bronchiectasis, ABPA with HAM and ABPA with chronic pleuropulmonary fibrosis.

Laboratory Investigations

- A peripheral blood eosinophil count >1,000 cells/μL has been used as a threshold in the diagnosis of ABPA. However, as many as 60% of patients with ABPA present with a eosinophil count <1,000 cells/μL at diagnosis, and a quarter of ABPA patients have a count <500 cells/μL. In a recent study, the sensitivity and specificity of eosinophil count >1000 cells/μL were found to be approximately 30% and 93%, respectively, for the diagnosis of ABPA among asthmatics. Due to the poor sensitivity of this cut off, an eosinophil count >500 cells/μL is proposed as the limit in the recent diagnostic criteria.

- Serological tests: Increase in total IgE and specific IgE and IgG precipitating antibodies against A. fumigatus. Both total and specific IgE levels are high during development of pulmonary infiltrates and decrease after remission. The total IgE levels are >1,000 IU/mL may be as high as 20,000 IU/mL in acute cases except in cases that are in remission or on steroids therapy. Precipitating antibodies against A. fumigatus are present in most of cases of ABPA with pulmonary infiltrates and diminished after steroid therapy.

- Skin test: Positive skin tests (Type 1 and Type 3) are more reliable than precipitin tests. Immediate type 1, skin reaction is positive in most of the cases but also positive in 25% of asthmatics without ABPA. Late onset (Type 3) erythema and edema occur usually after 4-6 hours and reache at peak within 8 hours and subside by 24 hours due to deposition of IgE, IgM, IgA, and complement components.

- Sputum smear and culture for Aspergillus: Nearly two-thirds of patients of ABPA show positive smear and culture for Aspergillus, positive culture with Aspergillus species in sputum has been reported in 58% cases of ABPA.

- Pulmonary function test: Is neither sensitive nor specific and does not help to define the extent of disease or exclude it, during remission patient may have normal lung function even in presence of bronchiectomy. The status depends upon the stage at which they are performed. Acute and chronic pulmonary function changes in ABPA have been described. In acute episodes obstructive changes are observed, while during irreversible stages with bronchiectasis and fibrosis restrictive changes are found. In chronic-cases diffusion capacity is reduced.

Classical Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

**Major Criteria**

Bronchial asthma, radiological pulmonary infiltrates, immediate skin test positivity to A. fumigatus antigen, elevated total serum IgE, precipitating antibodies against A. fumigatus antigen, peripheral blood eosinophilia, elevated serum IgE and IgG against A. fumigates, and central/proximal bronchiectasis with normal tapering of distal bronchi.

**Minor Criteria**

History of expectorating golden brown plugs in sputum, positive sputum smear and culture for Aspergillus species and Type III (Arthus) skin reactivity to A. fumigatus.

The presence of six of eight major criteria makes the diagnosis almost certain and latest criteria do not differentiates in major and minor, eight diagnostic criteria are laid down to detect ABPA suggested by Patterson et al. 1997 are: Asthma (mild or severe) or cystic fibrosis, immediate cutaneous reactivity to Aspergillus antigen, current or previous pulmonary infiltrates, elevated total IgE concentration (>1 mg/L), precipitin antibodies to A. fumigatus, peripheral blood eosinophilia, elevated serum IgE and/or IgG-against A. fumigatus and central bronchiectasis.

Since, previous ABPA diagnostic criteria lacked a consistent case definition, International Society for
Human and Animal Mycology (ISHAM) criteria for ABPA diagnosis in asthmatics was published in 2013, which included:48

- **Obligatory criteria (both should be present):**
  - Total IgE >1,000IU/mL
  - Positive Aspergillus specific (Af) IgE or skin prick test

- **Other criteria (2 out of 3):**
  - Raised Af IgG or precipitins
  - Eosinophils >500 cells/μL
  - Radiological features consistent with ABPA

### Staging of Allergic Bronchopulmonary Aspergillosis

Five stages of allergic bronchopulmonary aspergillosis have been described according to Patterson et al.:6

- **Acute stage:** Symptoms consistent with ABPA and fulfilling the diagnostic criteria of ABPA.

- **Remission:** Control of respiratory symptoms with radiological clearing and decline in IgE levels.

- **Exacerbation:** Clinical and/or radiological deterioration associated with an increase in IgE by >50%.

- **Steroid dependent asthma:** Patient requires oral or parenteral glucocorticoids for the control of asthma.

- **Fibrosis:** Manifestations of fibrotic lung disease.

Also, a revised classification was proposed by Agarwal et al. in 2013, which divided ABPA into seven stages:48

- **Stage 0 asymptomatic:** No previous diagnosis of ABPA with well controlled asthma and fulfilling the diagnostic criteria of ABPA.

- **Stage 1 acute:** Symptoms consistent with ABPA and fulfilling the diagnostic criteria of ABPA. **Stage 1a:** With mucoid impaction on thoracic imaging. **Stage 1b:** Without mucoid impaction on thoracic imaging.

- **Stage 2 response:** Clinical and/or radiological improvement with decline in total serum IgE level by ≥25%.

- **Stage 3 exacerbation:** Clinical and/or radiological deterioration associated with an increase in IgE by >50%.

- **Stage 4 remission:** Sustained clinical and radiological improvement with total serum IgE levels persisting at or below baseline for ≥6 months off treatment.

- **Stage 5a (Treatment dependent ABPA):** Two or more exacerbations within 6 months of stopping therapy or clinical and/or radiological worsening, along with increase in total serum IgE levels. **Stage 5b (Glucocorticoid dependent asthma):** Patient requires oral or parenteral glucocorticoids for the control of asthma.

### Treatment of Allergic Bronchopulmonary Aspergillosis

Oral corticosteroid remains the cornerstone for the treatment of ABPA.49 The goal of therapy is to achieve symptom resolution, clearance of radiographic infiltrates, and establishment of a stable baseline serum level of total IgE. There are two dose schedules of oral glucocorticoid therapy, low dose, and high dose. In low dose oral glucocorticoid therapy, prednisolone 0.5 mg/kg/day is given for 2 weeks, then on alternate day for 6–8 weeks and then tapered 5–10 mg every 2 weeks and then discontinued. In high dose glucocorticoid therapy, prednisolone 0.75 mg/kg is given for 6 weeks, followed by 0.5 mg/kg for 6 weeks, then taper 5 mg every 6 weeks to continue for a total of at least 6–12 months. Repeat chest X-ray in 1 month should demonstrate clearing of the infiltrates. The total serum IgE level also regresses along with the infiltrates. The failure of the total serum IgE level to decrease suggests continuation of active disease and requires additional corticosteroids. The total serum IgE level, chest X-ray, absolute eosinophil count should then be followed at 6–8 weeks of interval regularly. The goal of glucocorticoid therapy is not normalization of total serum IgE but reduction in total serum IgE by 35–50% from baseline defines remission by 6 weeks. Serial total serum IgE levels are important for follow-up care.48 Patients who have remission of ABPA may discontinue prednisone. The remission may last for years or may be permanent. In patients with recurrent flares of ABPA or in those with severe persistent asthma, long-term corticosteroid therapy may be necessary to control their symptoms. Patients in the fibrotic stage of ABPA may have increased sputum volume as a result of infection. Measures such as postural drainage and antibiotics may be useful, but with deterioration, exercise tolerance decreases, and oxygen therapy may be needed. Optimization of baseline asthma therapy is essential with inhaled corticosteroid and β2-adrenergic agonist.
agonists. In addition, prophylactic measures should be instituted when indicated to prevent the adverse effects of long-term corticosteroid treatment such as osteoporosis. Thus, patients who take prednisolone for more than 2–3 months should be considered for bone mineral density analysis to direct commencement of calcium/vitamin D supplementation with or without bisphosphonates.50

**Alternative to Corticosteroid Treatment**

Even though oral corticosteroid is the treatment of choice in ABPA, the fact that it is associated with numerous adverse effects cannot be neglected. Inhaled corticosteroids are associated with fewer side effects, and hence considering them as a viable treatment option for ABPA seems appropriate. Not a lot of studies have been conducted to evaluate the role of inhaled corticosteroids in the management of ABPA. Inhaled corticosteroids, while useful for concomitant asthma management in patients with ABPA, do not control the pathophysiology or clinical manifestations of ABPA.51-53 In contrast to the inhaled corticosteroid therapy "pulse" therapy (10–20 mg/kg/day IV methylprednisolone infused on three consecutive days every 3–4 weeks) was found out to be generally safe and effective in two open labeled series of thirteen steroid dependent ABPA CF patients.54,55

**Anti-fungal Drugs**

The most efficacious alternative to long-term oral corticosteroids is the use of antifungal agents either in conjunction to the steroid therapy or even as a standalone therapy. Use of antifungal therapy in the treatment of ABPA is based on the assumption that allergic inflammatory responses arise in part from noninvasive airway fungal infection. Pooled analysis showed that itraconazole could significantly decrease IgE levels by ≥25% when compared to placebo, reduction in steroid dose by ≥50%; increase in exercise tolerance by ≥25%, improvement of ≥25% in results of spirometry, resolution of pulmonary opacities but failed to reach statistical significance, and did not cause significant improvement in lung function. Itraconazole modified the immunologic activation associated with ABPA and improve clinical outcome at least over the period of 16 weeks. The effectiveness of itraconazole in the treatment of ABPA was also demonstrated in two randomized, double-blind, placebo controlled trials in patients with asthma.56,57 Also, a randomized trial of itraconazole versus prednisolone in acute stage ABPA found out that oral glucocorticoids were more effective than itraconazole monotherapy in producing treatment response.58 At present, itraconazole should be limited in cases where oral steroids are contraindicated or refused by patients. The use of azoles for ABPA in asthma patients was reviewed by the Cochrane collaboration which suggested that itraconazole modifies the immunologic activation associated with ABPA and improves the clinical outcome, at least over a period of 16 weeks, though adrenal suppression with inhaled corticosteroids and itraconazole is a potential concern.59 Newer generation triazoles such as voriconazole and posaconazole have also been reported as beneficial in the treatment of ABPA. Treatment with voriconazole as a monotherapy was shown to be associated with improvements in clinical status, lung function, and serologies.59 A newer agent isavuconazole has been shown to be effective in a study conducted by Jacobs et al. in a patient of ABPA who was successfully treated with marked improvement and minimal adverse effects.61

**Alternatives to Azoles**

Amphotericin deoxycholate has been frequently used via inhalational route in the treatment of pulmonary fungal infection, primarily in the setting of cancer treatment and lung transplantation. Amphotericin B can be delivered via nebulization to the lower respiratory tract in doses which are capable enough to exceed the minimal inhibitory concentration of Aspergillus in the epithelial lining.62 However, data regarding the efficacy of amphotericin B is pretty scarce as of now and thus more studies need to be conducted in order to determine its actual role in the treatment of ABPA.

**Omalizumab**

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that binds IgE with high affinity and has been associated with improvement in symptoms, reduction in exacerbations, asthma hospitalizations, improvement in lung function, and reduction in dose of oral steroids.48 However, a recent retrospective series conducted in France has found variable results in 32 patients of ABPA with cystic fibrosis, which though reported a reduction in the steroid need over a 21-month observation period, but there was no significant improvement in the lung function or the use of antibiotics.63
Conclusion

Presently ABPA is one of the important emerging immunologically mediated respiratory diseases, commonly presenting in patients of asthma. It should be highly suspected in patients presenting with history of asthma, peripheral blood eosinophilia, recurrent pneumonitis, or transient (fleeting) pulmonary infiltrates mimicking pulmonary tuberculosis. In such suspected patients, detailed evaluations are needed to prove the diagnosis. Early diagnosis and proper treatment may alter the prognosis of disease and further prevent end-stage lung fibrosis.

References

Abstract

Obstructive sleep apnea is a severe form of sleep disordered breathing, which affects over 9% of middle aged urban Indians. Male sex, obesity, age, upper airway and craniofacial anomalies, genetic, and other environmental factors, particularly ambient air pollution are risk factors for OSA. These factors result in upper airway collapse during sleep, leading to obstructive respiratory events and symptoms of OSA, such as excessive daytime sleepiness, nocturnal breathing disturbances, morning headaches, and many more. Home sleep apnea testing or polysomnography is diagnostic. A plethora of complications can result from OSA, including metabolic, cardiovascular, cerebrovascular, and neuropsychiatric complications. Obese patients with OSA should be encouraged for weight loss, and other lifestyle modifications. Positive airway pressure therapy is the cornerstone of management of the disease; with only some patients requiring surgical management.

Introduction

Sleep disordered breathing is an umbrella term, consisting of disorders characterized by an abnormal respiratory pattern during sleep, which may coexist with other respiratory, cardiovascular, nervous, or endocrine diseases. It encompasses conditions ranging from snoring at the mild end of the spectrum to obstructive sleep apnea (OSA) at the severe end.

There are three main types of sleep apnea:
- Obstructive sleep apnea (OSA), seen in more than 80% of sleep apnea patients, occurs due to blockage of air from entering and leaving the lungs.
- Central sleep apnea (CSA), occurs when the brain stops responding to breathe until it senses a lack of O₂ and/or a increased level of CO₂ that needs to be exhaled.
- Complex sleep apnea is a combination of these two. OSA or hypopnea syndrome is the most common sleep-related breathing disorder. It is caused by repetitive collapse of the upper airway during sleep and is characterized by obstructive apneas, hypopneas, and/or respiratory effort related arousals (RERA). It leads to daytime sleepiness, behavioral problems in children, increases cardiovascular risk in adults, and can be factor in work place or motor vehicle accidents.

Epidemiology and Risk Factors

The prevalence of OSA is high and on a rising trend due to the increasing rates of obesity in the world. A literature-based analysis to estimate the global prevalence of OSA suggested that nearly 1 billion adults in the age group of 30–69 years were affected, with India standing at the fourth spot among the countries with the highest burden.

Male sex is a major risk factor, with the prevalence of sleep disordered breathing estimated at 24% for men and 9% for women aged 30–60 years, with 4% of men and 2% of women meeting the minimal diagnostic criteria for sleep apnea syndrome; later estimates reaching up to 4%
for women and 9% for men. An Indian study conducted among middle-aged urban Indians estimated an overall prevalence of OSA at 9.3% (Men—13.5%; Women—5.5%). OSA is thus two to four times more common in males than females, but the risk appears to become similar to men in postmenopausal women.

Obesity is the second major risk factor for development of OSA. Up to 60% of patients with OSA are overweight or obese. A high body mass index (BMI) is associated with a higher risk for OSA, with BMI being more strongly associated to OSA in younger adults. A substantial decrease in OSA severity following weight loss has been demonstrated, and longitudinal analysis indicate that a 10% increase in weight leads to sixfold increase in the risk of developing moderate to severe OSA, and a 32% increase in Apnea-hypopnea index (AHI). Almost 90% of the patients with obesity hypoventilation syndrome have coexistent OSA.

Age is another important risk factor for the development of OSA, the prevalence increasing from young adulthood up to the sixth or seventh decade, and then it plateaus. Age is an independent associated risk factor for OSA, with odds ratio reaching 34.5 for the 60–80 year age group as compared to 20–29 year age group.

Upper airway abnormalities (such as enlarged tonsils or adenoids, small nasal cavity) and craniofacial anomalies (such as micrognathia, retrognathia, a wide craniofacial base) have also been implicated in increasing the risk of OSA. Another study noted that a majority of Asian men who had severe OSA, were non-obese and differences in craniofacial anatomy was considered an important risk factor in this population (vs. White men).

Genetic factors that produce the OSA phenotype usually affect body fat distribution, craniofacial morphology and neuromuscular factors. Relatives of patients with sleep apnea have two- to fourfold greater risk of sleep apnea and familial factors can explain up to 40% of the variance in AHI.

Other risk factors associated with a higher risk of OSA are smoking, menopause (hormonal differences could account for the sex differences in OSA, with hormonal replacement being protective), nasal congestion, and ambient air pollution (particularly nitrogen dioxide and PM 2.5). A number of comorbid conditions are also associated with a higher prevalence of OSA, although whether this association is etiological or simply reflects the common risk factors of these conditions is still under evaluation. These conditions include diabetes, hypertension, congestive heart failure, stroke, coronary artery disease, atrial fibrillation, chronic lung disease, pregnancy, endocrine disorders (hypothyroidism, acromegaly), end stage renal disease, gastroesophageal reflux, and many others.

Pathophysiology

The pathogenesis of OSA is not fully understood. The upper airway collapse during sleep results from an interplay of several factors. Unfavorable upper airway anatomy (small airway due to obesity, genetics, age, craniofacial, or upper airway abnormalities) may lead to its collapse when subjected to a collapsing transmural pressure (Figs. 1A and B).

Decreased central respiratory output during sleep, which reduces tonic upper airway dilator muscles activity can predispose to such a collapse. Upper airway caliber decreases normally during sleep and has a higher compliance. Upper airway and nervous system reflex activity is also impaired during sleep, leading to inability to maintain ventilation and increasing arterial carbon dioxide levels. However, patients with OSA are observed to have a low arousal threshold, waking up frequently to increased carbon dioxide levels and hyperventilating. The resultant hypocapnia can further decrease the respiratory drive and reducing tonic muscular output, leading to upper airway collapse and apneic episode. Neuromuscular incoordination and diseases that lead to it may also play a role in the pathogenesis of apnea.

Lung volume decreases with increasing age, obesity, and during sleep; which removes the caudal traction on the upper airway applied by the inflated lung, increasing airway collapsibility. Rostral fluid shifts during sleep, particularly in conditions with extracellular volume overload, can also narrow the airway.

Clinical Features

Patients with OSA often complain of daytime symptoms such as inability to remain fully awake or alert, fatigue (more common in women), tiredness, and poor focus; referred to as daytime sleepiness. They do not wake up feeling refreshed (non-restorative sleep). A quantitative assessment of the sleepiness and fatigue can be done by the Epworth Sleepiness Scale.
Bed partners of patients with OSA report that the patient has nocturnal breathing disturbances such as snoring, gasping, choking, snorting, or breathing pauses while sleeping. A systematic review of 42 studies noted that nocturnal gasping or choking was the single most useful clinical symptom for identifying patients with OSA (likelihood ratio 3:3); and while snoring was a frequent complaint, it had no value in suggesting OSA as a single finding (likelihood ratio 1:1). For the diagnosis of OSA, snoring had a higher sensitivity (80%), but a lower specificity (50%) as compared to gasping or choking (sensitivity—52%, specificity—84%).

Other symptoms found in patients with OSA are morning headaches (12–18% of patients), lasting for several hours after waking up on most days of the week. There is also a high prevalence of insomnia in patients with OSA (up to 30%), and females had more insomnia symptoms as compared to males. Up to 40% patients experience nocturia (even correlating with severity OSA in patients <50 years of age); treatment with continuous positive airway pressure (CPAP) significantly reduces the number of night-time urinations.

Physical evaluation of patients with OSA reflects the comorbid conditions and etiological factors for the disorder. The most common clinical finding is obesity, particularly central obesity. Patients often have large waist circumference and neck circumference (>17 inches for men and >16 inches for women). Oropharyngeal examination can indicate craniofacial abnormalities and crowded upper airway. Mallampati classification and Friedman tongue position can be used to rapidly assess the severity of airway narrowing; a meta-analysis indicating it positively correlated with predicting OSA severity. Associated conditions and complications that can be found in patients with OSA are systemic hypertension, heart failure, and pulmonary hypertension.

**Diagnosis**

The American Academy of Sleep Medicine (AASM) has established guidelines for the diagnosis of OSA. Diagnostic testing should be performed in patients with excessive daytime sleepiness and the presence of at least two of the following features—habitual loud snoring, witnessed apnea or choking or gasping during sleep, and systemic hypertension; patients fulfilling these criteria are at high risk of moderate to severe OSA.

The AASM recommended against the use of clinical tools, questionnaires, and prediction algorithms to diagnose OSA in adults, in the absence of polysomnography or home sleep apnea testing. Examples of such tools include the Berlin questionnaire, STOP-Bang questionnaire, the NoSAS score (which performed significantly better than the previous two), the Multivariable Apnea Prediction instrument (MVAP), etc.

The use of home sleep apnea testing (HSAT, also known as out-of-center sleep testing or OCST) or polysomnography (PSG) is recommended for the diagnosis of OSA. An in-laboratory PSG is considered...
the gold standard for diagnosis, and should be performed in cases where HSAT is negative, technically inadequate, or inconclusive. The diagnostic criteria for OSA, as per AASM, International Classification of Sleep Disorders (ICSD), 3rd edition are:

- ≥15 predominantly obstructive respiratory events per hour of sleep during PSG or OCST, in the absence of associated symptoms or disorders
- OR
- ≥5 predominantly obstructive respiratory events per hour of sleep during PSG or OCST, with ONE or more of the following:
  - Complains of sleepiness, non-restorative sleep, fatigue, or symptoms of insomnia
  - Waking up with breath holding, choking, or gasping
  - Habitual snoring, breathing interruptions, or both noted by a bed partner or other observer
  - Comorbidities—hypertension, type 2 diabetes mellitus, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, cognitive dysfunction, or mood disorder

The respiratory events include obstructive apnea (≥90% reduction in airflow for >10 seconds with continued respiratory effort), hypopnea (a ≥30% reduction in airflow for ≥10 seconds with arousal or ≥3% desaturation) and respiratory effort-related arousal, that is, RERA (arousals associated with decrease in airflow lasting at least 10 seconds, that do not meet criteria for apnea or hypopnea). The quantitative data generated from sleep study can be expressed in the form of two indices:

- Apnea-hypopnea index (AHI)—Number of apneas plus hypopneas per hour of sleep
- Respiratory disturbance index (RDI)—Number of apneas plus hypopneas plus RERAs per hour of sleep

RDI is the preferred index and can be used to classify the severity of OSA into mild (5–14 events per hour), moderate (15–29 events per hour), and severe (≥30 events per hour).

**Differential Diagnosis**

Conditions that can mimic OSA and should be kept as a differential diagnosis include:
Primary snoring—Most patients with OSA snore, but not all patients who snore have OSA
Pulmonary disease—Asthma, chronic obstructive pulmonary disease
Insufficient sleep
Other sleep disorders—Central sleep apnea, narcolepsy, periodic limb movement disorder, restless legs syndrome
Neurological disorders leading to daytime sleepiness
Neuromuscular disorders
Medical diseases—Hypothyroidism, end stage renal disease, hepatic encephalopathy
Medications—Sedatives (benzodiazepines, barbiturates, non-benzodiazepines, antihistamines, antidepressants, etc.), opioids, etc.
Psychiatric disorders (depression, anxiety) and substance abuse (alcohol, narcotics, etc.)
Gastroesophageal reflux disease

Complications
OSA can lead to several cardiovascular, cerebrovascular, and metabolic complications, which can lead to adverse clinical outcomes and even premature death (Fig. 3).

Fig. 3: Adverse outcomes of OSA
The repeated arousal events associated with intermittent hypoxia in OSA, lead to increased sympathetic activity, hemodynamic changes, inflammation, metabolic changes, and endothelial dysfunction. There is increased incidence of hypertension, cardiovascular events (myocardial infarctions, heart failure, etc.), coronary artery disease, atrial fibrillation, QT prolongation, pulmonary hypertension, and even venous thromboembolism.

It has been noted that patients with OSA tend to have a “non-dipping” pattern of blood pressure (lack of the typical 10% drop in blood pressure during sleep). A meta-analysis of 31 articles indicated that CPAP therapy resulted in a small, but statistically significant reduction of blood pressure in patients with OSA.

There was also an increased incidence of stroke in patients with OSA, particularly in men. OSA has also been implicated in causing two times the increased risk of depression, risk being higher in women than men. Other neuropsychiatric complications include memory and cognitive defects, difficulty in maintaining attention, which combined with the excessive daytime sleepiness, can lead to motor vehicle and workplace accidents.

The reported prevalence of pulmonary hypertension in OSA patients varied between 17% and 70%. OSA associated pulmonary hypertension is classified under group 3 pulmonary hypertension and most of these cases are only of a mild degree.

Metabolic alterations and complications are frequent in patients with OSA. Studies have demonstrated an increased prevalence of type 2 diabetes mellitus and its complications, which is independent of the shared risk factors (e.g., obesity) of both the diseases. An increased incidence of diabetes was independently and significantly associated with OSA severity (30% higher hazard with AHI >30), time spent with oxygen saturation under 90%, and the AHI in rapid eye movement (REM) sleep. Sleep disordered breathing is also independently associated with metabolic dysfunction such as insulin resistance and glucose intolerance, its severity correlating with the RDI and the degree of sleep related hypoxemia.

The prevalence of moderate to severe OSA in patients with metabolic syndrome is very high (60%), the combination of OSA, and metabolic syndrome (syndrome X) being called “Syndrome Z.” Independent association of OSA with increased triglyceride and glucose levels, inflammatory markers, atherosclerosis, and arterial stiffness in patients with metabolic syndrome has been observed. Effective treatment with CPAP reduces several components of metabolic syndrome in these patients.

The chronic intermittent hypoxia in OSA is also a potential candidate for leading to progression of fatty liver in obesity.

**Management**

Patient education and behavior modification is the initial step in management of all patients with OSA. They should be educated about the natural history, risk factors, potential complications, and the increased risk of accidents due to drowsiness. Overweight and obese patients should be encouraged for weight loss via dietary therapy, exercise, drug therapy, or even bariatric surgery. Patients who suffer from OSA primarily in the supine sleep position on PSG, should be initiated on positional therapy (use of a positioning device, monitoring and sometimes the use of an objective position monitor). All patients should be instructed to avoid alcohol and medications, which have an inhibitory effect on the nervous system or cause weight gain.

The mainstay of therapy for OSA in adults is positive airway pressure therapy, delivered in continuous (CPAP), bi-level (BiPAP), or autotitrating (APAP) modes. CPAP prevents upper airway collapse, which leads to respiratory events. CPAP treatment is indicated in treatment of any severity of OSA. It reduces AHI, excessive daytime sleepiness, lowers blood pressure, and improves quality of life, but its effect on mortality remains to be demonstrated.

Other strategies include the use of oral appliances such as mandibular repositioning appliance or tongue retaining device, which enlarge the upper airway and improve its patency. These devices have lower efficacy than CPAP, but have better compliance rates. They are indicated for use in mild to moderate OSA, patients who fail behavioral measures, or fail or do not respond to or are not appropriate candidates for CPAP.

Patients with a surgically correctable obstructive lesion of the upper airway (e.g., adenoid hypertrophy, tonsillar hypertrophy, craniofacial abnormality) can be considered for primary surgery and correction of the obstructive lesion. Surgery can also be a secondary therapy if there is intolerance or failure of positive airway pressure (PAP) or oral appliance therapy. Hypoglossal nerve stimulation may be considered in selected OSA patients (failed CPAP,
BMI <32 kg/m²), a meta-analysis indicating a statistically significant reduction in AHI and daytime sleepiness at 12 months of therapy.²⁹ Tracheostomy eliminates OSA by bypassing the upper airway, but reduces the quality of life substantially.¹⁵,²²

Currently no pharmacologic agent with proven long-term effectiveness is available for replacement of above therapies for OSA. A Cochrane review on drug therapy for OSA, concluded that out of the 25 drugs reviewed, only 10 drugs had some effect on the severity of OSA, but long-term outcomes of these drugs is still unknown.⁴¹ Dronabinol (a synthetic cannabinoid) has been shown to reduce AHI in moderate to severe OSA, but it is not yet recommended in OSA, and needs further Phase III trials to support its efficacy.⁴²

OSA patients continuing to have residual daytime sleepiness, despite effective PAP therapy may benefit from the addition of modafinil or armodafinil (central nervous system stimulants), after other causes of residual sleepiness are ruled out.²²

**Conclusion**

Obstructive sleep apnea, the most common sleep disordered breathing, affects almost a billion people worldwide. India stands fourth among countries with the highest burden and the increasing obesity and air pollution rates worldwide will only serve to increase its prevalence. It leads to morbidity and mortality due to its cardiovascular, cerebrovascular, and metabolic complications; and impacts the patient’s quality of life. Management relies upon lifestyle modification, positive airway pressure therapy, and other strategies (sometimes including surgery) for successful treatment. No pharmacotherapy is yet approved for primary therapy.

**References**

Abstract

Multiple connective tissue diseases (CTDs) manifest interstitial lung disease (ILD) and cause significant morbidity and mortality. Till date, there is no effective therapy. There are new evolving concepts of pathogenesis and rapid progress in identifying the effector cells. Serum biomarkers provide new insights for early diagnosis and disease progression. But management of patients with CTD-ILD remains sub-optimal. Multi-disciplinary clinics are now established for early diagnosis, improved management, and effective therapy.

Introduction

Connective tissue diseases (CTDs) are a group of diseases with heterogeneous systemic features and show immune-mediated multi-organ dysfunction. The respiratory tract can be affected in virtually every CTD. Interstitial lung disease (ILD) is a potential complication in many of the CTDs. In ILD a group of parenchymal lung disorders share common radiologic, pathologic, and clinical manifestations. There are six most common and important forms of ILD namely smoking related, connective tissue or autoimmune disease related, hypersensitivity pneumonitis, occupation related, medication related, and idiopathic pulmonary fibrosis (IPF). The CTDs associated with ILD are as follows:

- Systemic Sclerosis (SSc)
- Rheumatoid Arthritis (RA)
- Polymyositis/Dermatomyositis (PM/DM)
- Sjögren’s Syndrome
- Systemic Lupus Erythematosus (SLE)
- Undifferentiated CTD
- Mixed CTD

Sometimes they are asymptomatic and require high-resolution computed tomography (HRCT) of lungs or pulmonary function testing (PFT) for detection. Lung involvement is a decisive contributor to mortality in CTD. The fibrosing forms are often incurable and lead to significant morbidity and mortality.

ILD associated with CTDs share a common clinical presentation such as cough (non-productive), shortness of breath to progressive dyspnea. At times ILD may be the presenting feature that predates the CTD. Prevalence of ILD in CTDs appears to be higher than previously thought. In order to initiate proper treatment early recognition of pulmonary involvement is very important.

An accurate ILD diagnosis requires thorough medical history and physical examination along with autoimmune serologic testing, high resolution chest tomography imaging, and lung biopsy (if necessary). Severity of disease and response to treatment is assessed by restrictive pattern of ventilatory defect and abnormal diffusion capacity (DLco). Frequency of ILD in different CTDs is shown in Table 1.

Pathogenesis of CTD-ILD

Three factors interplay in the pathogenesis. They are vascular injury, inflammation, and autoimmunity. It is characterized by a combination of
Respiratory Disease

- chronic inflammation within the lungs consisting of an accumulation of chronic inflammatory cells and increased levels of numerous proinflammatory cytokines, chemokines, and cell surface molecules;
- varying degrees of fibrosis.

In the pathogenic process of pulmonary fibrosis initially there is microvascular injury, which leads to endothelial or alveolar epithelial damage. Then proinflammatory and profibrotic extra cellular mediators like chemokines, cytokines, growth factors, lipids, and prostanoids come into play. The pivotal mediator of fibrosis is the Cytokine Transforming Growth Factor Beta (TGFbeta). TGFbeta along with platelet derived growth factor, endothelin-1 (ET-1) play the key role in fibroblast production (Flowchart 1).

Histology

In response to lung injury in CTD associated ILD, three major histopathologic patterns occur. They are:
- Usual interstitial pneumonia (UIP),
- Non-specific interstitial pneumonia (NSIP), and
- Organizing pneumonia (OP).

UIP is recognized by dense fibrotic areas heterogeneously distributed with areas of normal lung architecture, numerous microscopic cysts filled with mucus called honeycomb change and fibroblastic foci juxtaposed to honeycomb cysts.

NSIP shows diffuse cellular inflammation and/or fibrosis in the lung interstitium. The distribution is homogeneous pattern throughout the lungs.

OP is recognized by multiple round or oval deposits consisting of extra cellular matrix proteins and myofibroblasts.

Treatment and prognosis in ILD is determined by the etiology of ILD rather than a specific histologic pattern.

Therefore, biopsy is not advocated unless absolutely necessary.

Radiology/HRCT Imaging

HRCT imaging of chest is essential for making accurate ILD diagnosis. Three features of chest imaging deserve specific mention.
- Distribution of opacities within the lungs—upper lobe versus lower lobe, peripheral versus central/peribronchiolar, and whether spare extreme periphery. Specific forms of ILD have characteristic distributions and no known explanation for that.
- Next, findings of fibrosis be recognized- reticular opacities often seen in periphery of the lungs, traction bronchiectasis (dilated and distorted bronchi and bronchioles due to traction by surrounding fibrosis) and honeycomb change (clusters of small cysts in extreme periphery) and volume loss. Honey combing and traction bronchiectasis occur in advanced fibrosis. These findings portend poor prognosis irrespective of etiology.
- Lastly, presence of ground glass opacities and/or consolidation—areas of hyperattenuated lung considered to be inflammatory in nature and likely to be reversible.

<table>
<thead>
<tr>
<th>Connective tissue diseases</th>
<th>Frequency of ILD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>20–30</td>
</tr>
<tr>
<td>Systematic sclerosis</td>
<td>45</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Up to 25</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>20–50</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2–8</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>20–60</td>
</tr>
</tbody>
</table>

**TABLE 1** Frequency of ILD in different CTDs

Flowchart 1: Mechanisms involved in pulmonary fibrosis. Endothelial and alveolar epithelial injury initiates activation of coagulation cascade, release of various growth factors and cytokines. This leads to activation of fibroblast and development of fibrosis.
Imaging pattern on HRCT is characterized by reticulation associated with fibrotic features, architectural distortion, traction bronchiectasis and honeycombing.

UIP pattern on HRCT shows peripheral and basal predominant involvement. There is reticulation associated with fibrotic changes and also includes traction bronchiectasis and honeycombing.

In NSIP pattern ground-glass opacity and reticulation with traction bronchiectasis is seen predominantly, basal and bilateral OP pattern consists of patchy, subpleural, peripheral, and peribronchiolar consolidation (Figs. 1A to C).

Relative Frequency of Pattern of Involvement in ILD Associated with CTDS

See Table 2.

Autoantibodies in the Diagnosis of CTD-ILD

In specialized ILD clinics detection of autoantibodies assist diagnosing unrecognized CTD-ILD. These autoantibodies tests change the diagnosis (in about 4–19% cases) from idiopathic ILD to CTD-ILD. Distinguishing idiopathic interstitial pneumonia from CTD-ILD is absolutely important as regards prognosis and management. The major autoantibodies and their associated CTDs are given in Table 3.

Prognosis of CTD-ILD

High mortality and more aggressive disease is seen in male sex, a history of smoking, older age, South Asian ethnicity and UIP pattern. Another survival analysis showed disease...
course and intensity of ILD lesions at baseline as critical indicator for survival. In yet another study of 359 patients with median follow-up time 4 years, there were 85 deaths (23.7%).

**Connective Tissue Diseases Associated with ILD**

**Systemic Sclerosis**

Systemic sclerosis (SSc) is a rare CTD and is characterized by immune dysfunction, vasculopathy, cellular inflammation, and fibrosis of skin and multiple internal organs. Initial tissue injury is followed by excessive collagen deposition. Nearly one-half of cases develop clinically significant ILD and is a leading cause of death in these patients. Risk of ILD is greater in African-American ethnicity and in those with more extensive skin involvement (diffuse SSc).²

Risk factors for the development of progression of ILD are older age at disease onset, shorter disease duration and the presence of anti-Scl-70 (anti-topoisomerase antibody) and absence of anti-centromere antibody.³ But none of these risk factors is absolute. All the patients diagnosed as systemic sclerosis should have assessment of respiratory symptoms, HRCT scan of chest and PFTs to ensure early identification of ILD. The risk of developing ILD is greatest early in the course of disease. PFTs and DLco are very useful to monitor the progression. Therefore, suggested to repeat the tests every 4–6 months for 3 years. Most patients will show a slow decline in lung function, but some have rapid progression.

Certain biomarkers serve as indicators of disease and predictors or progression. Serum levels of surfactant proteins A&D (SP-A and SP-D) and glycoprotein KL-6 were elevated when compared to healthy controls. Recently a novel biomarker chitinase-like protein YKL-40 is gaining interest.

Most of the cases show NSIP pattern in HRCT scan and histopathology. Some with advanced disease with severe fibrosis may show UIP pattern. The utility of HRCT is sufficient to make the diagnosis of UIP/IPF in about 50–60% cases.

**Management/Treatment Considerations of SSC-ILD**

There are no approved drugs. Current approach to treatment include routine follow-up alone in mild disease...
with no signs of progression. On the other hand in patients with progressive ILD active immunosuppression is advocated along with monitoring. Based on available data, decisions for treatment is made case by case basis. All do not need treatment. Decline in lung function, progression of fibrosis on HRCT or worsening respiratory symptoms due to ILD will require active drug treatment.

In early stage of disease (requiring treatment) evidence of inflammation is commonly present, and therefore therapies target inflammatory response. Corticosteroids, cyclophosphamide, azathioprine and mycophenolate mofetil are the immunosuppressive agents used. Corticosteroid therapy is generally ineffective. Others show modest benefit.

Oral cyclophosphamide at 2 mg/kg/day was tried for 12 months in Scleroderma lung study. It showed slowing of decline in lung function, improvement in dyspnea and skin thickening. At 24 months only benefit of reduction in dyspnea remained.

Mycophenolate mofetil is a less toxic and better tolerated drug as compared to cyclophosphamide. Therefore, this drug is a better option for long term use.

Azathioprine is an alternative agent for those who do not tolerate cyclophosphamide. Data suggests Azathioprine for maintenance therapy following intravenous cyclophosphamide.

Endothelial-1 receptor antagonists (Bosentan)—BUILD-3 study did not reduce morbidity and mortality. As regards 6-minute walk test it was no better than placebo.

Tyrosine kinase inhibitors (Imatinib) blocks platelet derived growth factor receptor. A recent large multicenter randomized controlled trial showed no significant benefit in treatment of IPF.

Pirfenidone has both anti-inflammatory and anti-fibrotic effect. It inhibits collagen synthesis & TGFbeta production. It improved exercise capacity and showed no radiological progression of disease.

Nintedanib completely inhibits tyrosine kinase, fibroblast proliferation, migration & transformation. It is recommended for use in IPF where forced vital capacity (FVC) is less than 80% of predicted. Though Pirfenidone and Nintedanib are both approved for use in IPF there is no recommendation for use in SSC-ILD. Results of ongoing Scleroderma Lung Study III and SENSCIS trial may guide us regarding their use in progressive and fibrotic variety.

Lung transplantation is an option in SSC-ILD patients who fail to respond to pharmacotherapy.

Rheumatoid Arthritis (RA)
ILD is seen in 20–30% cases of RA and is second leading cause of death. Development of ILD is associated with shortened survival. Smoking, older age, severe joint affection, high rheumatoid factor, and MUC5B gene association are the risk factors. Between 3–5% of patients showed ILD prior to RA diagnosis. Although RA is more common in females, RA-ILD occurs more frequently in males.

Pathogenesis of ILD in rheumatoid arthritis patients is not clear. Both rheumatoid factor and anti-CCP antibodies in high titers are linked to development of ILD. There is growing evidence suggesting perhaps rheumatoid arthritis starts in lungs. Because some patients with high anti-CCP antibodies do not have any articular manifestation. Cigarette smoking plays a role in inducing antibody production. Smoking may promote citrullination of lung proteins particularly those having HLA-DRB1 shared epitope.

HRCT scans in RA patients show a variety of patterns. UIP pattern is most common which occurs in 40–62% cases. NSIP is second most common pattern. Patients with UIP pattern on HRCT scan have worsened survival as compared with those having NSIP pattern. Therefore, all RA patients should undergo annual screening for ILD and if ILD is suspected HRCT scan be obtained.

Optimal therapy of RA-ILD is not known. Corticosteroids and immunosuppressants though widely used show limited benefit in RA-UIP. In NSIP or organizing pneumonia corticosteroids are the mainstay of therapy. Cyclophosphamide and azathioprine have been used with varying success. Mycophenolate mofetil is another option for treatment. In fibrotic group, immunosuppressants along with Nintedanib/Pirfenidone may be used.4

Five-year survival in RA-UIP patients is less than 50%. Lung transplant is a reasonable option for these patients.

Polymyositis/Dermatomyositis (PM/DM)
ILD is common and found in 25–45% cases of PM/DM. In 18–20% cases ILD presents prior to myositis. ILD markedly influences the disease course of inflammatory myositis. The strongest predictive factor is the presence of specific autoantibodies. Most important are JO-1 and KL-7 (associated with anti-synthetase syndrome) and MDA5 (associated with Amyopathic dermatomyositis). ILD associated with those Myositis specific autoantibodies
is severe, rapidly progressive, and non-responsive to treatment, and therefore have very poor prognosis. Pattern of radiological involvement is NSIP, UIP, Cryptogenic organizing pneumonia or diffuse alveolar damage.

There are no large controlled trials to confirm the efficacy of treatments in ILD-PM/DM. Treatment is designed differently for chronic progressive and rapidly progressive cases. In RP-ILD treatment protocol is aggressive. About 20–40% of RP-ILD with anti-MDA5 patients die within 6 months of diagnosis even if treated intensively.

Corticosteroid is the mainstay of therapy along with steroid sparing immunosuppressants. Tacrolimus, mycophenolate mofetil, rituximab, and iv immunoglobulin also show benefit in some series.

**Sjögren’s Syndrome**

ILD is associated in about 25% cases of Sjögren’s syndrome and is an important extra glandular manifestation. Sub-clinical lung disease is even more frequent.

Association of lymphocytic interstitial pneumonia was first described in 1973. However, NSIP in its fibrosing variant is the most common manifestation. Organizing pneumonia, usual interstitial pneumonia, and lymphocytic interstitial pneumonitis are the other types of ILD. Dyspnea and cough are the main symptoms. Presence of anti-SSA is a predisposing factor.

The course of NSIP is unpredictable. It may progress, remain stable, reverse, or can be progressive and irreversible even with treatment. UIP pattern shows irreversible lung disease and has worse prognosis than NSIP.

Corticosteroid is the mainstay of treatment along with azathioprine and cyclophosphamide in NSIP. Immunosuppressive drugs do not benefit patients with UIP. There is no standard regimen of treatment. ILD is a significant cause of death.

**Systemic Lupus Erythematosus (SLE)**

In SLE pleuropulmonary involvement is not uncommon. But prevalence and severity of ILD is lower. Two important pulmonary manifestations of SLE are acute lupus pneumonitis and diffuse ILD. ILD is seen in about 3–8% of cases. The presenting symptoms are dyspnea, cough, fever, and pleuritic pain. These two conditions have major impact on morbidity and mortality. Therefore, it is essential to recognize and treat them properly. HRCT scan of chest and pulmonary function tests help in diagnosis.

Predominant lung pathology determines the treatment. High dose corticosteroids are the mainstay of treatment. Other agents such as cyclophosphamide, azathioprine, iv immunoglobulin, and rituximab are used if there is no prompt improvement. In acute lupus pneumonitis, weekly rituximab shows rapid improvement in PFT and symptoms.

**Mixed Connective Tissue Disease (MCTD)**

Pulmonary impairment is not evident clinically in early stage of disease. In a study published in 1976, 80% cases of MCTD had pulmonary disease but 69% were asymptomatic. The most relevant autoantibody associated is U1RNP.

Although MCTD is characterized by overlap features of SSC, PM/DM, and SLE the HRCT findings appeared remarkably homogeneous. NSIP is the most common pattern in MCTD. More than 50% of patients of MCTD have abnormality in DLco. Lung fibrosis is associated with increasing mortality. About 47% patients respond well to corticosteroid 2 mg/kg/day monotherapy or combination of corticosteroid and cyclophosphamide.

**Undifferentiated Connective Tissue Disease (UCTD)**

Undifferentiated CTD defines clinical entities with features suggestive of CTD and yet do not meet the criteria of a specific single disease. Patients with established UCTD lung involvement usually appears as a complication. About 88% cases have NSIP pattern. Lung involvement is associated with worse prognosis. Treatment is same as other CTD-ILD with NSIP pattern.

**Conclusion**

ILD is a frequent and serious complication of CTDs. Accurate and early diagnosis is challenging, but crucial to offer appropriate treatment. Lack of international guidelines to standardize clinical, radiologic, histopathologic, and biologic parameters is a great hurdle. There is no consensus regarding drugs to be used, duration of treatment, and optimal timing. Multi-disciplinary clinics involving pulmonologists, rheumatologists, radiologists, and pathologists are necessary to design treatment modalities for optimal outcome.
References

Abstract
Superior vena cava syndrome is clinically manifested by dyspnea, facial swelling and facial edema, venous engorgement of neck and chest wall due to extrinsic, and/or intrinsic obstruction of superior vena cava causing reduction in venous return from head, neck, and upper extremities. It may develop quickly or gradually depending on underlying etiology which may compress, invade, or thrombose a thin-walled vessel in superior mediastinum.

Introduction
Superior vena cava syndrome (SVCS) is clinically manifested by dyspnea, facial swelling, and facial edema, venous engorgement of neck and chest wall due to extrinsic and/or intrinsic obstruction of superior vena cava causing reduction in venous return from head, neck, and upper extremities. It may develop quickly or gradually depending on underlying etiology which may compress, invade or thrombose a thin walled vessel in superior mediastinum.

Historically, it was first described in 1757 by William Hunter in patient of syphilitic aortic aneurysm. Nearly two hundred years later Schechter described more than 200 patients of SVCS, out of which 40% were due to syphilitic aortic aneurysm or tubercular mediastinitis. Subsequently, advances in antibiotics decreased infectious causes considerably and currently malignancy is the leading cause of SVCS.

Anatomy
It’s large, valveless and thin walled vein formed by union of right and left brachiocephalic veins at first costal cartilage in superior mediastinum; traverses through middle mediastinum behind second costal cartilage and terminates into right atrium within pericardial sac at level of third costal cartilage. Azygos vein, which is main tributary enters at T4 level and drains upper lumbar and thoracic wall. It is surrounded by relatively rigid structures of thorax including sternum, trachea, right main bronchus, aorta, pulmonary artery, and perihilar and paratracheal lymph nodes. It’s easily compressible by any space occupying process in surrounding. Its diameter is around 2 cm and length around 6–8 cm. Its low pressure vessel draining venous blood from head, neck, upper extremities, and upper thorax.

Pathophysiology
Superior vena cava can be partially or completely obstructed through:
- Extrinsically by benign or malignant tumors
- Intrinsically by thrombus or aneurysm
- Combination of both processes

Gradual obstruction ensures formation of collateral/s mainly through azygous vein, internal mammary veins, lateral thoracic veins, parascapular veins, and esophageal venous network. It is manifested as engorged superficial...
subcutaneous veins with diverted blood flow direction. Despite collateral systems, venous pressure is raised up to 300 mm of saline in severe cases. 

**Etiology**

**Malignant Causes (60%)**
- Lung cancer, small cell (SCLC), and squamous cell (50%)
- Non-Hodgkin lymphoma (5%)
- Other malignancies (5%)
- Metastatic tumor mostly from breast cancer
- Mediastinal germ cell tumors
- Hodgkin's lymphoma
- Thymoma

**Benign Causes (40%)**
- Intravascular devices including central venous access devices, pacemaker/defibrillator leads, etc.
- Benign tumors including teratoma and dermoid cyst
- Cardiac causes including pericarditis and atrial myxoma
- Vascular causes including aortic aneurysm, vasculitis (Behcet's syndrome)
- Infectious causes including tuberculosis, histoplasmosis, and syphilis
- Fibrosing mediastinitis due to prior irradiation
  - Malignant causes predominate, especially lung cancer including SCLC and squamous cell carcinoma owing to central predisposition. In young males, lymphoma especially large cell variants like diffuse large B cell lymphoma, lymphoblastic lymphoma, and primary mediastinal lymphoma may cause rapidly progressing SVCS. Rarely germ cell tumors may be found in young males. In recent years prevalence of benign causes is on rise due to expanding use of central venous catheters.

**Clinical Features**

Signs and symptoms depend on the following:
- Degree, site, and rapidity of obstruction of superior vena cava
- Underlying etiology
- If malignant etiology then its subtype and overall tumor burden
- Partial obstruction may not manifest clinically and patient may remain asymptomatic. Few subtle signs may go unnoticed. Gradually developing obstruction allows adequate time for collateral development delaying the manifestations to appear in advanced stages. Obstruction proximal and distal to azygous vein will exhibit differently.

The most common symptom of SVCS is dyspnea followed by neck and facial swelling/fullness of head. Other symptoms include cough, arm swelling, chest pain, dysphagia, hemoptysis, epistaxis, dizziness, syncope, and lethargy. Symptoms may aggravate by bending forward or lying down due to obstruction to outflow of blood from head and neck. The most common sign of SVCS is venous distention of neck and chest wall followed by facial edema, cyanosis, plethora of face, and edema of arms in descending order of frequency.

Signs may progress through four stages which may considerably overlap:
- Due to increased venous pressure, swelling of neck, face, upper extremities manifests initially, which may be demonstrated through Pemberton’s sign (though classically described in retrosternal goitre). Bilateral arms elevation above head for 2 minutes manifesting as above due to decreased venous outflow aggravating obstruction is considered as positive sign.
- Involvement of cardiorespiratory system may manifest as dyspnea, cough, and hoarseness and suggest severe airway and vascular obstruction. Risk of cardiac arrest and respiratory failure is high in patients receiving sedatives or general anesthetic agents.
- As venous stasis progresses, neurological symptoms manifest, including headache, dizziness, syncope, visual disturbances due to cerebral edema, which entails poor outcome. Seizure is more likely due to brain metastases rather than cerebral edema. Small
cell lung cancer with SVCS is more likely to have brain metastases than without SVCS.

- Life threatening manifestations include stridor (due to laryngeal edema which is poor prognostic sign), syncope without aggravating maneuvers, confusion, and hemodynamic instability. All of these require emergent intervention.

“Downhill” varices where direction of blood flow is from cephalad to caudal is indicative of esophageal varices due to collateral formation. Venous obstruction proximal to azygous vein leads to varices in upper third of esophagus in contrast to distal obstruction, which causes varices in entire length of esophagus.6

Life expectancy is unchanged in benign causes in contrast to malignant etiology, where it is dependent on tumor histology. Lymphoma has better survival than small cell lung cancer after irradiation and disease-specific treatment.

### Investigations

SVCS is a clinical diagnosis with characteristic manifestations. Current treatment is directed toward underlying etiology. Hence, work up is individualized to ascertain etiology. The most commonly employed initial modality is chest X-ray, which shows superior mediastinal widening and right sided pleural effusion in around one-fourth patients. Pleural effusions are mainly exudative in nature and exceptionally chylous, especially in lymphoma.7

Contrast enhanced computed tomography (CECT) scan is a modality of choice, which delineates detailed anatomical information regarding superior vena cava and its tributaries with respect to other critical structures like trachea, bronchi, esophagus, and spinal cord. CT suggests reduced or absent opacification of central venous structures and collateral venous circulation.8 Magnetic resonance imaging (MRI) is indicated only when CECT is contraindicated in renal dysfunction.

Integrated whole body positron emission tomography-CECT is the preferred modality of choice in lymphoma and lung cancer patients as it helps in complete staging, and hence intent of treatment (definitive vs. palliative).

Histopathological evidence of malignancy is essential and it may be obtained through endobronchial fine needle aspiration, CT guided needle biopsy, mediastinoscopy, or thoracotomy (if all other modalities fail). Mediastinoscopy and thoracotomy have minimum complications and high tissue yield.9 Thoracocentesis in pleural effusion can also establish diagnosis in two-thirds of patients.

### Management

#### Treatment Deciding Factors

SVCS treatment entails a judicious use of available measures on a case by case basis. There are no evidence-based guidelines or recommendations available. Various factors guiding the management decision algorithm include:

- Etiology
- Treatment responsiveness of the underlying disease
- Grade of severity
- Nature of underlying disease
- Overall prognosis
- Goals of therapy

#### Treatment Modalities

Overall treatment is a mix and match of various available modalities in individualized sequences and combinations. Various therapeutic modalities include nursing in semi-inclined position, securing the airway, fluid restriction, avoiding upper body cannulation, diuretics, inhaled oxygen, steroids, radiotherapy, chemotherapy, removal of the foreign body (viz., catheter), endovascular thrombectomy, intravascular pharmacological or mechanical thrombolysis, stent placement, oral or parenteral anticoagulation, and surgical venous bypass.

#### Treatment in Various Clinical Settings

**SVCS with Life-threatening Symptoms**

It is not uncommon to see aggressive malignancies like acute hematological malignancies and small cell lung cancer present with stridor, respiratory failure, or altered sensorium. It is a medical emergency.

**Symptomatic Management**

Place the patient in semi-inclined position and access lower limbs for venous cannulation. Following securing airway and addressing issues like dyselectrolytemia and tumor lysis syndrome (TLS), emergency endovenous recanalization (e.g., mechanical or pharmacologic thrombolysis and balloon angioplasty), and SVC stenting
should be the preferred modality depending on the availability of equipment and expertise. This will be accompanied by other supportive modalities including fluid optimization, diuretics, steroids, oxygen, and anticoagulation. If the SVCS is only due to stenosis without accompanying thrombosis, the role of anticoagulants is debatable.

**Definitive Management**

Before commencing definite management, an adequate tissue biopsy is must. Steroids should be used carefully in lymphomas as they may melt the tumor jeopardizing the biopsy findings. They may also aggravate the tumor lysis syndrome, which is again another medical emergency, needing expeditious management. It includes treating the primary pathology by surgery, radiation, or chemotherapy depending on the type and extent of disease.

**SVCS without Life-threatening Symptoms**

**Symptomatic Management**

Symptomatic management is almost same in all non-emergent cases. Upper limb, neck, or subclavian cannulation should be avoided. Depending on the severity of symptoms, diuretics may be used to reduce venous congestion in SVC drainage area including brain. Fluid intake should be optimized to avoid worsening of edema and to overcome dehydration. This is even more relevant in cases likely to have TLS. Malignancy related SVCS is frequently associated with thrombosis as well as a risk of DVT; hence, anticoagulants should be initiated in all cases unless proved otherwise. Oxygen supplementation should be reserved for cases having respiratory compromise. Steroids are important component of chemotherapy in NHL, but caution should be taken about the risk of worsening TLS and should only be started after obtaining the tumor tissue biopsy. Use in cases other than NHL is questionable.

**Definitive Management**

Since malignancy is the most common cause of SVCS. It is pertinent to discuss treatment in two parts: malignancy related and SVCS due to other causes.

**Malignant SVCS:** It incorporates treating the primary malignancy with surgery, radiation, or chemoradiation. In most cases, after this, SVCS disappears; however, in case of persisting symptoms, endovascular interventions or surgical venous bypass may be used. As an example, SVCS in case of a large thymoma may be corrected by surgical venous bypass. Non-Hodgkin lymphoma is a chemosensitive tumor. The most common subtype is diffuse large B cell lymphoma, if localized then treated with radiation therapy and in advance stages treated with chemotherapy mainly anti CD20 chimeric monoclonal antibody Rituximab in combination with cyclophosphamide, adriamycin, vincristine, and prednisolone. Responses are quick within 7 days. Patient must be watched and treated for tumor lysis syndrome. SCLC is chemosensitive and radiosensitive tumor. SVCS related to SCLC is treated with chemotherapy alone or in combination with thoracic irradiation. Response rates are to the tune of 73–93%. Within 1–2 weeks relief from SVCS is achieved. Chemotherapy agents of choice are etoposide and platinum. Non-small cell cancer response rates with chemotherapy (59%) and radiation therapy (63%) are comparable. Nearly one-fifth patients are destined to have recurrence from SVCS.

**Non-malignant SVCS:** The treatment is cause dependent. Most cases are iatrogenic due to some kind of catheter. They are managed with urgent removal of the catheter followed by anticoagulation. The rare cases due to chronic inflammatory processes may be managed by endovenous stenting. Overall survival in benign causes is unchanged if timely diagnosed and treated. Recent times have shown increase in use of central venous catheters, and hence superior vena cava thrombosis. It can be treated with streptokinase, urokinase, or recombinant tissue type plasminogen activator. Heparin and oral anticoagulants reduce progression of thrombus. Removal of catheter should be considered along with anticoagulation. In case of pacemakers, electrode wires should be changed.

**Complications and Care of SVCS**

**Treatment Modalities**

**Bleeding risk:** Thrombolytic and anticoagulants are associated with significant risk of bleeding. Patients should be regularly monitored for the same.

**Stent migration:** Stent migration into the heart and pulmonary vasculature may be immediately life threatening. A high index of suspicion is warranted.
**Respiratory Disease**

*Pulmonary embolism:* Tumor, thrombus fragment, or rarely a stent can embolize and cause a catastrophe.

*Stent occlusion:* Long-term anticoagulation is a need in a patient with a stent. Hence, its long-term safety in benign causes is questionable.

*Tumor lysis syndrome:* As explained earlier, it may be aggravated by the use of steroids. Hence, it again requires a high index of suspicion.

**Conclusion**

Superior vena cava syndrome may expedite to life threatening emergency if not treated urgently. Early institution of underlying etiology has curative potential in nonmetastatic solid malignancy, advanced lymphomas, and nonmalignant causes. Tissue diagnosis and appropriate imaging is essential in management of SVCS. Palliation of symptoms can be done with diuretics, steroids, stenting, and anticoagulation as indicated.

**References**

Abstract
As such overlap of asthma and COPD is not a new clinical condition but had been discussed since long in context with patients having obstructive airway disease, where it was difficult to decide whether it is asthma or COPD. Asthma-COPD overlap (ACO), previously referred as asthma-COPD overlap syndrome (ACOS), is characterized by persistent airflow limitation consistent with COPD, together with several distinguishing features of asthma.

Till date there is no universally accepted definition of ACO, but in recent past there is increasing recognition and stress on better diagnosis, management, and prevention of asthma-COPD overlap. It is difficult to define it as a single disease entity, as it is a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms. It has been observed that ACO patients as compared to asthma or COPD have more rapid decline in lung functions, frequent exacerbations, worsening quality of life, higher mortality rate, and are difficult to treat.

In this chapter, attempt will be made to discuss briefly salient features of ACO.

Introduction
Chronic obstructive pulmonary disease (COPD) and asthma are two obstructive airway diseases, responsible for significant morbidity and mortality; creating serious global health problem. Although asthma and COPD are clinically two distinct disease entities, having diverse etiopathogenesis, management protocols, and response to treatment, but some features at some point are overlapping and compatible with both diseases leading to a mixed picture of overlapping clinical presentation and comorbidities creating difficulties in differentiating whether it is asthma or COPD. These patients are labeled as Asthma-COPD overlap (ACO); previously referred to as asthma-COPD overlap syndrome (ACOS).1

Definition
As such overlap of asthma and COPD is not a new clinical condition but had been discussed since long in context with patients having obstructive airway disease, where it was difficult to decide whether it is asthma or COPD.

As early as in 1961, Prof. Orie and colleagues proposed that all obstructive airway diseases, including asthma, emphysema, and chronic bronchitis, should be considered as different manifestation of a single disease with common genetic origins. Although it generated lot of controversy but discussion at different levels on this hypothesis (Dutch hypothesis) is still continue.2,3

In 1995, COPD guidelines from American Thoracic Society defined asthma, chronic bronchitis, emphysema, COPD, and other clinical situations having airflow limitation (Fig. 1), and identified 11 distinct clinical entities related to obstructive airway diseases dominated by COPD and asthma and overlap between two or more conditions as depicted in Table 1.4-6

Further guideline developed for asthma and COPD had placed more emphasis on recognizing them as two distinct
diseases where complete or incomplete reversibility of airflow obstruction is the defining characteristic. This is useful as it facilitate easier recognition of asthma and COPD, but obstructive airway diseases other than these two entities, for example, having ACO and others received less attention especially during clinical evaluation, management, and research.

In recent past there is increasing recognition and stress on better diagnosis, management, and prevention of asthma—COPD overlap.

‘ACO,’ also labeled as ‘asthma + COPD’ are terms used to collectively describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD.1

It is difficult to define it as a single disease entity, as it is a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms.

Till date there is no universally accepted definition of ACO. The description proposed by Global Initiative for Asthma (GINA) and the Global initiative for chronic Obstructive Lung Disease (GOLD) committees jointly created the term ACOS later renamed it as ACO, to much extent is of help as diagnostic tool for clinician, managing obstructive airway diseases.7

Others academic groups/associations, for example, Spanish Society of Pneumology and Thoracic Surgery (SEPAR), Roundtable Groups, Czech Republic guidelines, Australian Asthma management Handbook have offered different definitions of ACOS, based on persistent airflow limitation as assessed by spirometry and bronchodilator response; documented history of asthma and atopy, exposure to tobacco smoke and/or biomass burning, peripheral eosinophil count, fraction of NO in the exhaled breath (FNO) and IgE levels in different combinations.8-13

Salient practical features of the GINA/GOLD (2020) and other recommendations related to definitions and parameters of ACO, COPD, and Asthma are summarized in Table 2.
TABLE 1
Clinical entities with airway obstruction

<table>
<thead>
<tr>
<th>Clinical entities (Prefix Nos. as per Fig. 1)</th>
<th>Definition</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chronic Bronchitis</td>
<td>Symptomatic cough and sputum daily for at least 3 months over 2 years</td>
<td>Persons with chronic bronchitis and/or emphysema without airflow obstruction are not classified as having COPD</td>
</tr>
<tr>
<td>2. Emphysema</td>
<td>Abnormal airspace enlargement</td>
<td></td>
</tr>
<tr>
<td>3. Chronic Bronchitis with Emphysema</td>
<td>Usually occur together</td>
<td></td>
</tr>
<tr>
<td>7. Asthma</td>
<td>Mostly reversible airway obstruction, airway hyper-responsiveness with bronchodilator responsiveness</td>
<td></td>
</tr>
<tr>
<td>4, 5&amp;6. COPD</td>
<td>Persistent airflow limitation</td>
<td></td>
</tr>
<tr>
<td>4. Chronic Bronchitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Emphysema</td>
<td>Usually occur together</td>
<td>MIAO</td>
</tr>
<tr>
<td>6. Chronic Bronchitis with Emphysema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8, 9&amp;10. Asthma - COPD Overlap</td>
<td>Clinical features that are consistent with both asthma and COPD</td>
<td>Varying incompletely reversible Airway Obstruction</td>
</tr>
<tr>
<td>8. Chronic Bronchitis with (VRAO)</td>
<td>Some patients with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough</td>
<td>Difficult to differentiate patients with asthma whose airflow obstruction is not completely reversible from persons with Chronic Bronchitis and/or emphysema that have partially reversible airflow obstruction with airway hyperreactivity</td>
</tr>
<tr>
<td>9. Emphysema with (VRAO)</td>
<td>Some patients with asthma who have developed fixed airway obstruction may have abnormal airspace enlargement</td>
<td></td>
</tr>
<tr>
<td>10. Chronic Bronchitis with Emphysema with (VRAO)</td>
<td>Some patients with these two disorders may have clinical asthma</td>
<td></td>
</tr>
<tr>
<td>11. Diseases with known etiology or specific pathology</td>
<td>e.g., cystic fibrosis or obliterative bronchiolitis etc.</td>
<td></td>
</tr>
</tbody>
</table>

MIAO, mostly irreversible airway obstruction; VRAO, varying reversible airway obstruction

Prevalence and Morbidity of Asthma-COPD Overlap

Globally more than 339 million people are living with asthma; and 65 million people have moderate to severe COPD.1,14

Prevalence rates for ACO have been reported to be in the range between 9% and 55% of those with either diagnosis of asthma or COPD. This variation reflects the different criteria used by different investigators at different places in the world. Concurrent doctor diagnosed asthma and COPD has been reported between 15% and 32% with one or other diagnosis.1

In a systematic review and meta-analysis, based on the random-effects model, the pooled prevalence of ACO was found to be 2.0% in the general population, 26.5% among patients with asthma, and 29.6% among patients with COPD, whereas the prevalence of asthma-only was 6.2% and COPD-only was 4.9%.16 In one of the study it has been reported to be more common amongst females & young population.15,16

Studies suggest that patients having asthma-COPD overlap have frequent exacerbations, have poor quality of life, a more rapid decline in lung function, higher mortality, higher prevalence of comorbidities and greater use of healthcare resources as compared with patients with asthma or COPD alone.1,7,17-19

Risk Factors for Asthma-COPD Overlap

Cigarette smoking: Tobacco smoke may modify the small airway inflammation and remodeling associated with bronchial asthma. It is suggested that FEV1 decline in subjects with ACO is more due to air way inflammation so caused than the pulmonary emphysema.20
TABLE 2 Parameters in asthma, ACO, and COPD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Asthma</th>
<th>ACO</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Any age</td>
<td>40 or above 40</td>
<td>Usually above 40</td>
</tr>
<tr>
<td>Exposure to tobacco smoke</td>
<td>Usually none</td>
<td>≥ 5 pack years or equivalent</td>
<td>≥ 10 pack years or equivalent</td>
</tr>
<tr>
<td>Exposure to Biomass burning</td>
<td>Usually none</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Past medical history of “atopy” Asthma</td>
<td>Asthma (doctor diagnosed) allergies</td>
<td>Asthma (doctor diagnosed) Allergies</td>
<td>Usually none of these</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Vary over time. Often triggers by exposure to dust or allergen, exercise change in weather, emotions, etc.</td>
<td>Usually persistent but may vary</td>
<td>Chronic, continuous, usually progressive</td>
</tr>
<tr>
<td>Course of disease</td>
<td>Often improves with treatment or spontaneously. In few patients may persists because of development of fixed airway obstruction</td>
<td>Partially or fully improve with treatment, slowly progressive, needs high doses of treatment</td>
<td>Usually progressive</td>
</tr>
<tr>
<td>Post bronchodilator response in FEV1</td>
<td>Almost always &gt;12% &amp; 200 mL increase Frequently &gt;12% &amp; 400 mL increase</td>
<td>Usually &gt;12% and 200 mL increase Rarely &gt;12% and 400 mL increase</td>
<td>Usually &lt;12% and 200 mL increase in FEV1</td>
</tr>
<tr>
<td>X-ray chest</td>
<td>Usually normal</td>
<td>Same as COPD</td>
<td>Hyperinflation and other changes of COPD</td>
</tr>
</tbody>
</table>

**Atopy**: There is no direct evidence that atopy alone causes pulmonary emphysema or the chronic bronchitis typical in COPD. However, α1-anti-trypsin deficiency in airways may increase the likelihood of developing asthma. Some of the COPD patients may manifest allergic symptoms, but it is not clear whether this represents late-onset atopy or asthma.21,22

**Age**: Age is not definite risk factor for ACO. Decline in lung functions with ageing is a normal phenomenon, may create confusion while screening for ACO. Adults with asthma, especially if they are smokers, lose FEV1 more rapidly as compared to nonsmoking asthmatics. In one of the study patients with asthma tend to be younger (mean age: 51.3 years) than those with ACO (mean age: 66.7 years), and those with COPD (mean age: 72.4 years).23

A history of childhood or adult-onset asthma should be a major criterion for ACOS. As the prevalence of COPD increases after age 40 years, an age cutoff of 40 years is reasonable to improve the accuracy of the diagnosis.21

**Pathogenesis/Mechanisms Underlying Asthma-COPD Overlap**

Asthma and COPD are having distinct pathophysiology. ACO shares several pathological characteristics with both Asthma and COPD as it shares some of the clinical and spirometric parameters, but the mechanism underlying this overlap is not clear.

Whether ACO is simply the coexistence of asthma and COPD or a distinct phenotype related to fundamental pathogenic mechanisms of asthma and COPD remains to be determined and the mechanisms underlying the overlap between asthma and COPD remain controversial.

“Dutch hypothesis” proposes that asthma and COPD are manifestations of the same basic disease process, where asthma predisposing to COPD in due course of time in the process of aging; where ACO may be a stage of this disease process. On the contrary British hypothesis suggests that asthma and COPD are two distinct diseases generated by different pathophysiological mechanism.2,7,24,25

As depicted in Figure 2, pathogenic processes in asthma are known to include mast cell-mediated bronchoconstriction, inflammation due to local antibody production, and eosinophilic inflammation. These are mediated by complex processes involving number of different messenger molecules, including histamine, cysteinyl leukotriene, prostaglandin D2, interleukins (ILs), and chemokines ultimately producing airway obstruction.25,26,28,29
In majority of asthmatics airflow obstruction so produced is typically reversible but in patients suffering from severe asthma it may partially or incompletely reversible (fixed airway obstruction) producing persistent airflow limitation.\textsuperscript{25,30}

Inflammation in COPD patients is dominantly neutrophilic where involvement of inflammatory cells and messenger molecules, for example, epithelial cells, macrophages, chemokines, monocytes, neutrophils, T-helper cells, and type 1 cytotoxic cells typically producing bronchoconstriction, mucus hypersecretion, alveolar wall destruction, and fibrosis. In contrary to asthma airflow limitation in COPD is not completely reversible\textsuperscript{30,31} (Fig. 1).

In patients with overlap between asthma and COPD, the extent of the contribution of the underlying mechanisms of the two diseases may vary significantly amongst individuals, affected mainly by genetic predisposition, environmental exposure, the initiating condition, and the evolution of the natural history of each patient.

As in both asthma and COPD, the pathogenic processes are triggered by interactions between host and environmental factors; the same assumption is made in patients having ACO. In addition to the multiple risk factors as shown in Figure 2, evidence suggests that asthma itself is an independent risk factor for COPD especially amongst adults who had childhood asthma.\textsuperscript{7,32}

Tucson cohort study observed that asthmatic subjects were 12.5 times more likely to develop COPD than healthy individuals; and about half of the older patients with obstructive airway disease have overlapping diagnoses of both asthma and COPD.\textsuperscript{33}

It has been observed that some asthmatic having long exposure to tobacco smoke and/or other environmental pollution, for example, biomass fuel smoke have more chances to develop COPD (asthma-COPD overlap). There
are conflicting data regarding the genetic component underlying ACO.\textsuperscript{7,34-36}

It has been observed amongst longstanding asthmatics, that about 20% patients develops fixed airway obstruction, and by enlarge it is not reversible with bronchodilators. This group of patients with fixed airway inflammation and eosinophilic inflammation are often labeled as suffering from COPD and they are denied inhaled corticosteroids (ICS), on the contrary they may have ACO and expected to be benefited by ICS.\textsuperscript{37,38}

**Assessment**

There is paucity of research data related to ACO, as these patients have been systematically excluded from clinical studies. Whatever few reports available are not exactly defining underlying mechanism, prevalence, clinical presentation, diagnosis, and management of ACO.\textsuperscript{39}

Dyspnea, cough, expectoration, wheezing, and chest tightness are common symptoms in asthma and COPD, with some qualitative and quantitative variation; are also present in ACO on similar pattern. Patients of ACO usually experiences reduction in day-to-day activities, frequent need for reliever drugs, and recurrent acute exacerbations despite adherence to standard pharmacotherapy. Pattern of other parameters in clinical evaluation depends upon the dominance of the overlapping disease asthma or COPD (Table 3).\textsuperscript{1,21}

Broad expected pattern of history and clinical evaluation of the patient suffering from obstructive airway diseases (Asthma, COPD, and ACO) have been summarize in Table 3.\textsuperscript{1,21}

**Investigations**

**Spirometry**

Persistent expiratory airflow limitation with or without bronchodilator reversibility, as assessed by spirometric data are considered to be strongly suggestive of ACO\textsuperscript{1} (Table 4).

**Biomarkers of asthma:** Mostly used in research as there is little agreement about the most appropriate cutoff point for making a diagnosis.\textsuperscript{11,40}

**Blood or sputum eosinophil count:** Measurement of blood eosinophil is well standardized and reproducible as compared to sputum eosinophil counts and are reported to be high in COPD patients with asthmatic features from 2\% to 5\%, or an absolute cell count 300 cells/µL\textsuperscript{-1}.

**Fractional exhaled nitric oxide (FeNO):** Measurements of FeNO is another biomarker of asthma which is increased in asthma [50 parts per billion (ppb) in non-smokers].

**Serum IgE titers:** Levels are higher amongst asthmatic patients.

**Carbon monoxide diffusing capacity (DLco):** DLco is usually normal or low in ACO as compared to asthma (normal) and COPD (<80\% predicted). DLco is a good indicator of functioning of gas exchange mechanism of lung, which is deranged in COPD.

**Imaging Studies**

**X-ray chest:** As such X-ray chest is not of much diagnostic significance for obstructive airway diseases (OAD) but of immense value in excluding other respiratory disease, for example, respiratory infections (especially tuberculosis), cystic fibrosis, obliterative bronchiectasis included in differential diagnosis of OAD.

**CT scan chest:** Valuable in assessing airway wall thickness and damage to peripheral lung tissues as seen in emphysema.

**Blood tests:** CBC, blood sugar, liver, and renal function studies to rule out systemic diseases included in differential diagnosis of OAD.

**Sputum examination:** For AFB and eosinophil count.

**Other patho-biochemical investigations:** For inflammatory cells, mediators, modulators, airway wall’s smooth muscles and basement membrane studies through bronchoscopy biopsy and lavage are practically less of diagnostic value, are useful for research.

**Diagnosis**

Although a consensus on the exact definition and the diagnostic criteria of ACO remains elusive, the recent report of the GINA and the GOLD has highlighted a stepwise approach for the diagnosis of ACO\textsuperscript{1} (Table 2).

On the basis of detailed medical history, physical examination, and other investigations (as already described) asthma and COPD and possibility of extend of their overlap can be assessed (Table 3).

Subsequently, diagnoses are confirmed through spirometric measures, including reversibility of airflow limitation. Post-bronchodilator (BD) increase in forced expiratory volume in 1 second (FEV1) $\geq$12\% and $\geq$200 mL
TABLE 3  History and clinical evaluation of the patient suffering from asthma, COPD, and ACO

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Asthma</th>
<th>ACO</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variability</td>
<td>Vary over time &amp; intensity</td>
<td>Intermittent or episodic</td>
<td>Dyspnea persisted for most days. May have been preceded by cough/sputum</td>
</tr>
<tr>
<td>Triggers</td>
<td>Allergen, seasonal, exercise, laughter</td>
<td>Allergen, seasonal, exercise, Spontaneous with bronchodilator</td>
<td>Nil</td>
</tr>
<tr>
<td>Improvement</td>
<td>Spontaneous/quick with bronchodilator</td>
<td>Spontaneous with bronchodilator</td>
<td>Limited response with bronchodilators</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;40 years</td>
<td>&gt;40 years; 50–65 years</td>
<td>≥65 years if not younger</td>
</tr>
<tr>
<td>Sex</td>
<td>Adult women &gt; Adult men</td>
<td>Slightly more amongst men</td>
<td>Men &gt; women</td>
</tr>
<tr>
<td>Smoking habit and/or exposure to biomass</td>
<td>Nonsmoker or smokers (&lt;5 pack years)</td>
<td>&gt;10 pack-years and/or exposure to biomass or other toxic exposure</td>
<td>&gt;10 pack-years and/or exposure to biomass or other toxic exposure</td>
</tr>
<tr>
<td>Obesity</td>
<td>More frequent</td>
<td>+/-</td>
<td>Usually not obese</td>
</tr>
<tr>
<td>Atopy/Rhinosinusitis/Asthma (Dr’s. diagnosed)</td>
<td>Atopy/Rhinosinusitis present</td>
<td>Atopy/Rhinosinusitis/Asthma present</td>
<td>Usually no past or current diagnosis of asthma or atopy</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>—</td>
<td>May have</td>
<td>May have</td>
</tr>
<tr>
<td>Respiratory illness specially infection, e.g., tuberculosis</td>
<td>Usually not</td>
<td>May have</td>
<td>May have</td>
</tr>
<tr>
<td>GERD</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Use of reliever drugs</td>
<td>Usually not frequent</td>
<td>Frequent</td>
<td>More frequent multiple daily doses</td>
</tr>
<tr>
<td>Limitation of exercise</td>
<td>Exercise not limited in between attacks</td>
<td>Limitation of exercise</td>
<td>Exercise significantly limited</td>
</tr>
<tr>
<td>Dependence</td>
<td>Patients with severe disease may frequently use Oral corticosteroid</td>
<td>Frequent use of oral corticosteroid</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Hallmark problem</td>
<td>Frequent exacerbations</td>
<td>Very frequent exacerbations &gt;COPD alone</td>
<td>Exacerbations and exercise intolerance</td>
</tr>
</tbody>
</table>

Based on clinical evaluation if suspected other alternative cardiorespiratory diagnosis such as heart failure, bronchiectasis and chronic bronchitis, and other forms of lung disease such as interstitial lung disease should be considered.

TABLE 4  Spirometric variables in asthma COPD overlap

<table>
<thead>
<tr>
<th>Spirometric variable</th>
<th>Asthma COPD overlap (ACO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator values</td>
<td></td>
</tr>
<tr>
<td>Reduced FEV1/FVC (less than lower limit of normal, or less than 0.7 (GOLD))</td>
<td>Required for diagnosis of ACO</td>
</tr>
<tr>
<td>FEV1 80% predicted or more</td>
<td>Compatible with mild persistent airflow limitation if post-BD FEV1/FVC is reduced</td>
</tr>
<tr>
<td>Increase in FEV1 (12% or more) and 200 mL from baseline (reversible airflow limitation)</td>
<td>Common and more likely when FEV1 is low</td>
</tr>
<tr>
<td>Increase in FEV1 more than 12% and 400 mL from baseline (marked reversibility)</td>
<td>Compatible with ACO</td>
</tr>
</tbody>
</table>

ACO: asthma COPD overlap; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for obstructive lung disease
### TABLE 5: Drug treatment of asthma, COPD and asthma—COPD overlap

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Bronchodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Beta 2 agonists</strong></td>
<td></td>
</tr>
<tr>
<td>• Short acting (SABA)</td>
<td>– Salbutamol</td>
</tr>
<tr>
<td></td>
<td>– Terbutaline</td>
</tr>
<tr>
<td></td>
<td>– Metaproterenol</td>
</tr>
<tr>
<td>• Long acting-(LABA)</td>
<td>– Formoterol</td>
</tr>
<tr>
<td></td>
<td>– Salmeterol</td>
</tr>
<tr>
<td></td>
<td>– Vila terol</td>
</tr>
<tr>
<td></td>
<td>– Carmoterol</td>
</tr>
<tr>
<td></td>
<td>– BI-1744-CL</td>
</tr>
<tr>
<td></td>
<td>– LAS-100977</td>
</tr>
<tr>
<td><strong>B. Anticholinergic or Anti-muscarinic agents (AMA)</strong></td>
<td></td>
</tr>
<tr>
<td>• Short acting (SAMA)</td>
<td>– Ipratropium Bromide</td>
</tr>
<tr>
<td>• Long acting (LAMA)</td>
<td>– Tiotropium Bromide</td>
</tr>
<tr>
<td></td>
<td>– Glycopyronium Bromide</td>
</tr>
<tr>
<td></td>
<td>– Darotropium</td>
</tr>
<tr>
<td></td>
<td>– Umeclidinium</td>
</tr>
<tr>
<td></td>
<td>– TiD-4208</td>
</tr>
<tr>
<td><strong>C. Phosphodiesterase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>• Methylxanthines</td>
<td>– Theophylline</td>
</tr>
<tr>
<td></td>
<td>– Atebrophylline</td>
</tr>
<tr>
<td></td>
<td>– Aminophylline</td>
</tr>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>• Inhaled (ICS)</td>
<td>– Beclomethasone</td>
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<td></td>
<td>– Flunisolide</td>
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<td>– Fluticasone</td>
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<td></td>
<td>– Mometasone</td>
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<td>• Systemic-Oral (OS), IV/IM</td>
<td>– Prednisolone</td>
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<td></td>
<td>– Methyl prednisolone</td>
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<tr>
<td><strong>B. Anti-leukotrienes</strong></td>
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<tr>
<td>– Zafirlukast</td>
<td>– Montelukast</td>
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<td>– Probiukast</td>
<td>– Pranlukast</td>
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<td>– Tomelukast</td>
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<tr>
<td><strong>C. Mast cell stabilizers</strong></td>
<td></td>
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<tr>
<td>– Cromolyn sodium</td>
<td>– Ketotifen</td>
</tr>
<tr>
<td>– Nedocromil</td>
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<tr>
<td><strong>D. Monoclonal antibodies against</strong></td>
<td></td>
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<tr>
<td>– IL-4 &amp; IL-13</td>
<td>– Dupilumab</td>
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<tr>
<td>– Lebrikizumab</td>
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<tr>
<td><strong>E. Anti-IgE Antibody</strong></td>
<td>– Omalizumab</td>
</tr>
<tr>
<td><strong>F. Anti-cytokine asthma therapies</strong></td>
<td></td>
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<tr>
<td>– Pascolizumab (anti IL4)</td>
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<tr>
<td>– Mepolizumab, &amp; SCHS5700 (anti IL5)</td>
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<tr>
<td>– Infliximab, Adalimumab and Golimumab (anti TNF-a)</td>
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<tr>
<td>– IMA-638, CAT-354, and AMG 317 (anti-IL-13)</td>
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<tr>
<td>– MT203 (Anti-GM-CSF)</td>
<td>– Anti-IL-25 (IL-17E), IL-25, IL-33, and TSLP</td>
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<tr>
<td>– Anti-IFN-g, -IL-9, -IL-17, and -IL-27</td>
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<tr>
<td><strong>G. Toll-like receptors (TLRs) agonists</strong></td>
<td></td>
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<tr>
<td>– CpG oligodeoxynucleotide of 1018 ISS (a TLR9 agonist)</td>
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<tr>
<td>– AZD8848 (a TLR7 agonist)</td>
<td>– MPTL* (a TLR4 agonist)</td>
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<tr>
<td>– VTX-1463 (a TLR8 agonist)</td>
<td>– CRX-675 (a TLR4 agonist)</td>
</tr>
<tr>
<td>– 1018 ISS &amp; QbG10 (TLR9 agonists)</td>
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<tr>
<td><strong>H. Immunomodulators &amp; Antimetabolites</strong></td>
<td></td>
</tr>
<tr>
<td>– Methotrexate</td>
<td>– Gold salt (oral auranofin)</td>
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<tr>
<td>– Troleandomycin</td>
<td>– Hydroxychloroquine</td>
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<tr>
<td>– Dapsone</td>
<td>– Gamma globulin (IV)</td>
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<td>– Cyclosporine</td>
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<td><strong>I. Phosphodiesterase-4 inhibitors</strong></td>
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<tr>
<td>– Roflumilast</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>• Drugs for smoking cession</td>
<td>– Nicotine replacement treatments</td>
</tr>
<tr>
<td></td>
<td>– Buproprion-Varenicine</td>
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<tr>
<td></td>
<td>– Nicotine vaccines</td>
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<tr>
<td><strong>Antimicrobial</strong></td>
<td>– Azithromycin</td>
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<td></td>
<td>– Azole antifungal agents, itraconazole</td>
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<tr>
<td><strong>Vaccines</strong></td>
<td>– NTHI oral immunotherapeutic (HI-164OV) against</td>
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<tr>
<td></td>
<td>– Haemophilus influenza</td>
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<tr>
<td></td>
<td>– Pneumococcal vaccine -Influenza vaccine</td>
</tr>
<tr>
<td><strong>Mucoregulators</strong></td>
<td>– Carbocisteine</td>
</tr>
<tr>
<td><strong>Management of comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reliever drugs</strong></td>
<td>– SABAs, SAMA, Non selective f1, agonist-Adrenaline &amp; other Catecholamines, I.V. corticosteroids &amp; theophylline &amp; aminophylline.</td>
</tr>
<tr>
<td><strong>Controller drugs</strong></td>
<td>– all other bronchodilators &amp; anti-inflammatory drugs.</td>
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</table>
from baseline is a common feature in ACOS patients, particularly if they had lower FEV1. Post-BD increase in FEV1 of ≥12% and ≥400 mL from baseline is also considered as a compatible factor for the diagnosis of ACOS\textsuperscript{41} (Table 4).

**Treatment**

Pharmacological and non-pharmacological treatment options available for asthma and COPD are used to treat ACO also depending upon the dominating disease in the overlap; asthma or COPD. Till date definite specific management protocol for treating ACO has not been evolved. Despite this, there is a common opinion among specialists that patients with characteristics of overlapping asthma and COPD should be considered and treated different from those with COPD.

Appropriate pharmacological and non-pharmacological treatment (Table 5) considering most effective doses, drug delivery, compliance, affordability, availability, as far as possible free from toxic side effects and patient-friendly therapy be started after due consideration for:

- There are broad spectrum drugs, for example, bronchodilators, corticosteroids, and antibiotics and narrow spectrum drugs, for example, leukotriene receptor antagonists (LTRAs) and monoclonal antibodies, such as omalizumab, to treat inflammatory obstructive airway diseases (Table 4). Depending upon the predominating overlap of asthma or COPD, they can be used in different combinations.
- ACO patients need aggressive treatment with combination of appropriate bronchodilator and optimal dose of inhaled corticosteroids (ICS).
- Monotherapy with ICS or bronchodilators should be avoided.
- ICS is essential in treatment to prevent exacerbations in future.
- Triple therapy with long-acting beta agonist (LABA) + long-acting muscarinic antagonist (LAMA) + ICS may be considered for more severe patients or patients having recurrent exacerbation.
- Additional COPD treatment as per guidelines should be given according to patient’s requirement.
- Some COPD patients continue to smoke or those who smoke and have asthma have poor response with ICS; in these patients theophylline, leukotriene modifier, roflumilast (used as per clinical status of the patient) are good add on drugs.
- Avoid maintenance oral corticosteroids.
- Non-pharmacological treatment should be considered as in asthma and COPD:
  - Avoidance/exposure of allergens, asthma triggers, tobacco smoke, biomass fuel and occupational and environmental toxins
  - Rehabilitation—physiotherapy and psychotherapy
- Bronchial thermoplasty may be considered in selected cases.

**Future Research**

There is need for better definition, recognition, safe and effective treatment through research on better understanding of pathophysiology, biomarkers, mechanism in larger population having respiratory manifestation of airflow limitation. Most clinical trials and research are focused on asthma and COPD excluding ACO and other airway diseases. There is need to diversify this trend.

**Conclusion**

Asthma and COPD both are basically inflammatory obstructive airway diseases dominantly involving upper or lower airways, of course with little difference in etiopathogenesis, type of inflammation and involvement of other parts of lungs and some systemic manifestation, may possibly part of same inflammation with different phenotype/endotype. Some patients of asthma and COPD (Chronic bronchitis + airway obstruction with or without emphysema) may have some overlapping manifestation of both the diseases; and are labeled as asthma-COPD overlap-ACO.

In coming time probably management of inflammatory obstructive airway diseases will be individualized for each patient depending upon the presence of quantum of chronic bronchitis, emphysema, asthma (atopy/allergy) and resultant inflammation leading to airway obstruction and manifestation of split over of airway inflammation.

**References**


Abstract
The etiology of advanced respiratory failure is varied and it is usually secondary to end stage respiratory diseases, which can stem from the lung parenchyma, chest wall, airways, and the pulmonary vasculature. Chronic respiratory failure (CRF) is defined as partial pressure of oxygen less than 60 mm Hg or partial pressure of carbon dioxide greater than 50 mm Hg, while breathing air at sea level. Respiratory failure in many respiratory diseases often starts during sleep. Thus, it is very important to evaluate the nocturnal saturation in patients with chronic respiratory diseases. Any features of SDB should raise an alarm in the physicians mind, and these patients should be subjected to nocturnal oximetry studies or full blown sleep studies. The management involves treating the underlying respiratory disease properly and offering rehabilitation and support in the form of oxygen, noninvasive ventilation, and pulmonary rehabilitation.

Introduction
Advanced or chronic respiratory failure (CRF) is a common and challenging problem faced by physicians. The etiology of advanced respiratory failure is varied and it is usually secondary to end stage respiratory diseases, which can stem from the lung parenchyma, chest wall, airways, and the pulmonary vasculature. Classically CRF is classified into hypoxemic and hypercapnic varieties. Often, patients have an overlap of both the varieties and it is not uncommon to see patients suffering from classical hypoxemic respiratory failure (e.g., interstitial lung disease—ILD), developing hypercapnia, during the course of their illness, owing to variable airway, and chest wall involvement, as the disease advances. Vice versa, also holds true as hypoxemia without hypercapnia, may be the dominant feature of chronic airways diseases such as chronic obstructive pulmonary disease (COPD) and bronchiectasis, where one usually expects to encounter hypercapnia.

Definition
The definition of this entity is based on arterial blood gas analysis. CRF is defined as partial pressure of oxygen (O₂) less than 60 mm Hg or partial pressure of carbon dioxide (CO₂) greater than 50 mm Hg while breathing air at sea level. It is often, not prudent, to look for water tight compartments between hypoxemia and hypercapnia, as both often coexist in a single patient, and the erstwhile differentiation into type I and type II respiratory failure becomes more and more redundant.

Etiology
Advanced respiratory failure can arise from chronic malfunction of any of the compartments of the respiratory system. Common etiologies associated with CRF include:
- Chronic airways diseases—COPD, bronchial asthma, asthma-COPD overlap, bronchiectasis, cystic fibrosis.
- Pulmonary parenchymal disorders—Interstitial and diffuse parenchymal lung disorders, sequel
of respiratory infections such as acute respiratory distress syndrome (ARDS) and coronavirus disease (COVID-19).

- Chest wall disorders—Neuromuscular disorders including myopathies and dystrophies, kyphoscoliosis.
- Pulmonary vascular disorders—Chronic thromboembolic and other forms of pulmonary hypertension (PH), pulmonary vasculitis, pulmonary AV malformations.
- Sleep disordered breathing—SDB, which includes obstructive sleep apnea and its overlap with other chronic respiratory disorders.
- Disorders of respiratory control—Chronic hyperventilation syndromes, spinal cord and brainstem injury, some toxins and poisonings.

Clinical Features, Diagnosis, and Evaluation

The diagnosis of CRF is often delayed and patients with chronic lung disorders often present for the first time to the respiratory clinic, when they can only be offered condolences and palliation. A very important reason, why this happens is that patients with chronic respiratory diseases often decrease their activity due to increasing dyspnea. As the patient becomes more and more bed bound, the underlying disease condition often increases to an extent that the room air PO2 falls below 60 mm Hg and PCO2 rises above 50 mm Hg, without the patient or the caregivers realizing it.

Respiratory failure in patients with chronic respiratory disorders first sets in during sleep. During sleep, there are multiple reasons of increase in hypoxia. The loss of sympathetic drive, pooling of secretions, nocturnal bronchoconstriction, and upper airway collapse, all add to nocturnal hypoxia. Patients with chronic hypoxia, function on the steep portion of their oxygen dissociation curve and tend to develop very severe hypoxia due to nocturnal changes, which take place during normal sleep. These changes have no effect on the saturation of normal people during sleep, but, in patients with long standing hypoxia, this sleep associated desaturation is often the first step in the development of CRF. These changes are often more pronounced in patients who have obstructive sleep apnea or other forms of sleep disordered breathing (SDB). The presence of SDB adds fuel to fire and pushes these patients toward frank respiratory failure.

Thus, it is very important to evaluate the nocturnal saturation in patients with chronic respiratory diseases. Any features of SDB should raise an alarm in the physicians mind, and these patients should be subjected to nocturnal oximetry studies or full blown sleep studies, as per situation. If respiratory failure is picked up during sleep and treated, the progression of these patients to frank respiratory failure can often be delayed.

Once a patient develops frank respiratory failure, he may develop frank cyanosis, fatigue, anxiety, confusion, and hypoxia. Rapid shallow breathing is often seen in patients with respiratory failure due to diseases such as ILD, wherein, patients are accustomed to breathing at very high respiratory rates. Tripod position, which implies, using limbs to support the chest wall is often seen in patients with advanced airways diseases. Cachexia and muscle wasting are ominous clinical signs in these patients, and signify advanced disease. Patients with hypercapnic predominant respiratory failure are often suffused and plethoric due to the vasodilatory effects of CO2. Chronically elevated CO2 levels can cause mental blunting and these patients develop subtle mental function decline, which is often overlooked.

Laboratory evaluation in these patients should be aimed at, finding the reason of CRF, if not already known. Basic evaluation should consist of a good quality HRCT Chest, 2D echo, arterial blood gas (ABG) analysis, complete pulmonary function testing including spirometry, lung volumes, and diffusion capacity. Six-minute walk test is a vital tool, which is often not done in clinical practice and provides important information regarding prognosis and response to drugs, oxygen, NIV, etc. in these patients. A very important clue in the ABG, which hints toward the development of CRF, is elevated bicarbonate levels. Bicarbonate levels more than 27 mmol/L represent a physiological response to persistently high CO2 levels. Any patient with chronic lung disease with high bicarbonate levels on ABG must be viewed with suspicion, and full CRF work-up protocol initiated.

Management

Treatment of underlying cause is not uncommon to see patients developing CRF due to suboptimal treatment of the underlying lung disease. The treatment modalities for many lungs are improving and providing hope to many such patients. A few path breaking treatment options
which are changing the face of many advanced lung diseases include:

**Airway diseases:** Airway diseases are among the most important and common causes of CRF in our country. One of the most important reasons why these patients reach the stage of CRF is avoidance of proper bronchodilator therapies. For COPD, excellent long acting bronchodilators are available. Newer anticholinergeric agents such as glycopyrronium and umeclidinium, improve lung function, decrease exacerbations, and improve mortality in patients with COPD. Lung volume reduction surgery, bronchoscopic vapor ablation, etc. are newer modalities for treatment of advanced COPD, which can add years to a patient’s life. For patients with advanced bronchial asthma, the key is to differentiate between Th1 and Th2 mediated inflammation. Th2 predominant patients respond to biological therapy, whereas, Th1 predominant patients may be offered bronchial thermoplasty, which is now readily available in India. For patients with advance bronchiectasis, the emphasis should be on airways hygiene and finding out the cause of bronchiectasis to personalize the therapy.

**ILD:** ILDs are being increasingly recognized as an important cause of CRF in our country. Owing to the more frequent usage of HRCT chest, we are picking up more ILD patients, than ever before. The first step of treating CRF in these patients is to first find out the reason of the ILD. Grossly, the ILDs may be divided into UIP (usual interstitial pneumonia) and NSIP (nonspecific interstitial pneumonia). UIP pattern on HRCT with any reason constitutes idiopathic pulmonary fibrosis. The diagnosis of IPF is associated poor outcomes. Currently approved therapies for IPF include Nintedanib and Pirfenidone, which modestly decrease lung function decline. For the NSIP, varieties of treatment would depend upon the underlying reason for ILD (sarcoidosis, hypersensitivity pneumonitis, connective tissue related), with most patients receiving a cocktail of oral steroid and immunosuppressant agents. Patients who present with frank CRF may be refractory to any kind of drug therapy and can only be offered oxygen therapy and pulmonary rehabilitation.

**Pulmonary vascular disorders:** PVDs are a group of challenging diseases to treat. Many of the advanced agents used to treat PH are still not available in the country, along with surgical options like pulmonary endarterectomy, which finds almost no takers in India. Riociguat is a newer agent, which is used to treat patients with chronic thromboembolic PH. Most patients with group 3 PH are treated only with oxygen therapy and should not be offered any of the pharmacological agents for treatment of PH, as this might increase the VQ mismatch and worsen the respiratory failure. Like ILD, many patients with CRF due to advanced pulmonary vascular disorders, may only be candidates for pulmonary rehabilitation and lung transplantation (LT).

**Oxygen therapy:** Oxygen therapy may be the only treatment option left for many patients with advanced CRF. Oxygen relieves the hypoxic vasoconstriction and improves the VQ mismatch. Survival benefit in CRF has only been demonstrated in CRF in patients with advanced COPD. The indication of oxygen therapy in other reasons of CRF has been extrapolated from its use in COPD. Use of injudicious oxygen therapy in patient with underlying hypercapnia should be avoided. Uncontrolled oxygen therapy in such patients might actually be counterproductive and worsen hypercapnia. In many patients with hypercapnic respiratory failure, oxygen may have to be given with noninvasive ventilation (NIV). The classical indications for use of domiciliary oxygen therapy in patients with advanced COPD include:

- Arterial oxygen tension (PaO₂) less than or equal to 55 mm Hg, or a pulse oxygen saturation (SpO₂) less than or equal to 88%.
- PaO₂ less than or equal to 59 mm Hg, or SpO₂ less than or equal to 89%, if there is evidence of cor pulmonale, right heart failure, or erythrocytosis (hematocrit >55%).
- For patients with normal awake oxygenation, oxygen may be prescribed during sleep if any of the following occurs during sleep: the PaO₂ is 55 mm Hg or less, the SpO₂ is 88% or less, the PaO₂ decreases more than 10 mm Hg, and/or the SpO₂ decreases more than 5% with signs or symptoms of nocturnal hypoxemia (e.g., impaired cognitive function, morning headaches, restlessness, or insomnia).

**NIV:** NIV is an important tool used to treat various forms of CRF. NIV revolves around giving an inspiratory and an expiratory pressure support to the lung. The IPAP, takes care of the hypercapnia and the EPAP, opens the upper airways and recruits and opens the smaller airways and
the alveolar air sacs. NIV usage is vital in patients with CRF, due to chest wall disorders including myopathies and kyphoscoliosis. Any form of CRF, which has a component of hypercapnia, may be benefitted to some degree, by using NIV. NIV also unloads the respiratory muscles and improves oxygenation. Specific criteria are used for initiating NIV in patients with CRF due to various disorders. However, the crux of the matter is to pick up nocturnal respiratory failure early in patients and offer them NIV early so that optimal benefits of NIV may be utilized.

**Pulmonary rehabilitation (PR):** PR is a broad therapeutic concept. It is defined by the American Thoracic Society and the European Respiratory Society as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise, training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviors."

PR can be utilized to help all kinds of patients with CRF. It is often overlooked, and we physicians tend to overlook this aspect of patient care, and focus most of our energies on pharmacotherapy only. PR programs include, exercise therapy, nutritional counseling, smoking cessation activities, psychosocial support, and an overall attempt to improve the patients quality of life. All patients with CRF should be offered the influenza and pneumococcal vaccines, as per the local guidelines and doses repeated when indicated. End of life care and advanced directives must always be taken well in time from these patients.

LT services are now available in India. LT is often offered to patients with CRF, when all other options have been exhausted. The road to LT is a long drawn one, and requires considerable financial and psychosocial support. As of now, LT in India is limited primarily to the private sector. Apart from cost and logistic issues, a major problem with LT in India is the post LT care, which requires extensive immunosuppression and multiple interval lung biopsies.

**Conclusion**

Advanced respiratory failure can be the culmination of many respiratory disorders. It used to be classically distinguished into hypercapnic and hypoxemic varieties. However, these classifications are not watertight compartments. The aim of therapy of various chronic lung diseases should be to prevent the development of frank CRF, and treating these patients with the best possible treatment modalities available. Once frank CRF develops, the physician should look beyond pharmacotherapy and offer the patient NIV, domiciliary oxygen, pulmonary rehabilitation, vaccination, and periodically assess and counsel them regarding LT.

**References**

Abstract
Pulmonary embolism (PE) is a major cause of morbidity and mortality among hospitalized patients. It should be promptly diagnosed and treated. All PE patients require anticoagulation. Recent advances in thrombolytics have improved the present treatment options for high risk PE who are hemodynamically unstable. If used judiciously, direct oral anticoagulation therapies are safe and convenient.

Introduction
Pulmonary embolism (PE) is a common and potentially fatal disease with a highly variable clinical presentation. PE is regarded as an extension of a deep vein thrombosis (DVT) and not a separate entity. De novo PE forming in the pulmonary arteries is rare. It is essential that therapy be administered in a timely fashion specifically in critically ill patients so that recurrent thromboembolism, post-thrombotic syndrome and death can be prevented.

Classification
Pulmonary embolism patients are stratified into high risk, intermediate risk, and low risk after carefully considering clinical variables, hemodynamic stability, biochemical and radiological parameters. The treatment of PE depends upon the risk of death.

High Risk
- This accounts for 5–10% of cases.
- Nearly half of pulmonary vasculature is affected by extensive thrombosis in those groups.
- Patients in this category are hemodynamically unstable.

PE patients are defined as hemodynamic unstable in following situations:
- Cardiac arrest or
- Obstructive shock
  - In spite of adequately resuscitating with fluids patient had persistent hypotension, systolic BP < 90 mm Hg or required vasopressor to achieve a systolic BP > 90 mm Hg & end organ hypoperfusion, or
  - 40 mm Hg drop in systolic BP lasting for more than 15 minutes, which is not caused by sepsis, hypovolemia or new onset arrhythmia.

Reperfusion Treatment
Thrombolytic: Thrombolytic agents activate plasminogen to form plasmin, which accelerates lysis of thromboemboli.

In acute PE thrombolytic therapy will rapidly dissolve the embolic burden and improve pulmonary artery pressure (PAP); pulmonary vascular resistance (PVR).\(^1\)\(^,\)\(^3\)

Successful thrombolysis will also reduce right ventricular (RV) dilation on echocardiography.

Sooner is better for administration of thrombolytic. Thrombolytic therapy should be offered as early as possible, preferably within first 2 days of symptoms onset for greater benefits.\(^4\)
Unlike in myocardial infarction and stroke; symptomatic PE patients can be thrombolyzed up to 2 weeks after onset of symptoms. However, thrombolytic therapy is associated with bleeding, which can be fatal and catastrophic.

The overall major bleeding rate is 10%, including a 2–3% risk of intracranial hemorrhage.

**Reperfusion Medication (Fibrinolytic & Thrombolytic) and Dose**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant tissue plasminogen activator (rtPA)</td>
<td>IV Total 100 mg infusion over period of 2 hours</td>
</tr>
<tr>
<td>Streptokinase (STK)</td>
<td>2,50,000 IU—loading dose over ½ an hour &amp; 1,00,000 IU/hour for next 24 hours</td>
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<tr>
<td>Urokinase</td>
<td>4,400 IU/kg—loading over 10 minutes and then by 4,400 IU/kg/hour for next 24 hours</td>
</tr>
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</table>

**Extracorporeal Membrane Oxygenation (ECMO)**6-11

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) may be helpful in patients with circulatory collapse or cardiac arrest and very high risk PE.

Specific attention needs to be given to bleeding complications particularly in patients receiving thrombolytics.

The outcome of ECMO depends upon number of factors including patient selection, expertise, and experience of center.

Till date no randomized clinical trial (RCT) done to prove statically significant improvement with ECMO in PE patients though case series showed survival in critically ill.

**Intermediate Risk**

Intermediate risk PE as acute PE that is associated with biochemical, echocardiographic, and/or imaging evidence of RV dilation or hypokinesis without systemic hypotension.

The intermediate risk group is the most heterogeneous and challenging.

In this group it is difficult to select patients who will benefit from thrombolytic treatment.

One needs to individualize the therapy and may require additional assessment.

While there is no agreed upon definition, some experts distinguish between intermediate-high risk and intermediate-low risk patients using the following:

- Intermediate-low risk PE—Abnormal RV function OR elevated BNP or troponin.
- Intermediate-high risk PE—Abnormal RV function AND elevated BNP or troponin.

Intermediate high risk PE may get benefitted by thrombolytics, but there is no definitive evidence to support this.

**Low Risk**

Patients with low risk PE do not require thrombolytic therapy and should be treated with anticoagulation alone. Low risk patients have excellent prognosis.

**Parenteral Anticoagulation**

Adequate and effective anticoagulation is the key for successful treatment of PE.

All patients with proven or suspected PE should receive anticoagulation as early as possible.

It can be done with subcutaneous, low-molecular weight heparin (LMWH) or IV unfractionated heparin (UFH) or Fondaparinux.

Fondaparinux is an anti Xa pentasaccharide synthesized in a laboratory.

LMWH has greater bioavailability and more predictable dose response and longer half-life.

Both LMWH and Fondaparinux require dose adjustments in renal failure and morbid obesity.

UFH anticoagulates by binding to and accelerating the activity of antithrombin, which prevents new thrombus formation.

Because lower risk of major bleeding and heparin-induced thrombocytopenia (HIT).

LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE.13-16

**Oral Anticoagulant**

**Warfarin:**

- This is Vit K antagonist.
- It requires 5 days to get full effect of warfarin.
- In acute thrombotic illness warfarin should be always overlap with UFH/LMWH/Fondaparinux for at minimum duration of 5 days.
A paradoxical exacerbation of hypercoagulability in acute thrombosis may be observed if warfarin is initiated as monotherapy.

**Novel Oral Anticoagulant (NOAC)**
- NOAC does not require laboratory monitoring.
- Rivaroxaban and Apixaban are direct factor Xa inhibitor are approved for treatment of PE without parenteral bridging anticoagulant.
- Dabigatran is direct thrombin inhibitor, will require an initial 5 days course of parenteral anticoagulation.

**Bleeding Risk**
It is necessary to evaluate the risk of bleeding before starting anticoagulation.

Major risk factors for bleeding are:
- Advanced age (>75 years)
- Previous bleeding, or anemia
- Active malignancy
- Previous stroke
- Chronic kidney disease or liver disease
- Concomitant antiplatelet therapy or non-steroidal anti-inflammatory drugs
- Poor anticoagulation control

Meta-analyses done by Kakkos SK showed that there is 40% reduction in the risk for major bleeding with NOACs compared with VKAs.17

**Duration of Anticoagulation**
All PE patients should receive at least 3 months of anticoagulation.18

After 3 months of treatment, physician should plan the therapy on case-to-case basis considering benefit—risk ratio of VTE recurrence and that of bleeding.

In view of their ambiguous nature and not very clear cut defining criteria provoked or unprovoked terminologies are not taken into consideration while planning the treatment duration.

Terminology such as “provoked” versus “unprovoked” may be misleading and create confusion, hence these are no more supported by European Society of Cardiologist.19

<table>
<thead>
<tr>
<th>Anticoagulation for Venous Thromboembolism</th>
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<tbody>
<tr>
<td>Unfractionated heparin</td>
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<tr>
<td>Enoxaparin</td>
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<tr>
<td>Dalteparin</td>
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<tr>
<td>Fondaparinux</td>
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<tr>
<td>Rivaroxaban</td>
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<td>Apixaban</td>
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<tr>
<td>Dabigatran</td>
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<tr>
<td>Warfarin</td>
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</tbody>
</table>

**Pulmonary Embolism in Cancer**19-22
In patients with cancer and PE, LMWH should be preferred over VKAs for first 6 months.

Edoxaban and Rivaroxaban are the two NOAC, which are tried in few cancer patients without gastrointestinal tumors.

Anticoagulation can be discontinued once cancer is cured but it is difficult to define the “cancer cure.”

**Pregnancy**23,24
Pregnancy is a procoagulant state with increased risk of PE.

In pregnancy LMWH is the drug of choice to treat PE. LMWH does not cross the placenta.

After delivery, anticoagulant treatment should be continued for more than 6 weeks and with a minimum duration of 3 months.

LMWH and warfarin can be safely administered to breastfeeding mothers.

In the event of life-threatening PE thrombolytic therapy can be attempted in pregnant patients.

VKAs and NOAC are not recommended in pregnancy possibly because of teratogenicity and fetal hemorrhagic risk.

In female patients of child bearing age, pregnancy, or breastfeeding should be excluded prior to commencing NOAC therapy.
Role of Inferior Vena Cava Filter\textsuperscript{26-27}

The placement of inferior vena cava filter (IVC-filter) in the treatment of venous thromboembolism is controversial.

In the patients who are actively bleeding that precludes anticoagulation and who had recurrent venous thrombosis in spite of intensive anticoagulation, IVC-filter may be tried.

Early prophylactic IVC-filter after major trauma is not found to reduce symptomatic PE or death at 90 days than no placement of filter.

No convincing clinical outcome data is available to recommend prophylactic IVC filter use.

Percutaneous Catheter Directed Treatment

Pharmacomechanical catheter directed therapy involves physical fragmentation of thrombus with catheter directed low dose thrombolytic (24 mg of tPA).

As data is lacking from RCTs on clinical efficacy outcomes, this approach should be used with caution.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)\textsuperscript{28}

Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients.

Pulmonary thromboendarterectomy, lifelong oral anticoagulation, and diuretics may give relief and reduce pulmonary hypertension.

Mobilization in DVT\textsuperscript{29,30}

Mobilization may be beneficial in reducing pain and edemas from DVTs, but large scale randomized control trials are required to validate these outcomes.

Conclusion

- Pulmonary embolism is life threatening, but potentially treatable and preventable condition.
- High risks (hemodynamically unstable) are benefitted by thrombolysis.
- All patients with PE should receive therapeutic anticoagulation for more than 3 months.
- LMWH is preferred drug for parenteral anticoagulation.
- NOAC are promising molecule to minimize bleeding risk.
- Role of IVC filter is controversial.

References


