1. Introduction

Pulmonary emphysema is a chronic disease defined pathologically as an abnormal permanent destruction and enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of alveolar walls without predominant fibrosis. Emphysema frequently occurs in overlapping association with chronic bronchitis which is clinically defined as chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded. Previously, emphysema and chronic bronchitis was regarded as distinct entities and grouped under the umbrella term Chronic obstructive pulmonary disease (COPD).

COPD is a collection of heterogeneous conditions characterized by persistent expiratory airflow limitation. There is significant overlap and co-existence of conditions like emphysema, chronic bronchitis and asthma (see Figure 1). COPD is heterogeneous clinically and at a pathophysiologic level and its recognition, has led to new initiatives to categorize and define COPD and its subsets. (American Thoracic Society [ATS], 1995, 2010; British Thoracic Society [BTS], 1997)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not emphasise on the distinction between emphysema and chronic bronchitis (GOLD, 2006). This report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) emphasised on the common feature of altered lung function recognizes both the systemic nature and the heterogeneity of COPD and defines it as follows:

“Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation...
that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." (GOLD, 2006)

Fig. 1. Schematic Venn diagram of subsets of COPD. This is a non-proportional Venn diagram adapted from Am J Respir Care Med (ATS, 1995) showing subsets of patients with chronic bronchitis, emphysema, and asthma (circles) and their relationship to airflow obstruction (box). The subsets comprising COPD are 4, 5, 6, 7, 8, and 9. Asthma is depicted by subset 3, whose airflow obstruction is completely reversible and are not considered to have COPD.

2. Historical background

COPD and its various subsets have been known in human history since pre-industrialisation era. (Snider, 1992 as cited in Shapiro SD, 2010). Badham is known to have first used of the term “chronic bronchitis” in 1808 (Badham, 1808 as cited in Shapiro SD, 2010). Fletcher and Laennec have presented early reviews and studies in 18th and 19th century (Fletcher et al., 1976; Laennec, 1835 as cited in Shapiro SD, 2010). Reid demonstrated increased mucus gland size in his pathologic studies and led to the development of the “Reid Index” and highlighted the anatomic basis for chronic bronchitis (Reid, 1960).

Ruysch described enlarged respiratory air spaces on the surface of human lungs in 1691 (Ruysch, 1691 as cited in Shapiro SD, 2010). Over the next centuries, work of Matthew Baillie, Laennec and Gough helped in describing the pathologic enlargement of airspaces and classified it between centriacinar emphysema and panacinar emphysema (Baillie, 1799, 1808; Gough, 1952; Laennec, 1835 as cited in Shapiro SD, 2010). Various “hypothesis” were proposed over the years to describe the disease pathogenesis:

i. “Dutch hypothesis” - originated by Orie (Netherlands) proposed that asthma and airway hyperreactivity leads to fixed airflow limitation. (Orie et al., 1961 as cited in Shapiro SD, 2010)

ii. “British hypothesis” - suggested the concept that mucus hypersecretion led to airway remodeling and airflow limitation. (Fletcher, 1976 as cited in Shapiro SD, 2010)
iii. “Protease-antiprotease hypothesis” (“Swedish hypothesis”) - association of homozygous alpha1 protease inhibitor deficiency with emphysema was discovered by Laurell and Eriksson in Sweden. (Laurell & Eriksson, 1963; Snider et al., 1974 as cited in Shapiro SD, 2010)

iv. “American hypothesis” - American pathologist Averill Liebow emphasised that altered repair mechanisms contribute to the development of COPD and that deficient maintenance of lung structure, could lead to emphysema. (Liebow, 1959; Rennard, 2004 as cited in Shapiro SD, 2010)

COPD has been described and subclassified on various clinical, etiopathogenetic and pathological basis. Chronic bronchitis has been associated with a “blue bloater” clinical phenotype on basis of the concept that altered airway anatomy would lead to heterogeneity of airflow distribution within the lung, resulting in ventilation-perfusion imbalance, hypoxemia, and right heart failure. On the other hand, emphysema has been described with the “pink puffer” phenotype based on the concept that it primarily causes decreased airflow from the obstruction and less prominent hypoxia.

Pathologic studies delineate inflammation of airway structures (bronchitis) from destruction of the alveolar wall (emphysema). Emphysema has been described as centriacinar, panacinar and paraseptal based on the location of emphysematous airspaces in an acinus. Centriacinar variety is common in cigarette smokers and panacinar emphysema is predominant in proteinase inhibitor deficiency.

3. Epidemiology

COPD is a major public health problem with a high and continually increasing morbidity. The Burden of Obstructive Lung Disease (BOLD) study showed that the worldwide prevalence of COPD (stage II or higher) was 10.1%. This figure varied by geographic location and by sex with prevalence among men at 11.8% (8.6-22.2%) and among women at 8.5% (5.1-16.7%) (Buist et al., 2007). The wide differences noted was partly due to site and sex differences in the prevalence of smoking. The true prevalence is likely higher because COPD is both under-recognized and under-diagnosed. COPD was the sixth leading cause of death worldwide in 1990 and is expected to become the third leading cause of death by 2020 (Murray & Lopez, 1997 as cited in Shapiro SD, 2010).

COPD has higher prevalence in low-socioeconomic population (Fletcher, 1976). Commonly, patients present in their fifth decade of life with productive cough or acute chest illness. Alpha-1 Protease Inhibitor (A1PI) deficient patients present earlier than other COPD patients in 3rd-4th decade of life. COPD progresses with age and is more prevalent in elderly populations. In the United States, 15% of the total population aged 55 to 64 will have moderate COPD (GOLD stage 2, FEVI < 80% predicted), and this increases to over 25% for those older than 75 (Stockley et al., 2009 as cited in Shapiro SD, 2010).

3.1 Risk factors

3.1.1 Cigarette smoking

Cigarette smoking is the most significant and predictable risk factor in pathogenesis of COPD. Almost 80% of individuals who have COPD and 80% who die from COPD in the
United States are smokers (Mannino et al., 2002 as cited in Shapiro SD, 2010). The estimated fraction of COPD mortality attributable to smoking was 54% for men 30–69 years of age and 52% for men 70 years of age or older (Ezzati & Lopez, 2003 as cited in ATS, 2010). There is a consistent exposure–response relationship which is demonstrated in evidence from cohort studies fulfilling the causal criterion of temporality (exposure preceding onset of disease). Although only 15% of smokers have clinically significant COPD, smoking leads to a predictable dose-dependent loss of lung function in pre-symptomatic phase which accelerates with age and has prognostic implications (Rennard & Vestbo, 2006 as cited in Shapiro SD, 2010). Smoking has supra-additive effect in worsening lung function and prognosis when combined with other risk factors like A1PI deficiency or occupational exposures (Silverman et al., 2009 as cited in Shapiro SD, 2010).

3.1.2 Genetic predilection

Genetically determined deficiency of alpha1–protease inhibitor (A1PI) represents a proven genetic abnormality that predisposes to COPD (Ericksson, 1964; Laurell & Eriksson, 1963 as cited in Shapiro SD, 2010). A1PI is inherited by codominant alleles on chromosomal segment 14q32.1. Early adult-onset emphysema associated with A1PI deficiency occurs most commonly with PiZZ (mutation in SERPINA1 gene) phenotype. It is prevalent globally but most commonly found in whites of Northern European ancestry. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 individuals with severe α1-AT deficiency. (Boas & Winnie, 2011)

Linkage analysis studies in early-onset COPD families have identified another serine proteinase inhibitor (serpin E2) on chromosome 2 as a potential defect site (DeMeo et al., 2006; Wilk et al., 2009 as cited in Shapiro SD, 2010). Twin and familial aggregation studies suggest that genetic factors likely influence variation in pulmonary function in nonsmokers, but may not necessarily increase the risk of developing a clinical diagnosis of COPD (ATS, 2010).

3.1.3 Occupational and environmental exposures

Farming and occupations with dusty environments increase the risk of developing chronic bronchitis two to threefold and, in combination with smoking, the risk increases to almost sixfold above average population (Melbostad et al., 1997; Salvi & Barnes, 2009 as cited in Shapiro SD, 2010). Environmental particulate air pollution and indoor smoke from biomass fuels have also been linked to COPD (Tashkin et al., 1984). There is strong evidence of an association between outdoor pollution (particulate matter, O₃, NO₂) and decreased pulmonary function (Gauderman et al., 2004, 2007; Rojas-martinez et al., 2007 as cited in Shapiro SD, 2010). Exposure to air pollutants, occupational exposure, second-hand smoke exposure, fumes from burning biomass fuel, etc can produce deleterious effects on the airway. Oxidative stress, pulmonary and systemic inflammation, reduction in airway ciliary activity, amplification of viral infections, and increases in bronchial reactivity could lead to irreversible loss of pulmonary function over time and COPD (ATS, 2010).

3.1.4 Gender

Epidemiological studies shows a male gender predominance related to the higher cigarette smoking habit or other inhaled toxins and occupational exposure among men within a
population (Buist et al., 2007). Increase in smoking among women has diminished the difference among gender prevalence. Mortality may be peaking among men in the United States but, among women, mortality continues to rise and deaths from COPD among women now even exceeds those among men (Mannino et al., 2002, Silverman et al., 2000 as cited in Shapiro SD, 2010).

### 3.1.5 Asthma

Accelerated loss of lung function has been noted among asthma patients (Lange et al., 1998; Peat et al., 1989 as cited in Shapiro SD, 2010). Functional changes in both the small airways and the alveolar parenchyma have been reported. Many individuals have bronchial inflammation with features of both asthma and chronic bronchitis/emphysema (Gelb & Zamel, 2000 as cited in Shapiro SD, 2010).

### 3.1.6 Socioeconomic status

Morbidity and mortality rates have been shown to be inversely related to socioeconomic status (U.S. Department of Health and Human Resources, 1984; Mannino & Buist, 2007). Relative lack of awareness, diagnostic and therapeutic facilities and poorer health conditions may in part be connected to the socioeconomic status of the affected population.

### 3.1.7 Developmental events

Impairment in early lung growth and development appears to increase the risk of development of COPD (Weiss & Ware, 1996 as cited in Shapiro SD, 2010). Maternal smoking, low-birth weight and recurrent childhood respiratory infections have been associated with higher incidence of adulthood COPD (Marossy et al., 2007; Shaheen, 1998 as cited in Shapiro SD, 2010).

### 3.1.8 Dietary factors

Observational studies strongly suggest that dietary factors, such as a higher intake of vitamin C and other antioxidants (carotenoids, Vitamin E, lutein, flavanoids) are significantly associated with better lung function (ATS, 2010). Some dietary elements like fruits and vegetables (antioxidants), fish (omega-3 polyunsaturated fatty acids) and Vitamin D seem protective while processed foods like cured meats (nitrites) may be deleterious for lung function preservation (ATS, 2010).

### 3.1.9 Tuberculosis

Pulmonary tuberculosis can lead to scarring and accelerated decline in lung function (Hnizdo et al., 2000 as cited in Shapiro SD, 2010). Some population-based surveys (PLATINO and PREPOCOL) reported strong association between previous tuberculosis and a greater risk of COPD (Caballero et al., 2008; Menezes et al., 2007 as cited in Shapiro SD, 2010).

### 3.1.10 Intravenous drug abuse

Emphysema is prevalent in approximately 2% of intravenous drugs abusers which can be attributed to pulmonary vascular damage possibly from the insoluble filler. Bullous cysts
are found in upper lobes of cocaine or heroin abusers whereas basilar and panacinar emphysema are associated with methadone and methylphenidate injections.

3.1.11 Immune deficiency syndromes

Human immunodeficiency virus (HIV) infection was found to be a risk factor for COPD, independent of confounding variables (Crothers et al., 2006 as cited in Shapiro SD, 2010). Apical and cortical bullous lung damage occurs in autoimmune deficiency syndrome and Pneumocystis carinii infection.

3.1.12 Vasculitis syndrome

Hypocomplementemic vasculitis urticaria syndrome (HVUS) and other associated conditions include angioedema, nondeforming arthritis, sinusitis, conjunctivitis, and pericarditis may be associated with obstructive lung disease.

3.1.13 Connective-tissue disorders

Several connective disorders have been implicated in causation of or co-existence with emphysema and poor lung function. Cutis laxa is a congenital disorder of elastin-tropoelastin that is characterized by premature aging and occasionally emphysema. Marfan syndrome (autosomal dominant inherited disease of type I collagen), Ehlers-Danlos syndrome, Salla disease (autosomal recessive storage disorder with intralysosomal accumulation of sialic acid), Birt-Hogg-Dube’ syndrome and familial spontaneous pneumothorax syndrome (mutations in folliculin gene) have been associated with poor lung function, blebs, pneumothorax and emphysema (ATS, 2010).

4. Pathology

4.1 Chronic bronchitis

Chronic bronchitis is a clinical entity defined by a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded. It is characterised by an overlapping pathologic process of bronchial wall inflammation. The submucosal glands show dilated ducts and hypertrophy and hyperplasia. Reid index (the ratio of glandular to bronchial wall thickness) as well as goblet cell frequency and airway smooth muscle thickness is increased in chronic bronchitis (Reid, 1960). The airway wall contains inflammatory cells predominated by macrophages and CD8+T lymphocytes. Bronchus-associated lymphoid tissue (BALT) is also present in late GOLD stages (Hogg & Timens, 2009 as cited in Shapiro SD, 2010). Increased numbers of neutrophils are found in the airway lumen and in the glands during episodes of exacerbations (Saetta et al., 1997; Thompson et al., 1989 as cited in Shapiro SD, 2010).

4.2 Emphysema

Pulmonary emphysema, a pathological entity defined as destruction and enlargement of air spaces distal to the terminal bronchiole involving respiratory bronchioles, alveolar ducts, and alveoli. Cigarette smoking, inhaled irritants, recurrent infections and proteinase-
antiproteinase imbalance lead to inflammatory cell recruitment, proteolytic injury to the extracellular matrix (ECM), and cell death. Alveolar walls become perforated and later due to incomplete and disorderly repair, become obliterated with coalescence of small distinct air spaces into abnormal and much larger air spaces, which is the pathological hallmark of emphysema (Shapiro & Ingenito, 2005 as cited in Shapiro SD, 2010). Emphysema has been classically described with absence of interstitial fibrosis to differentiate from restrictive lung diseases. However, scarring of the small airway subepithelial space and collagen accumulation around larger disrupted air spaces has been noted in emphysema.

Various subtypes of emphysema have been described based on location and distribution of the lesions in the acinus (Pipavath et al., 2009 as cited in Shapiro SD, 2010). In most patients, however, the process within the lung will be heterogeneous and in advanced stages, distinction becomes blurred. The following three patterns of emphysema are noted:

4.2.1 Centriacinar (centrilobular, proximal acinar) emphysema

Strongly associated with smoking, it begins in the respiratory bronchioles and spreads peripherally, primarily involving the upper and posterior parts of lungs (Leopold & Gough, 1957; Thurlbeck, 1991 as cited in Shapiro SD, 2010). Focal emphysema, a form of centriacinar emphysema, occurs in persons with heavy exposure to inert dust such as coal dust (Morgan & Seaton, 1984 as cited in Shapiro SD, 2010).

4.2.2 Panacinar emphysema

Involves the entire alveolus uniformly and is predominant in the lower half of the lungs (Snider et al., 1962; Thurlbeck, 1963, 1976 as cited in Shapiro SD, 2010). It is observed in patients with homozygous A1PI deficiency.

4.2.3 Paraseptal (distal acinar) emphysema

It usually involves the distal airway structures, alveolar ducts, and alveolar sacs around the septae of the lungs or pleura (Hogg & Timens, 2009; Kim et al., 1991 as cited in Shapiro SD, 2010). Apical and giant bullae described in this subtype may lead to spontaneous pneumothorax or compression of adjacent lung tissue.

4.3 Other pathologic variants mimicking emphysema

4.3.1 Air space enlargement with pulmonary fibrosis

It is commonly seen as an inconsequential lesion adjacent to scars but may be extensive arising as a complication of fibrosing diseases such as tuberculosis, silicosis, and sarcoidosis (Reid & Simon, 1962; Thurlbeck, 1991 as cited in Shapiro SD, 2010). The spaces have dense fibrous walls and are mostly lined by bronchiolar epithelium (Akashi et al., 2009 as cited in Shapiro SD, 2010).

4.3.2 Bullae

Bullae are marked focal dilation of respiratory air spaces that may result from coalescence of adjacent areas of severe panacinar emphysema, or from a ball-valve effect in the bronchi.
supplying an emphysematous area (Reid, 1967; Thurlbeck, 1976, 1991 as cited in Shapiro SD, 2010).

4.3.3 Blebs

These are intrapleural collections of air, a form of interstitial emphysema. They may arise from interstitial emphysema of the newborn period or pulmonary barotrauma complicating mechanical ventilation. Ruptured blebs can cause spontaneous pneumothorax.

4.3.4 Cysts

Cysts are air spaces lined by epithelium, which usually have the characteristics of bronchial epithelium. They are classically known as intrapulmonary bronchogenic cysts and usually occur near the tracheal bifurcation, but they may be seen more peripherally in the lung parenchyma (Reed & Sobonya, 1974; Rogers & Osmer, 1964 as cited in Shapiro SD, 2010).

4.3.5 Overinflation

Air space distention with or without alveolar rupture and is often reversible. “Simple air space enlargement” in which there is no destruction or loss of orderly appearance of the lung acinus, occurs in the contralateral lung following pneumonectomy (Compensatory overinflation or emphysema). Air spaces, particularly alveolar ducts, enlarge with advancing age, resulting in what has been termed “senile emphysema”. Obstructive overinflation results from partial obstruction of a bronchus or bronchiole, when it becomes more difficult for air to leave the alveoli than to enter; there is a gradual accumulation of air distal to the obstruction, the so-called bypass, ball valve, or check valve type of obstruction. These conditions are listed in Table 1.

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<tr>
<th>Compensatory Hyperinflation:</th>
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<tr>
<td>Atelectasis</td>
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<td>Post-lobectomy</td>
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<th>Intrinsic Obstruction of Major Bronchus:</th>
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<td>Tumor—benign or malignant</td>
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<td>Postinflammatory stricture</td>
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<td>Foreign body</td>
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<td>Amyloid</td>
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<th>Extrinsic Obstruction:</th>
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<td>Congenital</td>
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<td>Aberrant vessel</td>
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<td>Extrapulmonary sequestration</td>
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<td>Tumor</td>
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<td>Nodes</td>
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<th>Congenital Malformation of Bronchus: (Defective Cartilage or Mucosal Fold)</th>
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<td>“Congenital Lobar Emphysema”</td>
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<th>Intrinsic Obstruction of Bronchioles:</th>
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<tr>
<td>Unilateral acquired Bronchitis</td>
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<td>Bronchiolitis Obliterans</td>
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Table 1. Conditions with overinflation mimicking Emphysema

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4.4 Pediatric conditions with emphysema

Some pediatric conditions display emphysematous pathologic findings resulting from a variety of developmental abnormalities in alveogenesis leading to impaired septation and alveolarization with consequent enlarged air spaces. Some are briefly described as below:

4.4.1 Congenital lobar emphysema

It is characterized by hyperinflation of one or more of the pulmonary lobes resulting from congenital deficiency of the bronchial cartilage, external compression by aberrant vessels, bronchial stenosis, redundant bronchial mucosal flaps or kinking of the bronchus caused by herniation into the mediastinum. The disease usually becomes apparent in the neonatal period but are delayed for as long as 5-6 mo in 5% of patients. The disease primarily involves lower lobes and occurs in familial preponderance. Treatment by immediate surgery and excision of the lobe may lifesaving, but some patients respond to medical treatment or selective intubation of the unaffected lung.

4.4.2 Overinflation of all three lobes of the right lung

Rarely produced by anomalous location of the left pulmonary artery impinging on the right main stem bronchus or occasionnally with absent pulmonary valve type of tetralogy of Fallot and secondary aneurysmal dilatation of the pulmonary artery. Some neonates have lobar overinflation while on assisted ventilation, suggesting an acquired cause.

4.4.3 Broncho-pulmonary dysplasia

A form of chronic lung disease that develops in preterm neonates treated with oxygen and positive-pressure ventilation. Injury to small airways and pulmonary vasculature can interfere with alveolarization (alveolar septation), leading to alveolar simplification and reduction in the overall surface area for gas exchange. Premature birth and subsequent events (eg, exposure to oxygen, mechanical ventilation, inflammatory agents, infection) shifts the lung development towards premature maturation with an arrest in development and a loss of future gas exchange area.

4.4.4 Pulmonary interstitial emphysema

Collection of gases outside of the normal air passages and inside the connective tissue of the peribronchovascular sheaths, interlobular septa, and visceral pleura may result from alveolar or bronchiolar rupture commonly in premature infants on mechanical ventilation. It is a radiographic and pathologic diagnosis frequently in conjunction with respiratory distress syndrome, meconium aspiration syndrome, amniotic fluid aspiration and infection.

4.4.5 Acute generalized overinflation of the lung

Usually reported in infants and children secondary to a number of clinical conditions affecting bronchioles, including asthma, cystic fibrosis, acute bronchiolitis, interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis.
4.4.6 Bullous emphysematous blebs or cysts (pneumatoceles)

They result from overdistention and rupture of alveoli during birth, or as sequelae of pneumonia and other infections. They have been observed in tuberculosis lesions during specific antibacterial therapy.

4.4.7 Subcutaneous emphysema

It results from any process that allows free air to enter into the subcutaneous tissue. It can also result from pneumomediastinum or pneumothorax, fracture of the orbit, following tracheotomy, perforation in the esophagus or laryngopharyngeal area. Rarely, air is formed in the subcutaneous tissues by gas-producing bacteria.

5. Etiopathogenesis

The etiopathogenesis of COPD involves interplay of several overlapping and co-existing injuries, defects, inflammation and disorganized repair in a vicious cycle, ultimately leading to a chronic progressive impairment of lung function. These processes are shared by other airway and parenchymal diseases of lungs and aggravated by other pulmonary and systemic co-morbidities. The key steps involved are epithelial injury, inflammatory cell activation, protease-antiprotease imbalance, airway inflammation, goblet cell hypertrophy and hypersecretion, recurrent infection, acute exacerbations, attempts to disorganized repair and fibrosis, ultimately leading to chronic progressive permanent airway obstruction (Barnes, 2008; Kasahara & Tuder, 2000; MacNee & Tuder, 2009; Rennard, 2003 as cited in Shapiro SD, 2010).

5.1 Cigarette smoke induced inflammation

Cigarette smoke initiates inflammation both by direct oxidative-irritative cellular injury and indirectly by recruiting several inflammatory cells in the air space (ATS, 1962, Barnes et al., 2008; Shapiro & Ingenito, 2005 as cited in Shapiro SD, 2010). Neutrophils rapidly accumulate in the lung in response to exposure to cigarette smoke (Rennard, 2003 as cited in Shapiro SD, 2010). Recruitment occurs via stimulated epithelial cells and macrophages releasing TNF-α and neutrophil chemokines CXCL1 and CXCL8 (IL-8) operating through the neutrophil receptor CXCR2 (Barnes, 2008 as cited in Shapiro SD, 2010). Neutrophils contain proteinases like neutrophil esterase (NE) and Matix metalloproteinases (MMPs), particularly MMP-9, which are preformed and stored in granules and readily released upon activation. In addition to causing matrix destruction, proteinases generate fragments of ECM proteins such as collagen and laminin, which are also chemotactic for neutrophils, leading to a vicious feedback cycle of inflammation and tissue destruction (Adair-Kirk et al., 2003; Gaggar et al., 2008; Mydel et al., 2008 as cited in Shapiro SD, 2010).

COPD is characterized by a gradual, progressive accumulation of macrophages in the lung most apparent in respiratory bronchioles which is the primary site of centriacinar emphysema (Niewoeherner et al., 1974 as cited in Shapiro SD, 2010). Stimulated macrophages produce both neutrophil and macrophage chemokine and cytokines like macrophage chemotactic protein-1 (MCP-1; CCL2), which recruits more monocytes from the peripheral blood (Barnes, 2008 as cited in Shapiro SD, 2010). Macrophages produce a variety of MMPs,
particularly elastases such as MMP-9 and MMP-12, resulting in lung tissue injury. Degraded elastin fragments are chemotactic for macrophages, thus ensuing a self-propagating cycle (Houghton et al., 2006; Senior et al., 1980 as cited in Shapiro SD, 2010).

T cells lymphocytes, especially CD8+ cells are increased in airway walls and alveoli of patients with COPD (Saetta et al., 1998 as cited in Shapiro SD, 2010). Airway epithelial cells in smokers with COPD have increased expression of CXCL10 (IP-10), the ligand for CXCR3 found on CD8+ T cells and thus may be the activation pathway for macrophages to produce MMP-12 (Grumelli et al., 2004; Saetta et al., 2002 as cited in Shapiro SD, 2010). Cytotoxic T cells may target epithelial cells and induce cell death, particularly those with (latent) viral infection.

Elastin fragments can serve as autoantigens and immunoglobulin G (IgG) autoantibodies with avidity for pulmonary epithelium have been found in patients with COPD (Feghali-Bostwick et al., 2008; Lee et al., 2007 as cited in Shapiro SD, 2010). Increased numbers of B cells and lymphoid follicles in the lung have raised interest in a possible autoimmune pathogenesis of COPD (Curtis et al., 2007; Taraseviciene-Stewart & Voelkel, 2008 as cited in Shapiro SD, 2010). Interplay of all these inflammatory pathways results in the tissue damage that keeps adding up over the years.

5.2 Proteinase-antiproteinase imbalance

Elastin and collagen is critical to the structural integrity of the lung. Experimental studies in animal lung models with instilled proteinases have replicated emphysematous changes (Gross et al., 1964 as cited in Shapiro SD, 2010) resulting in an initial rapid increase in air space size due to direct elastolysis with diminution of lung elastin content at 24 hours followed by rapid restoration of total lung elastin to normal levels (Janoff et al., 1977; Snider et al., 1984 as cited in Shapiro SD, 2010). The anatomic arrangement of the restored elastic fibers is grossly disordered (Kuhn & Senior, 1978 as cited in Shapiro SD, 2010). The tissue displays inflammation with neutrophils and macrophages with subsequent release of endogenous inflammatory mediators including IL-1β and TNF-α with endogenous proteolytic progression of the disease. Based on these studies and the association between A1PI deficiency with emphysema (Laurell & Eriksson, 1963 as cited in Shapiro SD, 2010), the proteinase-antiproteinase hypothesis proposed that the balance between matrix-degrading proteinases and their endogenous inhibitors determines whether the lung is protected or susceptible to proteolytic injury.

Some proteinases such as NE and MMP-9 are bound to the surface of the neutrophil, they are resistant to complete inhibition by A1PI and tissue inhibitors of metalloproteinases (TIMPs). “Microenvironmental” concentration of proteinases and their proximity to the target site of matrix proteins when released from the neutrophil and macrophages, may explain how the balance tilts towards the proteinase function even in presence of adequate overall anti-proteinase in circulation (Owen & Campbell, 1999 as cited in Shapiro SD, 2010). There are four classes of proteinases, serine, cysteine, aspartic, and MMPs:

5.2.1 Serine proteinases

The serine proteinase Neutrophil elastase (NE) is suspected to be the major causative agent of tissue injury in COPD after the findings that patients deficient in its endogenous
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inhibitor, A1PI, are at increased risk for emphysema and that instillation of NE caused emphysema in experimental models. NE also plays a role in airway disease as a potent secretagogue, facilitator of monocyte transvascular migration. NE is produced mainly by neutrophils, but also to a small degree by monocytes (Shapiro et al., 2003 as cited in Shapiro SD, 2010). Cathepsin G (CG) and proteinase 3 (PR3) are other neutrophil-monocyte derived serine proteinases. Other than NE, minor inhibitors are Alpha2 microglobulin, secretory leukoprotease inhibitor (SLPI) and elafin.

5.2.2 Matrix metalloproteinases (MMPs)

MMPs are a family of 24 enzymes that require coordination of zinc at the active site, have overlapping substrate specificity, and are inhibited by TIMPs (Parks & Shapiro, 2001 as cited in Shapiro SD, 2010). Several MMPs degrade elastin and contribute to emphysema including MMP-2, MMP-9 (gelatinase A and B), MMP-7 (matrilysin), and MMP-12 (macrophage elastase). MMP-1, -8, -13 are also collagenases, and thus degrade another critical matrix component.

Several MMPs have been associated with human COPD including MMP-1, MMP-9, MT1-MMP, and MMP-12 (Imai et al., 2001; Molet et al., 2005; Russell et al., 2002 as cited in Shapiro SD, 2010). Macrophages have the capacity to produce MMP-1, MMP-3, MMP-7, MMP-9, MMP-12, and MMP-19. MMP-12 is one of the most highly up-regulated genes in macrophages of human smokers (Atkinson & Senior, 2003 as cited in Shapiro SD, 2010). Role of MMPs in COPD pathogenesis is further supported by the epidemiologic prevalence of polymorphisms of MMP in caucasian COPD patients (Hunninghake et al., 2009 as cited in Shapiro SD, 2010).

5.2.3 Cysteine proteinases

Cathepsin L, S, and K are macrophage generated elastolytic enzymes. Cathepsin S also processes antigens in T cells (Riese et al., 1998 as cited in Shapiro SD, 2010). Cathepsin K is the most potent elastase and collagenase. Cathepsin B is an epithelial cell product that has proapoptotic properties (Foghsgaard et al., 2001 as cited in Shapiro SD, 2010). Cathepsins are inhibited by cystatins like Cystatin C which is the most ubiquitous cystatin found in all human tissues and body fluids. Cathepsins are being studied for their potential to contribute to COPD.

5.3 Cell death

Cell viability requires cell-matrix attachment via integrins, loss of matrix disrupts the contact and predisposes to cell death (termed “anoikis”). Experimental models show that noninflammatory cell death can initiate air space enlargement as demonstrated in studies involving rodent models with inhibition of vascular endothelial growth factor receptor or instillation of active caspase 3 in lung epithelial cell tissues (Aoshiba et al., 2003; Kasahara & Tuder; 2000; Tang et al., 2004 as cited in Shapiro SD, 2010). Thus cell death by injury or apoptosis can be an initiating trigger for emphysema.

5.4 Disorganised and incomplete repair

Injury is followed by aberrant repair of alveolar cells and matrix resulting in coalesced and enlarged air spaces with depleted and disordered parenchymal elastic fibers and excessive,
abnormally arranged collagen. Although following pneumonectomy, there is compensatory lung growth of the remaining lung in humans, whether the injured lung can ever reinitiate the process of septation and the intricate juxtaposition of matrix, epithelial, and endothelial cells to form functional alveoli during lung development is highly doubtful (Buhain & Brody, 1973; Nolen-Walston et al., 2008; Shifren & Mecham, 2006 as cited in Shapiro SD, 2010).

Elastin is the principal component of elastic fibers, which allows reversible extensibility and elastic recoil to the intercellular matrix of alveoli throughout the respiratory cycle. Elastin synthesis in the lung begins in the late neonatal period, peaks during early postnatal development, continues to slow through adolescence, and stops by adult life probably because of rapid mRNA degradation preventing expression of the protein (Shapiro et al., 1991; Swee et al., 1995 as cited in Shapiro SD, 2010).

Animal model studies involving intratracheal injection of elastase show an acute depletion of elastin followed by rapid ECM synthesis, although the lungs develop emphysema (Karlinsky et al., 1983; Kuhn & Senior, 1978). The newly synthesized elastic fibers appear disorganized, similar to the elastic fibers in human emphysema and thus emphasizing the role of impaired repair in its pathogenesis. Collagen is the other important ECM fiber to play a role in COPD. Total collagen content in the lung is actually increased in humans with COPD (Wright & Churg, 1995 as cited in Shapiro SD, 2010). Following tissue injury, excessive collagen deposition around the larger coalesced airspaces is noted. Small airway fibrosis is also prominent in COPD. These findings suggest that emphysema is not purely a destructive process but one of aberrant matrix turnover.

5.5 Alpha-1 protease inhibitor (A1PI) deficiency

A1PI, also known as alpha₁-antitrypsin, is a serine proteinase inhibitor (serpin) that is produced mainly in the liver and found in the bloodstream and permeates tissues including the lung. A1PI inhibits various serpins including pancreatic trypsin, chymotrypsin but the main target is the neutrophil elastase (Brantly et al., 1988; Travis, 1989 as cited in Shapiro SD, 2010). A1PI is also an acute phase reactant, with its serum concentration rising during pregnancy, during infections, after severe burns, and in the presence of malignant tumors. Smoking elevates the serum A1PI concentration by about 20%.

A1PI is coded by a single gene with two alleles on chromosome 14q32.1 producing a glycoprotein composed of 394 amino acids. The A1PI gene is highly pleomorphic and more than 75 alleles are known, and they have been classified into normal (normal serum levels and normally functioning A1PI), null (undetectable A1PI in the serum), deficient (serum A1PI levels lower than normal), and dysfunctional (A1PI levels are normal but does not function normally) (Brantly et al., 1988 as cited in Shapiro SD, 2010).

Most variants of A1PI arise point mutations with a single amino acid substitution. The Z variant (most common and severe disease) results from the substitution of a lysine for a glutamic acid at position 342, which changes the charge and the electrophoretic mobility of the molecule (Yoshida et al., 1976 as cited in Shapiro SD, 2010). The mutant protein polymerizes and the aggregated form causes hepatic cell injury. The Z protein is also incompletely glycosylated, which may interfere with the protein’s excretion from the liver into body fluids. (Ekeowa et al., 2009; Gooptu & Lomas, 2008 as cited in Shapiro SD, 2010). The protein loses its physiologic function of inhibiting the NE.
The normal (M) alleles are found in about 90% of persons of European descent with normal serum A1PI levels (150 to 350 mg/dL or 20 to 48 µmol/dL); their phenotype is designated Pi MM. More than 95% of persons in the severely deficient category are homozygous for the Z allele (Pi ZZ) and have serum A1PI levels of 2.5 to 7 µmol/dL (mean, 16% normal) with an estimated prevalence between 1 in 1600 to 1 in 4000. This allele is mostly found in whites of northern European descent.

Rarely observed phenotypes associated with low levels of serum A1PI include the following: Pi SZ and persons with nonexpressing alleles; Pi null, found in homozygous form as Pi null-null and found in heterozygous form with a deficient allele as Pi Z null. Persons with phenotype Pi SS have A1PI values ranging from 15 to 33 µmol/dL (mean, 52% of normal). The threshold protective level of 11 µmol/dL (35% of normal) is based on the knowledge that Pi SZ heterozygotes, with serum A1PI values of 8 to 19 µmol/dL (mean, 37% of normal), rarely develop emphysema. Pi MZ heterozygotes have serum A1PI levels that are intermediate between Pi MM normals and Pi ZZ homozygotes (12–35 µmol/dL; mean, 57% of normal). There appears to be a small increase in risk of COPD in all Pi MZ individuals.

COPD in homozygous A1PI deficiency patients is characterized by premature development of severe panacinar emphysema usually in the basilar regions of lung (Silverman & Sandhaus, 2009). The onset of dyspnea occurs at a median age of 40 years about 1-2 decades earlier than rest of the population (Silverman & Sandhaus, 2009 as cited in Shapiro SD, 2010). However, smoking has supradditive effect on poorer prognosis both with earlier onset severity and poorer prognosis of the disease (Janus et al, 1985 as cited in Shapiro SD, 2010). Radiographically, disease is more prominent in PiZZ patients and worse in basilar regions, sometimes hairline arcuate shadows separating markedly radiolucent areas in the lung bases from the less severely involved upper portions of the lungs (Gishen et al, 1982; Hepper et al, 1978 as cited in Shapiro SD, 2010).

A1PI deficiency is diagnosed by measuring the serum A1PI level, followed by Pi typing for confirmation. However, by the time they develop COPD symptoms, they already have significant liver disease often diagnosed in infancy/childhood with hepatomegaly or hepatosplenomegaly and evidence of cholestasis and elevation of hepatocellular enzymes. Screening for PiZZ in COPD patients is not recommended at present. Augmentation therapy with A1PI supplementation has been proposed for COPD patients with PiZZ genotype as per guidelines issued by ATS (ATS, 1995).

6. Natural history of disease

The natural history of COPD as we know, is based on multiple longitudinal studies, although most spanned much shorter duration than the actual length of disease progression (Rennard & Vestbo, 2008 as cited in Shapiro SD, 2010). The classic study of Fletcher and colleagues and extrapolation of the data of other studies have yielded the “Fletcher-Peto curve,” which is basically a plot of FEV1 versus age (Fletcher, 1976). The curve describes the gradually progressive permanent loss of lung function as age advances. Although it doesn’t include the concept of COPD in non-smokers and extrapulmonary effects of COPD, it serves a basic guide to understand the clinical course of the disease.
The natural history of COPD probably starts at pre-conception age related to genetics and intra-uterine lung development and growth, extending into early life events such as childhood and adolescent lung growth and injury from infections as well as later events such as adult lung exposures to cigarette smoke and occupational inhalants.

Since the disease progresses slowly over the years, the earlier stages of the disease are often “silent” and mostly unnoticed by the patient. Exertional dyspnea, the earliest symptom, primarily from dynamic hyperinflation from exercise induced tachypnea, results in subconscious preferential sedentary lifestyle and thus avoiding the symptoms till later stage.(O’Donnell et al., 2001 as cited in Shapiro SD, 2010).

The intrauterine growth of lung includes development of conducting airways, gas exchange structures, including respiratory bronchioles and alveoli, but branching of alveolar wall continues postnatally for several years and usually complete by the first decade of life (Ten Have-Opbroek, 1981 as cited in Shapiro SD, 2010). Subsequent growth of the lung is due to increase in alveolar size and increase in airway diameter, but not in number. Maximal lung function is attained in young adulthood and remains relatively constant as a plateau for some years before declining in a slowly accelerating manner in older age (Weiss & Ware, 1996 as cited in Shapiro SD, 2010). The decline averages 20 mL/yr increasing in an accelerating manner and by age 50, there is an average drop of FEV1 by 1L.

Smoking adversely affects the entire course, with interference in maximal lung capacity attainment if smoking starts in the early growth phase, to shortening of duration of the plateau phase, to rapid decline in lung function in later age (Burrows, 1990 as cited in Shapiro SD, 2010). This effect is very well depicted in the “Fletcher-Peto curve” shifting the plot downwards and earlier in age (Fletcher, 1976). The average COPD patient who smokes loses almost twice the lung function than usual (about 2 L of FEV1 over 50 years, an average decline of about 40 mL/yr). Acute exacerbations have descending step-ladder like effect with acute drops over short period with incomplete recovery resulting in faster drop of lung function (Burrows, 1990 as cited in Shapiro SD, 2010). Smoking has a predictable dose-dependent deleterious effect on the lung function and cessation of smoking has beneficial slowing of disease progression if initiated early enough in course of disease (Anthonisen et al, 1994; Buist et al., 1976 as cited in Shapiro SD, 2010).

Some individuals experience a rapid decline in lung function (Gottlieb et al., 1996 as cited in Shapiro SD, 2010). Faster decline in lung function is noted in patients with low baseline lung function, less reversibility to β2-agonists, more severe bronchial hyperresponsiveness, mucus production, male sex, and frequent exacerbations (ATS, 2010). Identification of slow and rapid decliners in longitudinal studies such as the Lung Health Study has allowed exploration of biomarkers to characterize these groups. Importantly, systemic markers of inflammation have been associated with poorer lung function, and, in some, studies, with an increased rate of decline in lung function (Fogarty et al., 2007; Shaaban et al., 2006; Sin & Man, 2003 as cited in Shapiro SD, 2010).

Although early stage COPD is difficult to diagnose, newer studies have shown a poorer prognosis among these population primarily from adverse cardiac events (Ashley et al., 1975; Mannino et al., 2003 as cited in Shapiro SD, 2010). The cardiac events may be linked to the extrapulmonary effects of COPD, especially elevated systemic inflammatory mediators. Identifying and treating this group thus can have valuable prognostic benefit.
With advanced disease, obvious exertional dyspnea, cough and frequent acute exacerbations dominate the picture. Morbidity and mortality increases with declining FEV1. Primary cause of mortality is cardiac events, however with advanced age and disease, pulmonary complications causing death, increase in proportion. Each exacerbation and the following recovery stage makes the patient most vulnerable to adverse outcomes as shown by the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments), which demonstrated a 49% 2-year mortality rate after hospital admissions with COPD exacerbation with CO₂ retention (Connors et al., 1996).

Various therapeutic and supportive medical and surgical intervention combined with rehabilitative measures help in alleviation of symptoms, slowing of pace of progression of disease and reduction of disability. Individualized plans for each patient based on the characteristic and stage of disease is important to achieve optimal results.

7. Clinical presentation

7.1 History

COPD is a gradually progressive chronic disease presenting with clinically obvious symptoms late in the course, usually in their fifth decade of life with productive cough or breathlessness or acute chest illness. A1PI-deficient patients present earlier than other COPD patients usually in 3rd-4th decades and by then they have significant liver disease, which usually starts in childhood.

Early COPD results in gradual progressive worsening of pulmonary function, which results in patients unknowingly avoiding exertional dyspnea (the most common early symptom of COPD) and fatigue by shifting their expectations and limiting their activity. Patients who have an extremely sedentary lifestyle but few complaints require further evaluation for possibility of underlying COPD as many patients reset their expectations with regard to health, termed “response shift” (Rennard et al., 2002 as cited in Shapiro SD, 2010). Generalised muscle weakness found in COPD patients can also contribute to this finding.

Most patients usually present in the fifth or sixth decade of life by when they have dyspnea with mild exertion and usually the forced expiratory volume in 1 second (FEV1) has fallen to 50% of predicted. Moderate to severe COPD patients report variability in symptoms over the course of the day or week-to-week; morning is typically the worst time of day. Dyspnea is related to both respiratory (hyperinflation and impaired gas exchange) and extra-respiratory (like muscle dysfunction, heart disease, anaemia and depression) features of COPD.

The chronic cough is characterized by the insidious onset of sputum production, which occurs in the morning initially, but may progress to occur throughout the day. The sputum is usually mucoid, but becomes purulent during exacerbations. Hemoptysis complicating chronic bronchitis usually occurs in association with acute exacerbation. Lung cancer and tuberculosis needs to be ruled out in this scenario (Thompson et al., 1992 as cited in Shapiro SD, 2010). Wheezing may also be found in some patients due to co-existence of asthma or COPD alone.

Acute exacerbations are characterized by increased cough, sputum, dyspnea, and fatigue, are increasingly frequent as the disease worsens. Each exacerbation may last for a few weeks
and followed by prolonged recovery over months and may be difficult to distinguish from other causes of dypsnea, cough, and/or sputum including pneumonia, congestive heart failure, pulmonary embolism, or pneumothorax (Spencer & Jones, 2003 as cited in Shapiro SD, 2010).

A history of cigarette smoking or alternative inhalational exposure is usually found in majority of COPD patients. A1PI deficient patients may develop disease without smoking, however presence of smoking significantly worsens the course of disease. Some patients develop COPD without an obvious risk factor. Other historical features that may accompany COPD include certain comorbidities (eg, lung cancer, coronary artery disease, osteoporosis, depression, skeletal muscle weakness). Although most patients are usually obese, weight loss can also occur in COPD and is associated with a worse prognosis.

### 7.2 Physical findings

Physical findings in early COPD is highly non-specific and unreliable. Early stage patients may have coarse crackles and rhonchi. Wheezing may be found occasionally especially associated with asthma or acute exacerbations.

The hallmark finding is obstruction of expiratory airflow. Measurement of the forced expiratory time maneuver is a simple bedside test and most consistent finding in symptomatic COPD. A forced expiratory time greater than 4 seconds indicates severe expiratory airflow obstruction. Objective measurement of airflow by spirometry, which is simple and accurate forms the basis of staging and follow-up of disease progression (Petty, 2001).

As the airway obstruction worsens, physical examination may reveal hyperinflation, decreased breath sounds, wheezes, crackles at the lung bases, and/or distant heart sounds. In addition, the diaphragm may be depressed and limited in its motion, and the anteroposterior diameter of the chest may be increased.

Patients with end-stage COPD may present with barrel-shaped chest, increased span of hyperresonant lung percussion, distended neck veins, full use of the accessory respiratory muscles of the neck and shoulder girdle, purse-lipped breathing, paradoxical retraction of the lower interspaces during inspiration (ie, Hoover's sign), emaciation, and frequently, inguinal hernias. They may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms (Tripod sign). This position stabilizes the shoulder girdle and helps to maximize intrathoracic volume. Late signs may include cyanosis, clubbing, asterixis due to severe hypercapnia, and an enlarged, tender liver due to right heart failure.

### 8. Complications of COPD

#### 8.1 Pneumothorax

Pneumothorax can precipitate severe dyspnea and acute respiratory failure and may be life threatening since they have only a marginal pulmonary reserve. Presence of giant bullae as part of disease predisposes to this complication. It can be difficult to treat if accompanied by a persistent air leak between the involved lung and the pleural space (bronchopleural fistula).
8.2 Pulmonary hypertension and Cor pulmonale

Both resting and exercise mean pulmonary arterial pressures may be elevated. Prolonged pulmonary hypertension can give rise to chronic cor pulmonale in late stages. Alveolar hypoxia, respiratory acidosis, remodeling of the pulmonary vasculature with medial hypertrophy of muscular pulmonary arteries, increased viscosity of blood due to erythrocytosis, increased blood volume, left ventricular dysfunction and chronic pulmonary thromboembolic disease can all contribute to the pulmonary hypertension (Farber et al., 1982; Fletcher et al., 1989 as cited in Shapiro SD, 2010). Correction of hypoxia and acidosis by long-term oxygen therapy and pulmonary vasodilators may slow this process.

8.3 Pneumonia

COPD predisposes the lungs to pneumonia as part of acute exacerbation or as discrete event. (Ewing & Torres, 1999; Griffith & Mazurek, 1991 as cited in Shapiro SD, 2010)

8.4 Systemic complications and co-morbidities

Ischemic cardiac disease is more common in COPD and cardiac events are the single largest cause of mortality in this population (Ashley et al., 1975; Mannino et al., 2003 as cited in Shapiro SD, 2010). Arrhythmia, congestive heart failure and aortic aneurysm are more common. COPD may lead to a hypercoagulable state due to erythrocytosis and systemic inflammation (mediated via TNF-α, IL-6) posing greater risk of stroke, pulmonary embolism and deep vein thrombosis (Bhowmik et al., 2000; Wouters et al., 2002 as cited in Shapiro SD, 2010). Weight loss, osteoporosis, skin wrinkling, anemia, fluid retention and depression are some of the other systemic co-morbidities commonly associated with COPD. Major chronic diseases (e.g. congestive heart failure, dementia, ischaemic heart disease, stroke, diabetes, cancer, asthma, COPD, depression and hypertension) were associated with at least one of the other diseases in 60–90% of cases (Charlson et al., 2007 as cited in Shapiro SD, 2010). A major question is whether coexisting chronic illnesses found in COPD subjects are merely related to common risk factors (e.g. aging, tobacco smoking and genetic predisposition) or are also consequences, at least in part, of the pulmonary and/or systemic inflammation that characterise COPD.

9. Diagnosis and laboratory work-up

9.1 Spirometry

Objective measurement of airflow obstruction is the mainstay of workup for diagnosis, staging and follow-up of COPD (Petty, 2001). The most important values measured are the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC) or the forced expiratory volume after 6 seconds, (FEV6), which is the recommended substitute for FVC (Enright et al., 2002 as cited in Shapiro SD, 2010). COPD is confirmed when a patient, who has symptoms that are compatible with COPD, is found to have airflow obstruction (FEV1/FVC ratio less than 0.70 and an FEV1 less than 80 percent of predicted) and there is no alternative explanation for the symptoms and airflow obstruction (e.g. bronchiectasis, vocal cord paralysis, tracheal stenosis). If airflow is abnormal, postbronchodilator testing should be performed. Correction of airflow to the normal range suggests a diagnosis of...
asthma and could exclude COPD. Because of variability in the FVC (or FEV₆) measure, the FEV₁/FVC ratio can establish a diagnosis of obstruction but is not useful to monitor disease progression (GOLD, 2006). FEV₁/FVC ratio is the basis for GOLD staging of COPD (see Table 2).

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV₁*/FVC**(in %)</th>
<th>FEV₁*(in % of predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild COPD</td>
<td>&lt;70 %</td>
<td>≥80 %</td>
</tr>
<tr>
<td>II: Moderate COPD</td>
<td>&lt;70 %</td>
<td>50 % to &lt;80%</td>
</tr>
<tr>
<td>III: Severe COPD</td>
<td>&lt;70 %</td>
<td>30% to &lt;50%</td>
</tr>
<tr>
<td>IV: Very Severe COPD</td>
<td>&lt;70 %</td>
<td>&lt;30% or &lt;50% with chronic respiratory failure***</td>
</tr>
</tbody>
</table>

*FEV1: forced expiratory volume in one second; **FVC: forced vital capacity; ***Chronic respiratory failure: arterial partial pressure of oxygen (PaO₂) less than 60 mm Hg (8.0 kPa) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 50 mm Hg (6.7 kPa) while breathing air at sea level.

Table 2. Staging of severity of COPD (GOLD, 2006)

Other spirometric findings include decreased inspiratory capacity and vital capacity, accompanied by increased total lung capacity, functional residual capacity, and residual volume are indicative of hyperinflation. The single breath carbon monoxide diffusing capacity (DLCO) decreases in proportion to the severity of emphysema because of the destruction of the alveoli and the loss of alveolar capillary bed (Bates, 1989).

9.2 Arterial blood gas

Arterial blood gases reveal mild or moderate hypoxemia without hypercapnia in the early stages of COPD. In the later stages of the disease, hypoxemia tends to become more severe and may be accompanied by hypercapnia with increased serum bicarbonate levels (Bates, 1989). The changes in ABG represent ventilation perfusion mismatch, which may be worsened during exercise, sleep and episodes of exacerbation.

9.3 Alpha1-antitrypsin level

Of the approximately 75 different alleles for alpha1-antitrypsin (AAT) deficiency variants, 10-15 are associated with serum levels below the protective threshold of 11 µmol/dL. The most common severe variant is the Z allele, which accounts for 95% of the clinically recognized cases of severe AAT deficiency. The diagnosis of severe AAT deficiency is confirmed when the serum level falls below the protective threshold value (ie, 3-7 µmol/dL). Specific phenotyping is reserved for patients in whom serum levels are 7-11 µmol/dL or when genetic counseling or family analysis is needed.

9.4 Sputum evaluation

In patients with stable chronic bronchitis, the sputum is mucoid and the predominant cells are macrophages (Miravitlles, 2002; Sethi et al., 2002 as cited in Shapiro SD, 2010). With an exacerbation, the sputum becomes purulent, with excessive neutrophils and a mixture of organisms visualized through Gram staining. Streptococcus pneumoniae and Haemophilus influenzae are pathogens frequently cultured during exacerbations.
9.5 Imaging studies

Chest radiographs and CT-scan of chest are the mainstay of COPD imaging. Although not contributing to diagnosis of COPD, they may add valuable information regarding severity, stage and special findings during the course of disease.

9.5.1 Chest X-ray

Radiographic features suggestive of COPD are prominent usually in advanced disease and include:

i. Signs of hyperinflation: Prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space, increased radiolucency of the lung, a flat diaphragm, and a long and narrow heart shadow on a frontal radiograph, accompanied by a flat diaphragmatic contour may be seen.

ii. Bullae, defined as radiolucent areas larger than one centimeter in diameter and surrounded by arcuate hairline shadows. They are due to locally severe disease.

iii. Rapidly tapering vascular shadows and cardiac enlargement may become evident only on comparison with previous chest radiographs. These findings are due to pulmonary hypertension and cor pulmonale, which can be secondary to COPD.

9.5.2Computed tomography

High-resolution CT (HRCT) scanning is more sensitive than standard chest radiography and is highly specific for diagnosing emphysema and outlines bullae that are not always observed on radiographs. CT can visualise whether the emphysema is centriacinar or panacinar(Hasegawa et al.,2006;Nishino et al.,2010;Washko et al.,2008 as cited in Shapiro SD,2010). A CT scan is not indicated in the routine care of patients with COPD but is helpful when the patient is being considered for a surgical intervention such as bullectomy or lung-volume reduction surgery(Fishman et al,2003 as cited in Shapiro SD,2010).

10. Stage of disease severity and progression

The GOLD staging system is based on the FEV₁/FVC ratio(see Table 2). It has been criticized for underestimating the importance of the extrapulmonary manifestations of COPD in predicting outcome(GOLD,2006;Bourdin et al,2009). The BODE index addresses this criticism. The four factors included in the BODE index are weight (BMI), airway obstruction (FEV₁), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walk distance)(see Table 3). This index provides better prognostic information than the FEV₁ alone to assess an individual's risk of death or hospitalization due to COPD. However, it is not used to guide therapy.

A component of disease assessment that is used in research studies is to evaluate the impact of airflow limitation on quality of life. The St. George's Respiratory Questionnaire (SGRQ) is a 76 item questionnaire that includes three component scores (ie, symptoms, activity, and impact on daily life) and a total score(Jones et al.,1991). It has been validated in patients with COPD, asthma, and bronchiectasis. Another questionnaire based instrument to assess quality of life is the Chronic Respiratory Disease Questionnaire (CRDQ) (Guyatt et al.,1987).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 Points</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
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</thead>
<tbody>
<tr>
<td>Body: BMI</td>
<td>&gt;21</td>
<td>≤21</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Obstruction: FEV1 (%)</td>
<td>≥65%</td>
<td>50–64%</td>
<td>36–49%</td>
<td>≤35%</td>
</tr>
<tr>
<td>Dyspnea: MMRC score</td>
<td>0-1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Exercise: 6-minute walk</td>
<td>≥350</td>
<td>250–349</td>
<td>150–249</td>
<td>≤149</td>
</tr>
</tbody>
</table>

BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second.

Table 3. BODE Index for Staging COPD (Celli et al., 2004)

11. Treatment

Treatment of COPD encompasses health promotion, prevention, control of symptoms and exacerbations, rehabilitation and palliation. Treatment plan needs to be individualized according to the stage and characteristics of the disease, age, co-morbidities in each patient. Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that pharmacologic and nonpharmacologic therapies should be added in a stepwise fashion to control symptoms, decrease exacerbations, and improve patient function and quality of life (GOLD, 2006). Patient should be educated about the disease and should be encouraged to participate actively in therapy and understand the need of proper dosing and timing of medications as well as proper inhaler technique is essential.

ATS Statement (1995) recommended symptomatic management after the patient presented to the healthcare system with specific complaints (ATS, 1995). However, new evidence suggests that the “pre-symptomatic” phase individuals progressively loose lung function in these years and also have poorer prognosis in terms of cardiac outcomes and hence earlier and more aggressive diagnosis and appropriate treatment of these previously unidentified individuals can help, not only by slowing progression but also by improving symptomatic control (GOLD, 2006).

Mainstays of drug therapy of stable COPD are bronchodilators, primarily beta agonists and anticholinergics, and inhaled glucocorticoids, given alone or in combination depending upon the severity of disease and response to therapy. Attention to co-morbidities like heart disease, depression, osteoporosis and rehabilitation for acceptable quality of life is also important. Reduction of risk factors like cigarette smoking and occupational exposure should be a central feature of every comprehensive treatment plan. The only medical therapies that clearly reduce disease progression and mortality are smoking cessation and supplemental oxygen (NOTT, 1980).

11.1 Cessation of cigarette smoking

Smoking cessation is the single most effective therapy for the majority of COPD patients (Anthonisen et al, 1994; Department of Health and Human Services (US), 2008). The transition from smoking to nonsmoking status involves following five stages: precontemplation, contemplation, preparation, action, and maintenance. Smoking intervention programs include self-help, group, physician-delivered, workplace, and community programs. Setting a target date to quit may be helpful. Physicians and other
health care providers should participate in setting the target date and should follow up with respect to maintenance. Successful cessation programs should include patient education, target date to quit, follow-up support, relapse prevention, advice for healthy lifestyle changes, social support systems, pharmacological agents.

According to the US Preventive Services Task Force (USPSTF) guidelines, recommends “5-A” approach to counseling that includes i) Ask about tobacco use, ii) Advise to quit through personalized messages, iii) Assess willingness to quit, iv) Assist with quitting, v) Arrange follow-up care and support. Behavioral counseling and pharmacotherapy are most effective when used together. (USPSTF, 2009)

Supervised use of pharmacologic agents is an important adjunct as withdrawal from nicotine may cause unpleasant adverse effects during the first weeks after quitting smoking. Nicotine replacement therapies are available in the form of chewing gum and transdermal patches to counter the withdrawal symptoms (U.S. Public Health Service Clinical Practice Guideline, 2008). Long-term success rates have been 22-42%, compared with 2-25% with placebos. The use of an antidepressant medication, bupropion (Zyban, 150 mg bid) has been shown to be effective for smoking cessation and may be used in combination with nicotine replacement therapy. Varenicline (Chantix), is a partial agonist selective for α4, β2 nicotinic acetylcholine receptors and action is thought to result from partial agonist activity at a nicotinic receptor subtype while simultaneously preventing nicotine binding. Nortriptyline and clonidine have also been proposed to help in cessation of smoking (U.S. Public Health Service Clinical Practice Guideline, 2008).

11.2 Pharmacologic treatment

The U.S. Food and Drug Adminstration (FDA) recommends five treatment end points be considered for COPD: improvement in airflow obstruction, providing symptom relief, modifying or preventing exacerbations, altering disease progression (including mortality), and modifying lung structure. Effective treatment of the COPD patient requires effective integration of pharmacologic treatment and nonpharmacologic therapy, most importantly pulmonary rehabilitation.

11.2.1 Bronchodilators

Bronchodilators are the mainstay of any COPD treatment plan. The mechanism of action is primarily by dilating airways and thereby decreasing airflow resistance increasing airflow and decreasing dynamic hyperinflation which is the origin of early stage symptoms. Many patients with COPD will have reduced dyspnea and improved exercise tolerance with bronchodilator therapy, even if improvement in resting spirometry is very modest (O’Donnell, 2000 as cited in Shapiro SD, 2010). Unlike asthma, COPD patients mostly need bronchodilators both on a chronic basis as well as for “rescue”. All symptomatic patients with COPD should be prescribed a short-acting bronchodilator for as-needed basis and a regularly scheduled long-acting bronchodilator should be added if symptoms are inadequately controlled. Bronchodilators include beta agonists, anticholinergics, and theophylline, which is used less often.

The initial choice of agent remains debated. Historically, β2 agonists were considered first line and anticholinergics added as adjuncts. Studies have shown combination therapy
results in greater bronchodilator response and provides greater relief. The degree of bronchodilation achieved by short-acting beta agonists and anticholinergics is additive. The adverse effect profile may help guide therapy.

i. Beta2(β2)-agonists:

This group of medications bind to the β-adrenergic receptor present on airway smooth muscle, resulting in bronchodilation and improvement in airflow. They may also help by increasing ciliary beating frequency and improving mucus transport and may improve endurance of fatigued respiratory muscles (Nava et al., 1992; Santa Cruz et al., 1974 as cited in Shapiro SD, 2010).

Beta agonists are available in short-acting and long-acting inhaled formulations. The short-acting β agonists (SABA) like albuterol, its racemere levalbuterol, pirbuterol and terbutaline, have a relatively rapid onset of action after inhalation, in about 5 to 15 minutes, and the bronchodilation lasts for 2 to 4 hours. Long-acting β-agonists (LABAs) like salmeterol, formoterol, arformoterol and indacaterol have a longer onset and bronchodilation lasting for up to 12 hours or more. Salmeterol has also shown anti-inflammatory effects, to reduce edema, and to reduce airway epithelial cell injury in model systems.

Inhaled route is preferable owing to more favorable ratio of therapeutic effect to undesirable side effects (Shim & Williams, 1983 as cited in Shapiro SD, 2010). A metered dose inhaler (MDI), dry powder inhaler (DPI) is the preferred mode to deliver a bronchodilator medication by inhalation as it simplifies therapy, improves compliance, and may reduce extra medication usage and patient cost. Nebulizers may be more effective in patients too weak to use an inhaler device, in those with altered mental status, or in those whose inspiratory capacity is too limited to permit effective inhalation (Tenholder et al., 1992 as cited in Shapiro SD, 2010).

Benefits of treatment include improvement in airflow obstruction and symptom relief. Although the magnitude of improvement is less and incomplete as compared to asthma patients, 25-30% patients achieve “positive bronchodilator response” as defined by the ATS. Improvement in FEV1 (about 200- to 300-mL) and symptoms assessed by SGRQ have been elicited in multiple randomized placebo-controlled trials (Appleton et al., 2006; Calverley et al., 2003; Rodrigo et al., 2008 as cited in Shapiro SD, 2010). Modest benefit is noted in prevention of exacerbations with LABAs to the tune of 20-30% reduction in frequency of exacerbations (Appleton et al., 2006; Sin et al., 2003 as cited in Shapiro SD, 2010). However, they have no effect on disease progression and alteration of lung structure (Calverley et al., 2007 as cited in Shapiro SD, 2010).

Side-effects commonly include tremor, palpitations, anxiety, and insomnia. Ventricular arrhythmias and hypokalemia may also occur. These effects are dependent on systemic absorption and hence, spacer devices, DPIs, MDIs are preferable. R-enantiomer of albuterol, levalbuterol was promoted widely based on the possibility to have lesser side effects such as tachycardia and tremors as well as lacking the inflammatory effect of the S-enantiomer. The small difference noted in studies has raised doubts of its clinical relevance (Donahue et al., 2008 as cited in Shapiro SD, 2010).

A significant proportion of COPD patients have concurrent cardiac co-morbidities and although recent studies have failed to show any clinically significant adverse outcome of β2
agonists, caution is warranted. (Cazzola et al, 1998; Anthonisen et al, 2002 as cited in Shapiro SD, 2010)

ii. Anti-cholinergics:

Anticholinergic agents block M2 and M3 cholinergic receptors and result in bronchodilation (Rennard, 2000 as cited in Shapiro SD, 2010). In airway smooth muscle cells, acetylcholine stimulates the production of neutrophil chemotactic activity and anticholinergics could, theoretically, have anti-inflammatory action (Koyama et al, 1992; Wessler & Kirkpatrick, 2001 as cited in Shapiro SD, 2010).

Short-acting anticholinergic agents like ipratropium and oxtropium improve lung function and symptoms. In double-blinded studies, ipratropium improved lung function, increased exercise capacity, decreased dyspnea, and decreased cough when compared to placebo. Ipratropium produces bronchodilation in 10 to 15 minutes and lasts for 4 to 6 hours. Tiotropium is a longer-acting anticholinergic because it dissociates from the receptor extremely slowly achieving peak bronchodilator activity after 1 to 2 hours, but duration of action lasts long enough for once daily dosing. When administered chronically, the bronchodilator effect of tiotropium increases with daily dosing and is maximal after 1 week (Hansel & Barnes, 2002; Littner et al, 2000 as cited in Shapiro SD, 2010). It is relatively selective for M3 receptor, and this may have better clinical efficacy as it doesn't alter the M2 mediated feedback inhibition of acetylcholine (On et al, 2001 as cited in Shapiro SD, 2010). The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial studied the effects of use over a 4-year period and showed improvements in lung function, quality of life, and exacerbations but did not show a decrease in the rate of decline of lung function (Tashkin et al., 2008).

Benefits of treatment are similar to beta-agonist agents including improvement in airflow obstruction and symptom relief. Tiotropium improves airflow and lung volumes, reduces dyspnea, and improves health status and exercise performance (Tashkin et al, 2008). In combination with albuterol tiotropium has been reported to reduce risk of COPD exacerbation to the magnitude of the risk reduction by 20% to 25% (Niewoehner et al, 2005; Sin et al, 2003 as cited in Shapiro SD, 2010). However, as with other bronchodilators, anticholinergics have no effect on disease progression and alteration of lung structure. Reported adverse effects include dry mouth, metallic taste, and prostatic symptoms. Equivocal data exist regarding possible increased adverse cardiac events with chronic use of anti-cholinergic agents.

iii. Theophylline:

Theophylline is the only methylxanthine currently used to treat COPD patients. It has modest bronchodilator activity, but it also has additional potentially beneficial effects including anti-inflammatory, modest inotropic and diuretic effects, and may also augment skeletal muscle strength (Barnes, 2003; Culpitt et al, 2002 as cited in Shapiro SD, 2010). Dose-related adverse effects of theophylline include nausea and vomiting, seizures, and arrhythmias. Its use is also complicated by many drug interactions and concurrent morbidity that affecting liver and cardiac function can alter theophylline levels. The therapeutic index of theophylline is narrow and desired serum levels are 8 to 12 µg/mL. Dose-related adverse effects of theophylline include nausea and vomiting, seizures, and
arrhythmias. Hence, use of theophylline is usually limited to an add-on therapy when symptoms continue in patients with more severe disease despite the use of other treatments.

**11.2.2 Choice of bronchodilator and combination therapy**

Historically, β2 agonists were considered first line and anticholinergics added as adjuncts. Most patients in GOLD stage I disease will have acceptable relief of symptoms with one short acting bronchodilator used on as needed basis. Combination therapy with short and long acting β2-agonists and anticholinergics is supported by trials indicating greater bronchodilator response and achieving better symptom relief(Cazzola et al,2004;CIAS Group,1994;VanNoord et al.,2000 as cited in Shapiro SD,2010). In patients with GOLD stage II and above, whose symptoms are not well-controlled with a single long-acting bronchodilator, the combination of both an anticholinergic and a β2-agonist long-acting bronchodilator may provide better symptom relief and improve quality of life index(ATS/ERS Task Force,2004;GOLD,2006).

SABA, LABA, anticholinergics have been tried in various combinations and data suggests improved FEV1 and symptom control with combinations than either agent alone. The choice and order of agents can be guided by response, side-effects and co-morbidity profile (ATS/ERS Task Force, 2004; GOLD, 2006). Although clinical responses among individual patients may vary, poor compliance and ineffective use of the device must be considered before changing medications.

**11.2.3 Anti-inflammatory medications**

COPD is characterized by both airway and systemic inflammation as discussed in the pathogenesis and the primary reason of disease progression. Bronchodilators achieve temporary symptom control but have failed to show any effect on the underlying inflammation. Corticosteroids are by far the leaders of this class of medication, and some newer phosphodiesterases have shown promise.

i. Corticosteroids:

Inhaled glucocorticoids decrease frequency of exacerbations and modestly slow the progression of respiratory symptoms, but appear to have little impact on lung function and mortality. Because of their lack of effect on bronchodilation, inhaled glucocorticoids can be used only as part of a combined regimen, but are not as sole therapy.

Benefits from therapy include reduction in the frequency and severity of exacerbations of COPD by 25-30%, comparable to LABAs(Calverley et al.,2003,2007;Szafranski et al,2003 as cited in Shapiro SD,2010). Effect on improvement of airflow obstruction and symptom relief is minimal, although some additive benefit is reported for combination therapy with LABAs(Burge et al,2000;Pauwels et al,1999 as cited in Shapiro SD,2010). Though the anti-inflammatory effect promises possible alteration of disease progression and slowing of decline in FEV1, studies have failed to show any such benefit(Highland et al,2003;Soriano et al,2007;Sutherland et al.,2003 as cited in Shapiro SD,2010). Some studies have reported equivocal reduction in hospital admission and mortality rates(Sin & Tu,2001;Soriano et al,2002 as cited in Shapiro SD,2010). No study has proven any effect on lung structure remodelling.
Inhaled corticosteroids are only minimally absorbed and therefore systemic adverse effects are limited. Local effects include oral candidiasis and dysphonia (Pauwels et al., 1999 as cited in Shapiro SD, 2010). Systemic effects include increased bruising and reduced bone density, and possible susceptibility for pneumonia (Calverley et al., 2007 as cited in Shapiro SD, 2010). Appropriate caution and monitoring is recommended although the clinical importance of these effects remains uncertain.

Systemic steroids have been widely used in the treatment of acute exacerbation of COPD. A meta-analysis concluded that systemic corticosteroids significantly reduced treatment failure and need for additional medical treatment and increased the rate of improvement in lung function and dyspnea over the first 72 hours (Rice et al., 2000 as cited in Shapiro SD, 2010). The use of oral steroids in persons with chronic stable COPD is not recommended given the adverse effect profile, which includes hypertension, glucose intolerance, osteoporosis, fractures, and cataracts, among others (Burge et al., 2003 as cited in Shapiro SD, 2010).

Inhaled glucocorticoids are typically used in combination with a long-acting bronchodilator for patients in GOLD stage III-IV, who have significant symptoms or repeated exacerbations, despite an optimal bronchodilator regimen. Steroids may be introduced earlier if there are signs of inflammation or an asthmatic component to the COPD (Ferguson et al., 2008 as cited in Shapiro SD, 2010). In the TORCH (Toward a Revolution in COPD Health) trial involving patients with moderate to severe COPD, salmeterol plus fluticasone significantly improved the lung function, health status, and the rate of exacerbations compared to placebo, salmeterol alone, or fluticasone alone (Calverley et al., 2007). It also minimally decreased mortality compared to placebo (10.3 versus 12.6 percent, hazard ratio 0.81, 95% CI, 0.67-0.98). The Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) trial included 1323 patients with stable, mostly severe COPD and results failed to show significant benefits of combining inhaled steroids with LABAs (Wedzicha et al., 2008).

“Triple inhaler therapy” - with a long-acting beta agonist plus an inhaled glucocorticoid plus a long-acting anticholinergic is often used in refractory COPD patients. This approach is supported by some studies (Tashkin et al., 2008). These data are insufficient to warrant a change in the current guidelines in which the first step is initiation of a long-acting bronchodilator alone and then if response is inadequate or disease advances, to introduce a combination of long-acting beta agonist plus an inhaled glucocorticoid.

ii. Phosphodiesterase inhibitors:

Phosphodiesterase-4 (PDE-4) inhibition decreases inflammation and promotes airway smooth muscle relaxation. Cilomilast and roflumilast are highly specific, oral, second-generation PDE-4 inhibitors being considered for use in patients with asthma and COPD (Gamble et al., 2003; Profita et al., 2003 as cited in Shapiro SD, 2010). Recent trials have supported their inclusion in COPD combination treatment plans (Calverly et al., 2009; Chong et al., 2011 as cited in Shapiro SD, 2010). Several randomized, double-blind, placebo-controlled multicenter trials revealed increased FEV1 ($P < .0001$) and the rate of COPD exacerbations was reduced by 17% ($P < .0003$) in patients who received roflumilast compared with placebo. Additional studies are necessary before PDE-4 inhibitors can be recommended for routine use in patients with stable COPD.
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iii. Cromolyn Sodium Nedocromil and Leukotriene Antagonists:

There are no supportive data advocating a beneficial role for cromolyn, nedocromil, or cysteinyl leukotriene antagonists in treating COPD (DeJong et al, 1994 as cited in Shapiro SD, 2010).

11.2.4 Adjuvant pharmacologic agents

i. Augmentation therapy for A1PI deficiency:

The treatment strategies for A1PI deficiency involve reducing the neutrophil elastase burden, primarily by smoking cessation, and augmenting the levels of A1PI. Available augmentation strategies include pharmacologic attempts to increase endogenous production of A1PI by the liver (ie, danazol, tamoxifen) or administration of purified A1PI by periodic intravenous infusion or by inhalation. Tamoxifen can increase endogenous production of A1PI to a limited extent, so this may be beneficial in persons with the PISZ phenotype.

Intravenous augmentation therapy is the only available approach that can increase serum levels to greater than 11 mmol/L, the protective threshold. Studies show that the infusions can maintain levels of more than 11 mmol/L, and replacement is administered weekly (60 mg/kg), biweekly (120 mg/kg), or monthly (250 mg/kg) (Buist et al, 1989; Sandhaus, 2009 as cited in Shapiro SD, 2010). Uncontrolled observations of patients suggest that the FEV1 may fall at a slower rate in patients who receive A1PI replacement. It seems reasonable to weigh carefully the advantages and disadvantages of augmentation therapy and to reach a decision jointly with elderly persons or with those with severe lung function impairment (FEV1 values < 0.8 L) (Buist et al, 1989 as cited in Shapiro SD, 2010).

ii. Mucoactive and expectorant agents:

Mucolytic agents like acetylcysteine, dornase (DNAse), guaifenesin reduce sputum viscosity and improve secretion clearance. However, studies have failed to justify a role for these medications in management of COPD (Decramer et al, 2005 as cited in Shapiro SD, 2010). The role of oral expectorants like guaifenesin in promoting mucous clearance in COPD patients remains controversial.

iii. Antibiotic therapy:

Chronic infection or colonization of the lower airways with *S pneumoniae, H influenzae,* and/or *Moraxella catarrhalis* is common and in later stage disease, with Gram-negative organisms such as *Pseudomonas.* Macrolides like erythromycin, may have additional antiinflammatory effects. Patients whose COPD is associated with bronchiectasis may benefit from chronic antibiotic therapy. However, at present, chronic antibiotics are not recommended for stable COPD management.

The use of antibiotics for the treatment of acute COPD exacerbations and pneumonias is well supported (Adams et al., 2008). The patients who benefited most from antibiotic therapy were those with exacerbations that were characterized by at least 2 of the following: increases in dyspnea, sputum production, and sputum purulence (The Winnipeg criteria).

iv. Vaccine prophylaxis:

Infection is a common cause of COPD exacerbation and vaccination is the most effective way of prophylaxis. Pneumococcal polysaccharide vaccine should be offered to patients
with COPD who are ≥65 years old, or who are younger than 65 years with a forced expiratory volume in one second (FEV1) less than 40 percent. An annual influenza vaccine should be given to all patients with COPD.

11.2.5 Supportive management

i. Oxygen therapy:

Chronic hypoxemia may develop in patients with severe stable COPD (GOLD stage IV). Two landmark trials, the British Medical Research Council (MRC) study and the National Heart, Lung, Blood Institute's Nocturnal Oxygen Therapy Trial (NOTT) showed that long-term oxygen therapy improves survival by 2-fold or more in hypoxemic patients with COPD (Kvale, 1980; Medical Research Council Working Party, 1981). Improved quality of life is also achieved likely due to reduced dyspnea during exercise, which improves performance of activities of daily living. Other benefits include reduction in hematocrit, modest neuropsychological improvement, and some improvement in pulmonary hemodynamics (Heaton et al, 1983; Kvale, 1980; Timms et al, 1985 as cited in Shapiro SD, 2010).

Hypoxemia which is defined as a PaO2 of <55 mmHg or oxygen saturation of <90%. For those whose resting arterial PO2 is between 56 and 59 mmHg, long-term oxygen therapy is indicated if they demonstrate erythrocytosis (hematocrit ≥ 55%) or evidence of cor pulmonale. Stable ambulatory patients should meet these criteria after being on an optimal treatment regimen for at least 30 days (Petty, 1990; Petty & Snider, 1988; Tiep, 1990 as cited in Shapiro SD, 2010). Exercise-induced hypoxemia is also an accepted indication for supplemental oxygen because it improves exercise performance (Cotes & Gilson, 1956; Woodcock et al, 1981 as cited in Shapiro SD, 2010). Supplementary oxygen during air travel is recommended for only those individuals whose in-flight PaO2 is expected to fall below 50 mmHg since all commercial airline cabins are not always pressurized to sea level (Gong, 1984; Schwartz et al, 1984 as cited in Shapiro SD, 2010). Patients with major bullous disease run a high risk of life-threatening pneumothorax and hence, probably should not fly. Studies have failed to show any benefit arising from nocturnal oxygen supplementation targeted at correcting hypoxemic episodes during sleep (Chouat et al, 1999, 2001; Zanchet & Viegas, 2006 as cited in Shapiro SD, 2010).

The continuous-flow nasal cannula is the standard means of oxygen delivery for stable hypoxemic patients. The cannula is simple, reliable, and generally well tolerated. Each liter of oxygen flow adds 3-4% to the fraction of inspired oxygen (FiO2). Oxygen-conserving devices function by delivering all of the oxygen during early inhalation. Three distinct oxygen-conserving devices are available, and they include reservoir cannulas, demand-pulse delivery devices, and transtracheal oxygen delivery.

ii. Nutrition:

Patients with advanced COPD and a predominance of emphysema often experience progressive weight loss. The weight loss is multifactorial including a 15% to 25% increase in resting energy expenditure from elevated work of breathing and increased circulatory inflammatory cytokines, higher energy cost of daily activities and a reduced caloric intake (Barnes, 2009; Di Francia et al, 1994 as cited in Shapiro SD, 2010). This leads to reduced muscle strength including weakness of respiratory muscles thus worsening the dyspnea.
Improved nutrition can restore respiratory and general muscle strength and endurance (Wilson,1986,Whittaker et al,1990 as cited in Shapiro SD,2010).

iii. Pulmonary Rehabilitation:

Comprehensive pulmonary rehabilitation has been shown to improve exercise capacity, improve independence quality of life, decrease dyspnea, and decrease health care utilization and it may also reduce mortality (Celli et al.,1995 as cited in Shapiro SD,2010). Although airflow obstruction (FEV$_1$) is not improved, the effects of rehabilitation on health status (“quality of life”) are generally much greater than seen with pharmacologic treatments (Finnerty et al,2001 as cited in Shapiro SD,2010). Pulmonary rehabilitation should be considered as an addition to medication therapy for symptomatic patients who have GOLD Stage II, III, or IV COPD.

Pulmonary rehabilitation program usually requires a team approach, including physicians, nurses, dietitians, respiratory therapists, exercise physiologists, physical therapists, occupational therapists, recreational therapists, cardiopulmonary technicians, pharmacists, and psychosocial professionals. This multidisciplinary approach emphasizes on patient and family education, smoking cessation, medical management (including oxygen and immunization), respiratory and chest physiotherapy, physical therapy with bronchopulmonary hygiene, exercise, and vocational rehabilitation and psychosocial support.

Exercise conditioning is the single most important aspect of rehabilitation and comprises of aerobic lower extremity endurance exercises and upper extremity exercise training to improve dyspnea and allow increased activities of daily life(ATS,1987). Breathing retraining techniques (eg, diaphragmatic and pursed-lip breathing) may improve the ventilatory pattern and may prevent dynamic airway compression (Celli,1991;Lotters,2002 as cited in Shapiro SD,2010).

11.2.6 Treatment of respiratory failure

i. Chronic Ventilatory Failure - Intermittent Noninvasive Ventilation:

The use of noninvasive mechanical ventilators is based on the concept that, in patients with severe COPD, the respiratory muscles are at the fatigue threshold. Resting the muscles provides time for “recovery” and prevents small increases in respiratory requirements from precipitating fatigue and perhaps acute respiratory failure. Due to lack of evidence of clinical benefit in several studies, the routine use of this form of support for COPD patients is not recommended at present(GOLD,2006).

ii. Altering Ventilatory Control

a. Almitrine bismesylate - a peripheral chemoreceptor agonist, significantly improves resting room air arterial PO2 in about 80% of stable COPD patients mainly from improved ventilation-perfusion relationships because almitrine enhances hypoxic pulmonary vasoconstriction by way of sympathetic efferent pathways(Bury et al.,1989;Romaldini et al.,1983;Weitzenblum et al.,1991 as cited in Shapiro SD,2010). Further evidence is needed in its support before it can be recommended for regular use in COPD (GOLD,2006).

b. Analgoeptic agents: The benefit of the analgoeptic agents, like acetazolamide, which stimulates respiration by acidifying plasma and cerebrospinal fluid(Skatruc &
Dempsey, 1983 as cited in Shapiro SD, 2010), and medroxyprogesterone acetate, which directly acts on brainstem respiratory neurons, is not established for COPD patients. Clinical benefits are not established for these medications and their use to stimulate ventilation in COPD is not recommended (GOLD, 2006).

11.2.7 Surgical intervention

i. Lung Volume Reduction Surgery:

Various surgical approaches to improve symptoms and restore function in patients with emphysema have been described. Dr. Otto Brantigan pioneered resectional surgery in 1950s, but it was Cooper et al’s work showing remarkable improvement in physical measures and quality of life measures in patients of COPD who underwent lung volume reduction surgery, generated tremendous interest in the procedure and led eventually to the National Emphysema Treatment Trial (NETT, 1999). The NETT study found a substantial reduction in mortality and improvements in HRQOL and exercise capacity as a result of lung volume reduction surgery (LVRS) in properly selected patients (Pinto-Plata et al., 2007 as cited in Shapiro SD, 2010). Caution is recommended in proper selection of patients as individuals with an FEV\(_1\) less than 20% predicted and either homogenous disease or a diffusion capacity of less than 20% predicted were at very high risk for mortality if treated surgically.

ii. Bullectomy:

Removal of giant bullae has been a standard approach in selected patients for many years. Giant bullae may compress adjacent lung tissue, reducing the blood flow and ventilation to the relatively healthy lung. Giant bullectomy can produce subjective and objective improvement in selected patients, ie, those who have bullae that occupy at least 30%—and preferably 50%—of the hemithorax that compress adjacent lung, with an FEV\(_1\) of less than 50% of predicted and relatively preserved lung function otherwise (Kinnear & Tattersfield, 1990; Nickoladze, 1992 as cited in Shapiro SD, 2010).

iii. Lung transplantation:

Despite multiple difficulties and obstacles, single-lung transplant has become most common procedure of choice when transplantation is performed for emphysema. Available data suggest that lung transplantation offers improved function and HRQOL to patients with advanced COPD, but it is not clear that it offers any survival benefit (Marulli & Rea, 2008; Stavem, 2006 as cited in Shapiro SD, 2010). Worldwide, COPD is the most common reason for lung transplantation. Current guidelines by the International Society of Heart and Lung Transplantation recommends referring A1PI individuals with COPD for transplantation in a scenario with the BODE index greater than 5, post-bronchodilator FEV\(_1\) < 25 percent of predicted, resting hypoxemia (PaO\(_2\) < 55 to 60 mmHg), hypercapnia, secondary pulmonary hypertension or accelerated decline in FEV\(_1\) (Orens et al., 2006 as cited in Shapiro SD, 2010).

11.2.8 Management of acute exacerbations of COPD (AECOPD)

GOLD and WHO defines an exacerbation of COPD as an acute increase in symptoms beyond normal day-to-day variation which includes worsening of cough, increase in phlegm production, change in phlegm quality, and increase in dyspnea (GOLD, 2006).
Variable decrease in pulmonary function, and tachypnea are typical in acute exacerbations however, severe cases can lead to respiratory failure and death. Higher exacerbation frequency is associated with more loss of FEV\textsubscript{1}, impairment in quality of life and increase in dyspnea with time.

AECOPDs occur in clusters and patients with an AECOPD were at an increased risk of another attack in the 8 weeks following their initial episode (Hurst et al., 2009 as cited in Shapiro SD, 2010). Viral and bacterial infections and environmental pollutants incite most of the acute exacerbations. The single best predictor of exacerbations was a history of exacerbations. Other predictors of frequent exacerbations were chronic cough and phlegm production, episodic wheezing, pneumonia, active smoking, exertional dyspnoea, lower lung function, advanced age, duration of COPD, history of antibiotic therapy, COPD-related hospitalization within the previous year and having one or more comorbidities (eg, ischemic heart disease, chronic heart failure, diabetes mellitus or gastroesophageal reflux) (Foreman et al., 2007 as cited in Shapiro SD, 2010). Important differential diagnosis are heart failure, pulmonary thromboembolism, and pneumonia.

AECOPDs are a major reason for hospital admission for failure of outpatient treatment, marked increase in dyspnea, altered mental status, and increase in hypoxemia or hypercapnia and respiratory acidosis. Mild episodes may be managed as out-patient. Supplemental oxygen is a critical component of acute therapy. It should target an arterial oxygen tension (PaO\textsubscript{2}) of 60 to 70 mmHg (GOLD, 2006). If the episode is severe, the patient may require ventilatory support in the form of either noninvasive or invasive positive-pressure ventilation (GOLD, 2006). A Cochrane review showed NIPPV reduces mortality, avoids endotracheal intubation, and decreased treatment failure (Lightowler et al., 2003 as cited in Shapiro SD, 2010).

Pharmacological treatment of COPD includes bronchodilators, antibiotics, and steroids. Short-acting bronchodilators are the mainstay of therapy. Oral or parenteral steroids are indicated in the treatment of AECOPD and have been shown to shorten recovery time and improve outcome and reduce hospital stay. Most exacerbations are treated with full dose therapy (eg, prednisone 30 to 40 mg daily) for 7 to 10 days. Antibiotics have been shown to provide benefit in patients who present with dyspnea, increased purulence, and increased volume of sputum (Fagon et al, 1990; Iyer & Murphy, 2009 as cited in Shapiro SD, 2010).

12. Prognosis and follow-up

Several parameters correlate with prognosis in COPD, including forced expiratory volume in 1 second (FEV\textsubscript{1}), diffusion capacity for carbon monoxide (DLCO), blood gas measurements, body mass index (BMI), exercise capacity, clinical status and radiographic findings on CT scan. A widely used simple prognostication tool is the BODE index, which is based on the BMI, obstruction (FEV\textsubscript{1}), dyspnea (using Medical Research Council Dyspnea Scale), and exercise capacity (ie, 6-minute walk distance).

The 6-min walk test (6MWT) remains the most popular test for the evaluation of exercise tolerance in COPD patients. It is simple and well standardised, but its interpretation criteria remain controversial. A distance of <361m also predicted mortality in patients with FEV\textsubscript{1}, 50% predicted. The 6MWT is currently used to evaluate the impact of treatment. The classical 54 m is defined as the minimal significant difference to detect benefit of treatment.
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(Redelmeir et al.,1997 as cited in Shapiro SD,2010). The shuttle walk test offers the advantages of being perfectly standardized and highly related to peak oxygen consumption.

Health status is mostly impaired by exacerbations on the one hand and dyspnoea on the other, with its negative effect on daily activity. Some extrapulmonary parameters are also correlated with measures of daily activity, independent of GOLD stage and BODE score; they include left cardiac dysfunction (as assessed by levels of B-type natriuretic peptide and echocardiography) and systemic inflammation (C-reactive protein levels) (Watz et al., 2008 as cited in Shapiro SD, 2010). Frequent exacerbations have a negative long-term impact on the BODE index, a well known prognostic factor in COPD, and are not purely respiratory episodes but associated with systemic inflammation.

13. Recent advances

COPD is an area of intensive research, reporting important advances in the understanding of and care for the disease. Evidence from recent epidemiological studies have questioned the diagnostic value of the GOLD criteria of fixed FEV1/FVC threshold of 0.7 defining airflow limitation. These studies have demonstrated high false-negative rate in young subjects at risk and the false-positive rate in older patients (Cerveri et al., 2008; Hansen et al., 2007 as cited in Bourdin A, 2009). The lower limit of normal (LLN) as recommended by American Thoracic Society (ATS) and European Respiratory Society (ERS) seems to be much more reliable for defining obstruction, particularly for screening purposes (Swanney et al., 2008 as cited in ATS, 2010). The criteria of reversibility of airflow obstruction to differentiate COPD from asthma has come under question based on wide range of reversibility demonstrated in UPLIFT trial (Tashkin et al., 2008).

Some consider COPD as a component of a broader syndrome that was called “chronic systemic inflammatory syndrome”. Patients are diagnosed with this syndrome if they have three or more components of the following: age >40 yrs, smoking history >10 pack-yrs, symptoms and abnormal lung function compatible with COPD, chronic heart failure, metabolic syndrome and increased CRP (Fabbri & Rabe, 2007 as cited in Bourdin A, 2009).

New evidence has enhanced the understanding of oxidative stress, injury and protective antioxidants such as the glutathione system and the haemoxigenase (HO)-1 pathway. Reduced HO-1 expression has been described in macrophages from lung tissue and bronchoalveolar lavage (BAL) of smokers with COPD (Maestrelli et al., 2003; Slebos et al., 2004 as cited in Bourdin A, 2009). Moreover, the subtle molecular regulation of HO-1 and its key protein regulators, such as Nrf2, Bach1 and Keap1, is modified in COPD. Nrf2 protein level is significantly decreased in whole lung tissue and alveolar macrophages and conversely, Bach1 and Keap1 levels were increased in patients with emphysema (Goven et al., 2008 as cited in Bourdin A, 2009).

A specific antigen reaction is a hypothesis put forward in order to better understand COPD progression; T-cells (both CD4 & CD8) may play a role in this possible B-cell mediated response. Leptin has been described as a potential regulator of lymphocyte lifespan within the airways of COPD patients (Bruno et al., 2005). The production of RANTES (regulated upon activation, normal T-cell expressed and secreted) is increased, as shown in the sputum of patients with COPD. Regulatory T-cells (Tregs) are special T-lymphocytes that are important for preventing autoimmune reactions by inhibiting T-cell responses (Baraldo &

Scores used in clinical practice to assess health status have been modified to be useful in primary care setting. The simplified version of the original BODE index, BOD score and a new index called ADO (age, dyspnoea and airflow obstruction) have been studied and found to have similar accuracy for risk prediction (Puhan et al., 2009 as cited in Bourdin A, 2009).

Thoracic gas compression during forced expiration is a major event in COPD and a new index of gas compression defined as \( \frac{\text{NFEV1- FEV1}}{\text{NFEV1}} \) (in percent) was demonstrated to be higher at baseline in COPD (32%) than in controls (10%) and it decreased after albuterol only in COPD patients. Shuttle walk test for exercise testing, negative expiratory pressure (NEP) method and forced oscillation technique (FOT) to measure expiratory flow limitation (EFL), single-breath nitrogen washout test (SBN2) for small airway involvement, inspiratory muscle endurance (IME) for monitoring respiratory muscle training, diaphragmatic electromyogram (EMG) for neural respiratory drive, etc include some of the modalities to assess clinical function, response to treatment and some for purely research evaluations.

Newer imaging techniques have recently allowed for the possibility of evaluating pulmonary function as well as anatomy. Although helical CT and HRCT have become the cornerstone of pulmonary imaging, newer modalities such as PET and MRI may soon become critical components in the arsenal of tests used to evaluate pulmonary disease. Newer axial CT is as accurate as fiberoptic bronchoscopy (FOB) and virtual bronchoscopy (VB), or CT bronchography, has received considerable attention and excellent internal images of the tracheobronchial tree can be generated to the level of the 4th-5th generation bronchi.

Increasing evidence in support of therapy with phosphodiesterase-4 inhibitors, antioxidants and augmentation therapy with A1PI in deficient individuals, seem promising. Nonrespiratory treatments of co-morbidities with medications such as proton pump inhibitors, angiotensin-converting enzyme inhibitors, and statins show promise in the management of COPD. Bronchoscopic lung volume reduction (bLVR) is being developed to collapse areas of emphysematous lung in hopes of having the same effect on respiratory function as LVRS, but without the morbidity and mortality of surgery. Safety and effectiveness of minimally invasive approaches like video-assisted thoracoscopy for the treatment of giant bullae is under evaluation.

14. Summary

- Chronic obstructive pulmonary disease is a common condition with a high morbidity and mortality.
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a preventable and treatable disease characterized by progressive permanent airflow limitation that is not fully reversible. The airflow limitation is associated with an abnormal inflammatory response on exposure to noxious particles or gases particularly cigarette smoking.
- There is substantial overlap and co-existence of emphysema, chronic bronchitis, and asthma. Injury from smoking excites inflammation, which leads to cellular and
extracellular matrix injury which heals with incomplete and disorganized repair mechanisms ultimately leading to permanent progressive airflow obstruction. Deficiency of anti-protease deficiency makes individuals particularly susceptible to this pathologic process with earlier and more severe disease presentation.

- Patients with COPD present late with chronic respiratory symptoms and majority of early stage is asymptomatic and hence needs a high index of suspicion for diagnosis. Some patients present with an acute exacerbation.
- Pulmonary function tests reveal airflow obstruction (ie, a forced expiratory volume in one second [FEV1]/forced vital capacity [FVC] ratio less than 0.70) which is incompletely reversible.
- The GOLD staging system is based on spirometry and is well recognized and commonly used as a guide for management. It has been criticized for underestimating the importance of the extrapulmonary effects of COPD in predicting outcome, which is addressed by the BODE index.
- Cessation of smoking is a central point in treatment of COPD. A short-acting inhaled bronchodilator for use on as-needed basis is a reasonable initiation therapy for early stage disease (Stage IA). Addition of a long-acting inhaled bronchodilator and/or glucocorticoid should be considered to improve symptoms, improve lung function, and reduce the frequency of exacerbations in Stage IB disease and onwards.
- Pulmonary rehabilitation is recommended to improve symptoms, exercise capacity, and quality of life. Long-term oxygen therapy is indicated in COPD patients who have chronic hypoxemia.
- All patients with COPD should be advised to quit smoking, educated about COPD, and influenza/pneumococcal vaccines advised as recommended.
- Patients who continue to have significant symptoms despite the above interventions may be candidates for surgical therapy.
- Extensive research is ongoing in various aspects of understanding etiopathogenesis and treatment options for COPD.

15. References


US Preventive Services Task Force (USPSTF) guidelines April 2009: Counseling and Interventions to Prevent Tobacco Use and Tobacco-Caused Disease in Adults and Pregnant Women


A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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