Introduction to Lung Disease

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Waleed Hassan Almalki

Abstract

The global incidence of lung disease (LD) affecting children and adults is steadily increasing. The source of mortality and morbidity of lung diseases is unknown. However, current data from the WHO and other institutions show that there are approximately 400 million people worldwide suffering from mild to severe COPD and asthma. Lung diseases can be classified as non-infectious (asthma, chronic obstructive pulmonary disease (COPD), lung cancer, cystic fibrosis, and idiopathic pulmonary fibrosis (IPF)) or infectious (tuberculosis, influenza and COVID-19) disease and method transfer. Lung diseases have a huge impact on a global scale and are becoming more common due to the ageing population and the lack of appropriate interventions to minimise the risk factors that lead to the development of these diseases. Asthma, COPD, fibrosis, COVID-19, and influenza-like lung diseases have become life-threatening and life-threatening, effective treatments and appropriate preventive measures have become challenges for researchers.

Keywords

Lung diseases · Asthma · COPD · COVID-19 · Fibrosis

W. H. Almalki (✉)
Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: Whmalki@uqu.edu.sa com

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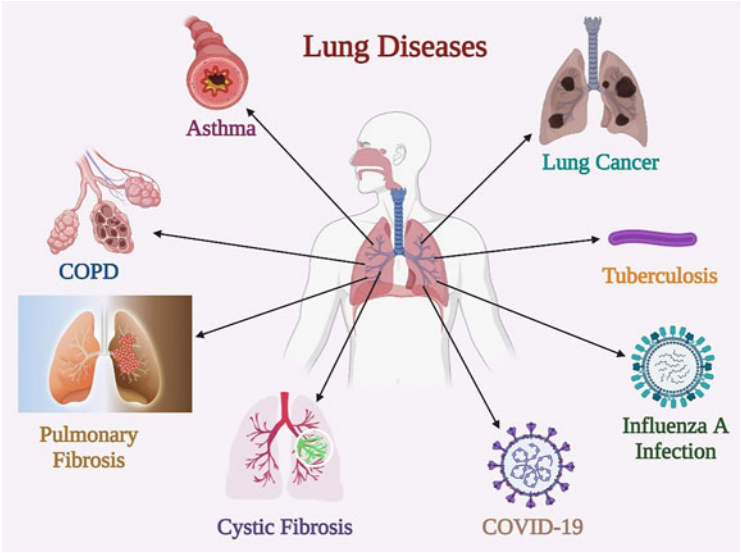

Fig. 1.1 Lung Diseases

1.1 Introduction

The enhancement of worldwide incidence of Lung Disease (LD), which affects both children and adults, is steadily rising. The source of pulmonary illness fatality and morbidity is unknown although current WHO and other agency figures indicate that about 400 million individuals worldwide suffer from mild to severe COPD and asthma alone. Furthermore, *Haemophilus influenzae* infection in the lower respiratory tract causes between 250,000 and 500,000 fatalities each year [1–3]. In 2015, *Mycobacterium* TB infection of the lower respiratory tract affected 10.4 million people globally, killing 14% of those infected. Other non-communicable illnesses, such as lung cancer induced by cigarettes smoking or exposure to environmental toxins, claim the lives of 1.6 million people each year and are on the rise. Lung disorders can be classified as non-communicable (asthma, chronic obstructive pulmonary disease (COPD), lung cancer, cystic fibrosis, and idiopathic pulmonary fibrosis (IPF)) or communicable (tuberculosis, influenza, and COVID-19) depending on disease etiopathology and method of transfer (Fig. 1.1) [4, 5].

1.2 Overview of Lung Diseases

Here we briefly discussed communicable and non-communicable lung diseases.

1.2.1 Asthma

Asthma is a diverse and complicated lung illness marked by varied airflow restriction, bronchial hyperactivity, and, most critically, elevated airway inflammation. Asthma impacts around 10% of the adult population in nearly every country, totalling around 300 million people worldwide. Furthermore, asthma is projected to be the main cause of 383,000 fatalities globally, with low- and middle-income nations accounting for nearly 80% of asthma-related deaths [6, 7]. Asthma is also a significant financial burden, costing up to $USD 3100 per person each year. Asthma is a prevalent but misunderstood respiratory condition that can strike anybody at any age. House dust mites, pollen, moulds, cigarette smoke, environmental exposures to harmful chemicals, and air pollution are all risk factors for asthma. Asthma is a complicated condition that can present as disease "episodicity", or times in which symptoms arise and then disappear after therapy. In addition, the illness may be "chronic" in people, as evidenced by the persistence of typical asthmatic clinical signs. Wheezing, breathlessness, rapid breathing, and coughing are all common asthma signs. Multiple factors, like contact to allergens, irritants, pulmonary tract infections with bacteria or virus, sinusitis, physical activity, thunderstorms, and extreme cold, might exacerbate symptoms. Asthma has been classified into phenotypic and/or endotypes based on current advances in asthma pathogenesis [8–10]. This is critical for effective asthma therapy, as advised by a new Lancet panel that describes the discovery of "treatable characteristics" in asthma patients and then precisely addresses these qualities for illness control.

According to studies, the most of asthma episodes are caused by Th2 activation, in which type 2 T-helper cells are mobilised into the airways in reaction to an outside or endogenous stimulus and release high levels of cytokines including IL-13, IL-9, IL-5, and IL-4. IL-4 is engaged in the transformation of B-cell IgE to immunoglobulin E that leads to the secretion of inflammatory intermediaries like cysteinyl leukotrienes and catecholamines, whereas IL-5 is only engaged in the intake of eosinophils that leads to the advancement of the upper airway's allergic rhinitis [11–13]. IL-4 and IL-13, in combination with inflammatory markers, produce contraction of airway muscle, leading in bronchospasm, overproduction of mucus, and enhance influx of immune cell, leading in hyperreactivity of airway and reduction in airway dimension in the lower respiratory tract, reducing airflow. The airway epithelium has been discovered to have a significant function in regulating Th2 responses by generating master moderators such as IL-33, IL25, or thymic stromal lymphopoietin, which govern the production of Th2 mediators and induce asthma to develop early in childhood [14, 15]. Wheezing and airway hyperactivity to nonspecific stimulation characterise the early phases of asthma; nevertheless, later phases (extreme forms) of asthma contribute in airway remodelling with successive recurrences due to enhanced inflammation assisted by systemic variables or other local (infections of bacteria or virus) [16, 17].

1.2.2 COPD

Emphysema, small airway degradation, chronic bronchitis, and chronic asthma are all examples of COPD, which is a unified name for a set of progressing, disruptive, incurable lung diseases. As per the WHO's total prevalence of illness research, there were 251 million COPD patients worldwide, with 90% of them coming from low- and middle-income nations. In 2015, an estimated 3.17 million people died, accounting for 5% of all fatalities, a rise of 11.6% from 1990. In contrast to death, the Centers for Disease Control and Prevention projected a financial impact of USD $32.1 billion in 2010 for health expenses and missed work days due to COPD in the U.S., which is expected to rise to USD $49.0 billion by 2020 [18, 19]. Moreover, the actual figure of COPD cases in the world is already a debatable point, based on the reality that so many asthma incidences in the older people are frequently misdiagnosed as COPD, and the lack of information sets from underdeveloped or developing Middle Eastern and Asian countries, which could bring up the fatality score by several millions. Individuals with any type of COPD encounter a broad variety of complaints, the most common of which is dyspnoea or breathlessness throughout daily routines, which increases with time, whereas people with severe COPD have repeated complications and ER visits throughout the year. This is due to the partial alveoli destruction (emphysema) or the aggregation of inflammatory cells and large amount of mucus in bronchioles (chronic bronchitis), which reduces the gaseous exchange abilities of the lungs and induces blockage to the flow of air, resulting in hypoxemia and consequent failure of organ, particularly in cigarette smokers and exsmoker having to suffer from COPD. Furthermore, individuals with any form of COPD may experience typical symptoms such as persistent cough (dry or wet cough), fatigue, wheeze, and tightness of chest, such symptoms are frequently misinterpreted as age-related [20, 21]. Some people may not show symptoms until the disease has progressed to the point where it is life-threatening. After years of investigation, there is no treatment for regenerating destroyed tissue and restoring pulmonary functioning. Furthermore, COPD is a chronic condition that worsens with age. Current therapies are intended to halt the course of etiopathogenesis and give short term relief to patients, but they are incapable of recovering affected areas' impaired functionality [22].

Tobacco smoking was discovered to be the single largest prevalent risk factor for COPD, as per current databases. Lengthy contact to non-cigarette smoking irritants (e.g., airborne grit particulates, anthropogenic particulates, and metal pollutants) has been linked in aggravation (smokers) or the establishment (nonsmokers) of COPD, according to recent findings, which is still relatively understudied. Furthermore, research suggests the significance of genetic susceptibility, such as alpha-1-antitrypsin (AAT) insufficiency, in the progression of COPD; however, the specific fundamental processes remain unknown. AAT deficient individuals, on the other hand, are more susceptible to pulmonary infections, and hereditary factors account for just 1% of all COPD occurrences, underlining tobacco smoking and air pollution as important contributors [23, 24]. It is worth noting that not all smokers or exsmokers acquire the condition; about 20–30% of smokers or exsmokers suffer

from the disease throughout the course of their lives. Passive smoking was even found among the risk variables for COPD (51.2%, $n = 87$) in the research; however, the specific fundamental processes are yet unknown. COPD is caused by a blockage of airflow and an inflow of inflammatory cells, particularly $CD8^+$ T lymphocytes, neutrophils, and macrophages, into the alveolar and peripheral regions as a result of cigarette smoke or atmospheric particulates/gases. The immune system's reaction to various types of COPD, though, was discovered to be varied [25, 26].

Over mucus generation, elevated inflammatory cells, increased MUC5AC gene expression in responding to secreted serine proteases, higher ROS levels from inhaled smoke, or triggered macrophages characterise chronic bronchitis, which inhibits the air space and causes destruction to adjacent cells, culminating in remodelling (fibrosis) of the respiratory tract and deterioration of pulmonary elasticity, while the emphysema is caused by cigarette smoke. Inhaled smoke increases inflammation in alveolar sacs and the bronchioles, resulting in narrower airway walls and the progressive deterioration of alveolar sacs, resulting in, function recoil, and alveolar structure loss [27, 28]. It is unclear how COPD patients' adaptive and innate immune defenses are activated. Moreover, immune cell MMP, IL8, and CXC overexpression as well as the mediators of proinflammatory secretion such as transforming growth factor beta (TGF-β), leukotriene B4, IL1 (Th1 responses), and TNF-α cause local fibrosis and a disequilibrium of oxidant-antioxidant proportion (ROS/RNS) and are thought to be important variables in disease worsening [29, 30].

1.2.3 Lung Cancer

Lung cancer-related fatality is primarily caused by late diagnosis and ineffective therapeutic approaches in 70% of lung carcinoma patients, who are usually in later stages of the illness (stage III or IV). It is a highly aggressive, quickly metastasizing cancer that affects both men and women. Lung cancer fatality is greater than the cumulative death rate of the other four main types of carcinoma in the U.S., according to statistics (pancreas, colon, breast, and prostate). Smoking histories of 20 years or more appear to be related with a higher risk of progression and death. Tobacco-induced lung carcinoma susceptibility is thought to be largely reliant on competing gene-enzyme connections at the level of procarcinogens, as well as the resulting amount of DNA destruction [31, 32]. As a result, lung carcinoma is thought to be usually avoidable through quitting smoking and prevention. To minimise the unavoidable growth in pulmonary malignancies in nations where smoking has risen, community awareness and support are necessary to limit or eliminate smoking tobacco. Lung carcinoma is the leading source of cancer associated mortality in both women and men throughout the world. According to a research by scientists, roughly 1.8 million new instances of lung carcinoma were diagnosed in 2012, account for 12.9% of all new cancer occurrences. As per the Global Burden of Disease Study 2020, lung carcinoma caused a significant amount of health impact and expenditure throughout the world. According to one investigation, men's cancer

deaths are unrelated to their economic status. Interestingly, the research found that a country's economic progress level is linked to lung cancer deaths in women. Lung carcinoma has a complicated diversity due to its genesis in many sites in the bronchial tree and the varying manifestations of patient signs as well as indications depending on the kind and anatomic site [33, 34]. Lung tumour is conventionally divided into two types: non-small-cell lung carcinoma (NSCLC) (85% of all lung cancers) and small-cell lung carcinoma (SCLC) (15% of all lung malignancies). Giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma are the three types of NSCLCs. Certain histology features and accurate immunohistochemical biomarkers were added to this classification of lung cancer, allowing for a convincing differentiation among preinvasive tumours and aggressive adenocarcinomas. Additionally, the development of molecular characterisation of lung tumours and the ever-expanding arsenal of effective treatments has had a significant impact on how lung carcinoma is categorised today. Even in the same histopathological subtype, findings suggest that lung carcinoma is a collection of molecularly and histologically diverse illnesses [35, 36].

1.2.4 Cystic Fibrosis

The cystic fibrosis (CF) is the greatest prevalent autosomal recessive illness, affecting around 1/3500 births. The majority of individuals show signs and symptoms at birth or shortly after delivery, with respiratory illnesses and low weight growth being the most common. Persistent pulmonary infections and pancreatic failure should lead to a diagnosis of CF. Before to CF newborn testing, however, a clinical odyssey with a sweat test generally followed the ultimate diagnosis. A sweat chloride content of more than 60 mmol/L is considered diagnostic for CF. High salt loss with perspiration and male sterility are two more common illness symptoms. Chronic pulmonary infections caused by particular microorganisms, as well as severe inflammation, can result to bronchiectasis, decreased pulmonary functioning, and finally pulmonary failure [37, 38]. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are common CF pathogens, but some patients will develop infections with more uncommon and difficult-to-treat infectious organisms including *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia,* and *Mycobacterium* further in the illness. Diseases can affect almost all organ and worsen with age, involving allergic bronchopulmonary aspergillosis, haemoptysis, gastrointestinal blockages, nasal polyps, CF-related hyperglycaemia, and liver illness, among others [39, 40].

Autosomal recessive illness is caused by mutations in the CF trans membrane conductance regulator (CFTR) gene, which is situated on the long arm of chromosome 7. The Cystic Fibrosis Mutation Database has found and published over 1400 individual variations, rendering population testing purely using genetic methods unfeasible. Although lung symptoms are the most common cause of morbidity and death, the typical CF phenotype is extremely complicated, encompassing numerous epithelium lined organs. In recent decades, substantial advancement has been

achieved toward a better knowledge of the route that connects CFTR gene alterations to clinical symptoms of CF, especially the processes that underpin the obvious failure of lung defense [41, 42].

1.2.5 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is amongst the very dangerous types of idiopathic intermittent pneumonias, with persistent increasing fibrosis, inexorable decrease in pulmonary functioning, increasing respiratory insufficiency, and a high death rate. Appropriate diagnosis is critical for prognosis and therapy choices. In North America and Europe, a comprehensive assessment of the worldwide prevalence of IPF indicated a rate of 2.8–9.3 per 100,000 annually, with substantially reduced rates in Asia and South America. Among nations, there is significant regional heterogeneity, which might be due to exposure to ecological or professional risk variables. Depending on previous statistics, IPF has a significant fatality rate, with a projected median survival of 2–3 years after diagnosis. Recent data suggests that survivability has not improved. Fatality rates seem to be growing as well, however this might be due to better detection and diagnosis [43, 44]. IPF is characterised by UIP, which is a histological marker. Temporal and regionally variable fibrosis, clustering of fibroblasts and myofibroblasts, and extensive accumulation of unorganised collagen and extracellular matrix, with or without honeycomb cyst development, are all characteristics. While the exact triggers for these activities are uncertain, present theories imply that IPF is the result of an abnormal healing mechanism in reaction to complex interplay among hosts and atmosphere. The "multiple strike theory" proposes that IPF is produced by the combination of a hereditary propensity to abnormal epithelial cell regulation and environmental stressors. Fibrosis is caused by the long-term effects of fibrotic diseases with a known aetiology and causes such as asbestos, immune complexes, medications, or radiation ingested [45, 46].

1.2.6 Tuberculosis

The acid-fast bacterial strains M. tuberculosis causes TB in humans, with the animal-adapted strain M. bovis accounting for a lower number of zoonotic cases (143,000 in 2018). M. tuberculosis is extremely infectious when transferred in aerosols from the airways of patients with active TB by coughing, spitting, or sneezing, despite missing many of the traditional pathogenic elements seen in other pathogenic bacteria such as exotoxins. The pathogenic organism inhalation into the alveoli of the lower airways occurs when a susceptible individual is exposed to droplets harbouring the bacteria. Local macrophages, which are typically the first immune cells to interact with M. tuberculosis in the lungs, internalise the bacteria [47]. Inhibition of a set of pathogenic genes in the bacteria leads in a loss of virulence in an experimental model of tuberculosis, but not a reduction of mycobacterial

proliferation in the lack of stress or famine under optimal in vitro circumstances. Protein kinases, metal transporter, proteases, gene controllers, macrophage activity inhibitors, cellular membrane proteins, lipids metabolism enzymes, and proteins of unknown activity, such as PE and PE PGRS proteins, are among the pathogenic determinants of M. tuberculosis. M. tuberculosis can resist RNS and ROS activity, as well as lysosomal fusion and phagosome acidification, after being phagocytosed by alveolar macrophages [48]. These activities are important for the pathogen's survival in the host in latent TB, as well as for bacterial multiplication, tissue dispersion, and destruction in active TB patients, as well as downstream person-to-person spread. The parenchymal destruction, traction bronchiectasis, bronchostenosis, cavitation, and fibrosis are examples of architectural lung destruction that can occur with respiratory TB [49, 50].

1.2.7 Influenza A Virus Infection

Influenza is a contagious respiratory illness caused by the influenza A and influenza B viruses in humans. The Centers for Disease Control and Prevention (CDC) estimates that influenza virus infection caused 9.2 million to 35.6 million infections and 140,000–710,000 hospitalised in the U. S. among 2010 and 2017. Influenza A viruses produce pandemic seasonal illnesses that kill around 500,000 people each year throughout the world, according to the most current estimates of 291,243–645,832 fatalities each year. Clinical signs of influenza virus infection range from a mild upper respiratory infection with tiredness, muscle aches, headache, coughing, runny nose, sore throat, and fever to serious and, in some instances, lethal pneumonia caused by the influenza virus or secondary bacterial infection of the lower airway [51, 52]. In certain circumstances, influenza virus infection can cause a variety of non-respiratory problems, including heart, central nervous system, and other organ systems. While yearly seasonal epidemics are the norm, rare and unexpected worldwide pandemic outbreak involving nonhuman influenza A virus subtypes do happen. Every 10–50 years, a pandemic influenza outbreak occurs, defined by the addition of a new influenza strain. A viral strain that is antigenically distinct from formerly circulating strains; in humans, the absence of pre-existing protection is frequently linked to the intensity of illness and increased fatality [53].

Human influenza viruses are spread by the pulmonary route, but avian influenza viruses are spread via the faecal–respiratory pathways, faecal–oral, faecal–faecal, or in wild birds. Based on the mode of propagation, the virus infects and replicates in epithelial cells of the pulmonary or digestive tract. Furthermore, human infections of the eye and conjunctivitis have been linked to several avian influenza A viruses, particularly those of the H7 subtype (inflammation of the conjunctiva). In humans, the intensity of infection is linked to viral multiplication in the lower airways, which is followed by significant inflammation caused by immune cell infiltration [54, 55].

1.2.8 COVID-19

A new coronavirus known as SARS-CoV-2 appeared in the Chinese city of Wuhan at the end of 2019 and triggered an epidemic of atypical viral pneumonia. This new coronavirus illness, also known as COVID-19, has spread rapidly throughout the globe due to its high transmissibility. In regard of both the numbers of sick persons and the geographic scope of epidemic locations, it has massively exceeded MERS and SARS. COVID-19 is still spreading across the world, posing a serious risk to human health [56, 57]. The first individual with SARS-CoV-2 infection was detected with pneumonia of unknown aetiology, with signs identical to infections of SARS-CoV and MERS-CoV and was hospitalised and died. Additionally, patients who required ICU admission had greater TNF-α, MIP-1A, MCP-1, IP-10, and G-CSF, levels than others who did not, suggesting that the cytokine outburst was connected to illness intensity [58–60].

SARS-CoV-2 infection tends to affect people of various ages, with the average age of infection being about 50 years old. Clinical symptoms, on the other hand, vary with age. Most young individuals and adolescents have relatively minor illnesses (moderate pneumonia or non-pneumonia) or are asymptomatic, but elderly men (>60 years old) with co-morbidities are more prone to suffer serious lung infections that needs hospitalisation or even death. Pregnant women did not have a greater risk of illness than non-pregnant women [61, 62]. But it was an isolated incident, confirmation of SARS-CoV-2 transplacental transfer from an affected mother to a newborn was described. Fever, tiredness, and a dry coughing are the main typical signs of infection. In investigations of patients in China, less typical signs include chest discomfort, diarrhoea, vomiting, nausea, haemoptysis, headaches, sore throat, sputum secretion, hunger, and fever. Patients in Italy also experienced self-reported olfactory and taste abnormalities. Following an incubation period of 1–14 days (most often around 5 days), most patients displayed symptoms of sickness, pneumonia, and difficulties in breathing occurred within a median of 8 days following disease start [63, 64]. COVID-19 indications that are serious, like acute respiratory distress syndrome (ARDS) and severe pneumonia, are connected to the virus's activation and secretion of cytokines and chemokines, which results in a "cytokine storm" which induces destruction and inflammation, especially in the lungs. COVID-19 produces IL-1, LTs, IL-2, TNF-α, IL-6, GM-CSF, IL-12, and other chemokines due to NF-κB expression in many cells such as the gastrointestinal system, lungs, kidney, liver, central nervous system, and cardiovascular system. Risks associated with T, such as a greater death rate [65, 66].

1.2.9 Conclusion

Lung diseases have a huge impact worldwide and are becoming more common due to the ageing population and the lack of appropriate interventions to minimise the risk factors that contribute to the progression of these diseases. Asthma, COPD, fibrosis, COVID-19, and influenza-like lung diseases are becoming life-threatening

and dangerous, so effective treatment approaches and adequate prevention are becoming a challenge for researchers.

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