Introduction

The entrance of a specific and sufficient volume of an organism into the lung parenchyma is called pneumonia, causing acute infection of the lower respiratory system. Pneumonia develops in response to different agents, including viruses, fungi, and bacteria (1,2).

Various risk factors such as diseases that compromise the immune system, advanced age, lung cancer, diabetes, and the like increase the risk of developing pneumonia (2).

Streptococcus pneumonia is one of the most common community-acquired pneumonia (CAP) bacterial pneumonia (7,8). In addition, Mycoplasma pneumonia is considered one of the most common atypical bacterial pneumonia; aging increases the chance of developing this type of pneumonia (2).

Legionella pneumonia is also one of the most pathogenic and infectious atypical bacterial pneumonia; if diagnosed late and left untreated, it causes the spread of the disease across the person’s body (2).

The treatment of bacterial pneumonia in developing countries is usually based on medical history and physical checkups, but determination of the etiology of the disease is rare (6).

Alveolar macrophages have phagocytotic and
antibacterial activities. Cigarettes can affect the normal functioning of the respiratory system. Indeed, inhaling cigarette smoke causes changes in the function and morphology of alveolar macrophages (9,10). Further, cigarette causes an increased risk of developing viral and bacterial infections (11).

Cigarette contains around 5000 different chemicals. One of them is nicotine, which also causes the suppression of the immune system through cholinergic anti-inflammatory activation (12).

Considering that cigarette smoke can cause extensive damage to the respiratory and immune systems of the body, the present review study aimed to investigate the effects of cigarette smoking on various bacterial pneumonia.

Methods
In this narrative review study, papers were collected from several databases, including ScienceDirect, Scopus, PubMed, and Google Scholar search engine. The applied keywords were bacterial pneumonia, Staphylococcus, Streptococcus, Haemophilus, Pseudomonas, Legionella, Mycoplasma, Chlamydia, tuberculosis, and cigarette and their titles and abstracts were searched based on the aim of the study. Papers were searched with no time constraints. The inclusion criteria were English papers and the availability of their full text. Overall, 90 relevant papers were chosen after a primary investigation of the titles and abstracts of 140 papers.

Results
Effect of Cigarettes on the Respiratory System
The respiratory system is part of the body that provides the oxygen required by the cells while excreting the carbon dioxide generated by the cells from the body. The diseases of the lungs as the most important parts of the system occur earlier than assumed (13). Cigarette smoking is a harmful habit that has spread and expanded as a pandemic worldwide and heavily affects the respiratory system. It causes a reduced lifespan of smokers, increases healthcare costs, and reduces productivity along the lifespan. Generally, cigarette smoking is one of the most dangerous factors found in the incidence of acute respiratory system diseases such as chronic obstructive pulmonary disease and respiratory infections and is even the cause of increased mortality rates caused by it (14,15).

Cigarette smoking is associated with various neurological and cardiovascular diseases. Cigarette smoke not only affects the smokers themselves but also negatively influences the health of other non-smokers (16). Exposure to cigarette smoke can induce mechanisms that cause adverse health effects and impairments in response to some treatments, including cigarette-associated airway inflammation and asthma, tissue regeneration, insensitivity to corticosteroids, and systemic low-grade inflammation (17).

Globally, adults suffering from asthma have often a history of cigarette smoking. Smokers have a risk factor for the development of asthma and worse clinical outcomes, including suboptimal asthma control, increased aggravation, reduced acceleration in the lung function, chronic obstruction of the airway, further comorbidities, and higher all-cause mortality. It is our duty to recommend to all smokers with asthma to quit smoking. However, it is not always feasible, raising the issue of substituting conventional cigarettes with cigarettes that need no nicotine for combustion such as E-cigarettes (18). Nevertheless, currently, there is no scientific evidence and definitive studies suggesting less harm caused by E-cigarettes compared to typical cigarettes (19).

Cigarette Smoking and Drug Resistance
Cigarette smoke causes an increased risk of developing viral and bacterial infections (20). Resistance to antimicrobes is one of the concerns of healthcare providers. According to previous evidence, the extent of antibiotic consumption in cigarette smokers for the treatment of bacterial infections is considerable (21,22). Antimicrobial resistance can affect different personal, economic, and public health aspects (23).

Cigarette smoking may cause bacterial resistance through mutation in part of the bacterial genes that perform antibiotic coding and through the formation of biofilm and limiting access to antibiotics to the pathogenic agents (20).

Typically, exposure to cigarette smoke can cause Pseudomonas aeruginosa infection; most of its strains show drug resistance, whose mechanism is poorly understood (22).

The prevalence of Staphylococcus bacterial infection was 26.3%; out of this value, 35.9% demonstrated resistance to methicillin. In this study, exposure to cigarette smoke (through parents) was one of the effective factors in this resistance to methicillin (24).

In a study on Helicobacter pylori bacterium, the effectiveness of treatment among cigarette smokers was far greater in the group who took bismuth in addition to omeprazole and amoxicillin when compared with those who did not use bismuth. Nevertheless, the extent of antibiotic resistance did not differ significantly between these two groups (25).

In another study, the effect of CAP bacterial infection among children was 5.6%; most bacteria represented resistance to the first and second lines of antibiotic treatment. Furthermore, the extent of CAP bacterial infection prevalence was 16.7% among children who were exposed to the cigarette smoke of their parents (26).

Cigarette and Tuberculosis
Tuberculosis falls in a group of bacterial infections that are
developed, in most cases, by *Mycobacterium tuberculosis* bacterium and is considered one of the most important infectious diseases worldwide (27-29).

Around one-fourth of the world’s population is exposed to this bacterium, and although great advances have occurred against this bacterium, the disease caused by it is still considered among the 10 top reasons for mortality worldwide (27,30). According to the WHO statistics, around 10 million people suffered from tuberculosis and 1.4 million of them died in 2019 (31).

Tuberculosis is a communicable disease that spreads through the sneezing and coughs of the patient and can be spread to another person (27,29). The mucous smear test is used as a method of disease diagnosis, as well as an indicator of the success or failure of tuberculosis treatment (32).

Numerous risk factors affect this disease, including human immunodeficiency virus, diabetes, addiction to illicit drugs, alcohol consumption, being underweight, and cigarette smoking (9,27).

Cigarette smoking exerts adverse effects on the respiratory system and increases the risk of respiratory disease (9,33). The alveoli of the respiratory system have macrophages, whose function is to remove microorganisms such as *M. tuberculosis*. The normal functioning and morphology of macrophages are impaired, and the antibacterial activity of alveoli is inhibited in cigarette smokers (10). Smoking also has an inhibitory effect on the immune system of the body, causing diminished immune response (10,34).

Cigarette smoking causes the development and increased risk of developing tuberculosis infections. Additionally, cigarette smokers may experience more severe infections compared to non-smokers and show poorer treatment outcomes (35-37).

The results of a study revealed that the prevalence of tuberculosis disease was 31.5% and 22.8% in cigarette smokers and those with a history of cigarette smoking, respectively (34).

Furthermore, cigarette smoking is considered one of the effective factors in treatment failure, increased drug resistance, and increased development of disease in patients with tuberculosis (27). Indeed, in a study, cigarette smoking was 2.58 times greater in those who failed in the treatment of this disease when compared with non-smokers. Nevertheless, this finding was not statistically significant which may have been due to the small sample size (27).

In another study, treatment failure was 1.5 times greater in current smokers in comparison to those with a history of smoking (9).

In another study on 25-69-year-old urban and rural men, the prevalence of tuberculosis-induced mortality was around four times higher in smokers compared to non-smokers (38).

Likewise, in the study by Masjedi et al, the mortality rate was 19% and 11.3% among smokers and non-smokers, respectively (39).

The cigarette is also a risk factor for posttreatment disease deactivation, implying that the bacterium remains latent in the body and may cause a relapse of the disease posttreatment (33).

**Cigarette and Legionella**

Legionella is a kind of Gram-negative, anaerobic, and intracellular bacillus. This bacterium is widely found in nature, especially in watery and moist environments, though there are members of this genus who do not belong to the normal human flora (40). From among the Legionella species, Legionella pneumophila is the major cause of pathogenicity in humans worldwide (41). Legionella enters the lungs through the respiratory tract without infecting the pharyngeal mucus and causes legionnaires’ disease. People may suffer from this disease and develop it at any age. Nevertheless, middle-aged, elderly, and those with compromised immune systems are more at risk of this disease. Particularly, the chance increases for cigarette smokers or those with chronic pulmonary disease. If left untreated, this disease can be fatal, and even insufficient or delayed antibiotic treatment has a poor prognosis in legionella pneumonia. Fluoroquinolones (levofloxacin or moxifloxacin) or macrolides (preferably azithromycin) are the first line of treatments recommended for treating legionnaires’ disease, though the preferred treatment is erythromycin (42-44). One of the main risk factors in all respiratory infections, especially legionnaires’ disease, is cigarette smoking. The nicotine in cigarettes, when defending the lungs and especially alveolar macrophage immune responses, weakens the cells that are effective in defending the lungs against infection, causing the prolongation of the duration of this disease treatment (45,46).

**Cigarette and Staphylococcus**

*Staphylococcus* is one of the Gram-positive bacteria, whose different pathogens cause staphylococcal infection. These bacteria usually colonize the skin and mucous spaces of the human host (47). Nevertheless, there is a chance of entrance to the body through cuts. It can also cause a wide range of diseases, ranging from relatively severe skin infections to fatal pneumonia and sepsis (48). Staphylococcal infections will probably cause a major challenge in pneumonia treatment in the future (49).

After the detection of this bacterium as the pathogenic agent, discharge of the infected area through surgery is performed for the treatment antibiotic therapy and if required and possible. Nevertheless, many strains of this bacterium are antibiotic resistance. Meanwhile, infections resulting from the strains of this resistant pathogen are growing, further complicating the treatment. Thus,
the prevention of *Staphylococcus* infections is crucial (50). For those who have this type of infection, fighting this disease should occur through their own immune system; now if that system is weak or threatened, the disease grows rapidly. A kind of golden *Staphylococcus* is resistant to beta-lactam antibiotics such as penicillin (methicillin, nafcillin, and oxacillin) and cephalosporins; thus, these antibiotics have no effect on the treatment of its resulting infections. Indeed, the antibiotic resistance of this pathogen has made it highly hazardous which can even cause death. Nevertheless, there is no effective vaccine available against it (48-51). There is the possibility of developing *Staphylococcus*-induced infection in all people. However, those with weaker immune systems such as pregnant women, children, and patients suffering from chronic diseases or compromised immune systems, along with addicts consuming intravenous illicit drugs, are at high risk of infection. New tests about the strains of methicillin-resistant *Staphylococcus aureus* show that cigarette smoke makes this bacterium more persistent, aggressive, and resistant to some antibiotics. This is because nicotine, which is a major component of cigarettes, interacts with *S. aureus* (52). Cigarette smokers’ exposure to *S. aureus*, through the increased effect of adhesion and formation of biofilm, may induce survival and pathogenesis-associated pathways and increase the risk of infection (47). It has been observed that the mean nasal carriage of *S. aureus* is higher in cigarette smokers compared to their healthy non-smoker counterparts (53). Cigarette smoking, through reducing cellular responses to pathogen-associated patterns, causes the suppression of the immune system and the chronicity of microbial colonization (54). Direct exposure to cigarette smoke increases the risk of severity of diseases and respiratory tract infections, as well as other aggressive infections. One of the examples is an aggressive pneumococcal disease, which is more common in cigarette smokers by 2-4 times (55). Cigarette smoking increases the risk of development, prevalence, and severity of the infection resulting from this bacterium with a mechanism involving adaptation to difficult conditions such as small adhesive and persistent colonies, complicating the treatment for physicians.

**Cigarette and Streptococcus**

*Streptococcus pneumonia* is a Gram-positive bacterial pathogen, which is the main cause of bacterial pneumonia, other invasive diseases, and community-acquired respiratory tract infections in less developed countries in both children and adults (56-58). This bacterium can spread from the upper respiratory tract to the sterile regions of the lower respiratory tract, thereby causing pneumonia (59). In case the infection is left untreated, it can cause serious complications since *Streptococcus* is an important pathogen of aggressive diseases such as sepsis, meningitis, and pneumonia, or even inflammatory diseases such as nephritis or rheumatoid fever (56). Pharmacotherapy is of high importance since it can reduce the risk of development of complications. Up until 50 years ago, this pathogen was uniformly sensitive to penicillin and other antibiotics (57). However, nowadays, antibiotic sensitivity is no longer predictable, and the rational use of antibiotics and the diversity of their usage in respiratory infections can limit the possibility of antibiotic resistance (60).

Today, the antibiotic resistance of *Streptococci* to penicillin has increased, which is because new antibiotics such as vancomycin, co-amoxiclav, as well as third and fourth-generation cephalosporins are used for treatment. However, some beta-lactams (amoxicillin, cefotaxime, and ceftriaxone), respiratory fluoroquinolones, and Telithromycin can still function effectively against the drug-resistant strains of this pathogen (57). Exposure to cigarette smoke, given that it contains a wide range of chemicals, irritates the respiratory tract and causes cellular damage, pneumonitis, and diminished pulmonary function. It also increases sensitivity to respiratory infection. For example, it elevates the risk of developing pneumococcal and aggressive infection resulting from *S. pneumoniae*. This is followed by impaired pulmonary clearance, and thus the disease will be more severe (61-63). According to observations, cigarette smoke considerably increases the capacity of biofilm formation by *S. pneumoniae* and the extent of pneumococcal colonization, thereby causing enhanced persistence of Pneumococcus and antibiotic resistance (54). Chronic cigarette smokers develop more severe pneumococcal pneumonia infections compared to non-smokers (64).

**Cigarette and Pseudomonas**

Pseudomonas is a Gram-negative bacillus bacterium. This aerobic organism has a large diversity and is among typical residents of soil, freshwater, and marine environments. *P. aeruginosa* is of more importance since it is present commonly and in small values in the normal intestinal flora and skin surface of humans, and is the most important pathogen of this group. This bacterium is an opportunistic nosocomial pathogen and is the cause of many human infections (65). Control of this pathogen using disinfectants is extremely difficult and has also great resistance to a wide range of antibiotics. All these seriously challenge its elimination (66). Most pseudomonas species are naturally resistant to penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and most beta-lactam antibiotics, and this resistance is progressively increasing (67). Meanwhile, cigarette smoking and the smoke cause increased antibiotic resistance and higher bacterial severity in this pathogen (68). When isolating drug-resistant bacteria from the upper respiratory tract in cigarette smokers and non-smokers, it was observed that the extent of drug-resistant bacteria was higher in
smokers. This indicates the effect of cigarettes on the antibacterial resistance of bacteria and demonstrates that these individuals are at higher risk of pulmonary infections. Furthermore, the cigarette itself is a risk factor for infectious diseases such as bacterial pneumonia (22).

Regarding the mechanism of cigarettes in increasing the chance of developing respiratory system infectious diseases, as well as their more severe manifestations, it suppresses the antibacterial activities of macrophages and affects the bacteria that are present in the airway tract. In turn, it also reduces human primary normal bronchial epithelial cells (69-71).

**Cigarette and Chlamydia**

Chlamydia is a pathogenic Gram-negative bacterium. It is an obligate intracellular pathogen, and only humans become infected with *Chlamydia pneumoniae*. This bacterium is a typical agent of both upper and lower respiratory infections in adults worldwide. Most respiratory tract infections (around 70%) resulting from *C. pneumoniae* are either asymptomatic or have mild symptoms. However, a small share of them (30%) are responsible for more severe respiratory diseases such as community-acquired pneumonia. Pneumonia is an infection of the lung parenchyma, which is developed by various pathogens, including the species of chlamydia bacterium (72). The disease is more severe in elders and those with underlying pulmonary disease. Chronic infection of *C. pneumoniae* can be expressed as a cause of adult asthma (73). Tetracyclines and erythromycin have so far been the most common drugs used in the treatment of *C. pneumoniae* infection. Other effective antibiotics include new macrolides, ketolides, and fluoroquinolones (74). *C. pneumoniae* is hardly diagnosable (75). There is evidence suggesting the relationship between cigarette smoking and seropositivity of *C. pneumoniae* infection (76). Cigarette smoke causes the chronic infection of endothelial cells by *C. pneumoniae* (77). In turn, *C. pneumonia* pulmonary infection is associated with an increased risk of developing asthma and causes a regulated immune response by dendritic cells. In the lungs of smokers with *C. pneumonia* infection, there are plasmacytoid cells that play a key role in the immune system, suppressing the environment of these individuals and causing increased risk of development and severity of this disease (78). Exposure to cigarette smoking is a highly important risk factor for infection with *C. pneumonia*, causing more inflammation and chronic inflammatory changes resulting from the infection (79).

**Cigarette and Mycoplasma**

The mycoplasma species are the smallest self-replicating organisms on the Earth. They can live without oxygen and have different appearances since they lack walls. *M. pneumonia* is considered one of the causes of pneumonia in humans (80,81). This bacterium usually causes upper respiratory tract infections. However, it can also cause pneumonia, and *M. pneumonia* is indeed one of the most common causes of bacterial infection in both upper and lower respiratory tracts (82,83). Considering that mycoplasma has no cellular wall on its membrane, it causes the insensitivity of this bacterium to antibiotics that are effective on walls, including penicillins and other antibiotics that affect this structure. Nevertheless, they are sensitive to different types of wide-spectrum antibiotics. Macrolides are also widely used for respiratory tract infections. Eradication of mycoplasmas from any host through antibiotic treatment is difficult because of resistance to antibiotics or the aggression of some mycoplasmas to eukaryotic cells. This is particularly true in those with suppressed or compromised immune systems in which the chance of disease development is high (84). In addition, cigarette smokers are highly susceptible to developing respiratory tract infections resulting from bacterial pathogens, including mycoplasma. This is because cigarette smoke has a direct impact on microbial pathogens, increasing the probability of developing infectious diseases, microbial severity, and antibiotic resistance (20). Cigarette smoking is associated with the presence of *M. pneumonia* in circulating leukocytes, causing the pro-inflammatory effects of cigarettes (85). Cigarette smoke, in addition to the function of alveoli macrophages, which are the first line of defense against invasive respiratory pathogens, also negatively influences the lung parenchyma, causing impaired bacterial clearance (42,86). Generally, cigarette causes the aggravation of respiratory tract-associated diseases, which is a progressive and major challenge worldwide (87).

**Cigarette and Haemophilus**

Haemophilus influenza is a bacterial infection and one of the important pathogenic agents in the respiratory system. Most strains of this influenza are opportunistic and live in the host body without inducing disease. Exposure to the bacterium is extensive, and the infection can occur through the respiratory system (88). Under special conditions such as viral diseases, diminished immune system function, and chronic inflammation such as allergies, the bacterium becomes activated and can cause serious and acute infections, including otitis media, sinusitis, pneumonia, and acute bronchitis attacks which mostly occur in children and neonates (88). This bacterium is categorized into two those classifiable with polysaccharide capsules and the non-classifiable group which lacks capsules. Non-capssulated strains have less aggressive features since they are mostly the normal flora of the upper respiratory system in many individuals, though they can cause opportunistic infections. The antibiotic treatment does not function very successfully
Cigarette smoking and bacterial infection

for this group (89). Haemophilus influenza is now preventable by vaccination. Nevertheless, the incidence of resistance or decreased sensitivity to many antibiotics in many strains of this organism is also observed with the generation of beta-lactamase enzymes or changes in penicillin-binding proteins (90). Meanwhile, in more severe cases of infection, cefotaxime and ceftriaxone are prescribed, while ampicillin, sulbactam, second- and third-generation cephalosporins, or fluoroquinolones are used in non-severe cases (91). Macrolides are used in patients who are sensitive to the beta-lactam antibiotic group (92). The bacteria inside the respiratory tract play a key role in the inflammation of the airways. Chronic disease of airways associated with the inhalation of harmful substances such as cigarette smoking is a highly important health issue. This is because exposure to cigarette smoke impairs the phagocytosis of alveolar macrophages, causing numerous pathological changes, and is one of the disease-predisposing factors (93). Among non-capsulated Haemophilus influenzae as the most common respiratory bacterial pathogens, there is a direct relationship between the colonization of the lower airways, the obstruction level of airways, and the extent of cigarette smoking (94). Cigarette smoke increases antibiotic resistance and complicates the treatment. It also leads to the aggravation of Haemophilus influenza inflammation through inducing inflammatory swelling. It also delays the recovery or aggravates the course of the disease (95,96).

Conclusion

Based on different results, previous evidence confirmed a positive relationship between smoking and exposure to cigarette smoke with effects on the respiratory system, increasing the severity of bacterial pneumonia.

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Competing Interests

None declared.

Ethical Approval

Not applicable.

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