The Effect of Smoking on the Increase of Infectious Diseases

Khadijeh Ahmadi⁎, Zahra Gharibi, Parivash Davoodian⁎, Hamed Gouklani, Mehdi Hassaniazad, Nahid Ahmadi

⁎Correspondence to Khadijeh Ahmadi, Infectious and Tropical Diseases Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
Tel/Fax: +987633346994, Email: khadijeh.6482@yahoo.com
Parivash Davoodian, Infectious and Tropical Diseases Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
Tel/Fax: +987633346994, Email: parivashdavoodian@yahoo.com

Abstract
Smoking is a well-known major risk factor for respiratory tract and other systemic infections. The World Health Organization estimates that between 2000 and 2025, about 9% of deaths will be caused by tobacco use, and more than half of all smokers die from smoking-related diseases. Smoking can damage almost all organs of the human body and is a major risk factor for respiratory infections and other infectious diseases. Smoking can increase the risk of respiratory infections through various mechanisms, which include changes in the structural, functional, and immune defenses of the host. Smoking is one of the most serious public health problems in the world. Promoting smoking cessation is the most practical and economical preventive measure to reduce the severity of tobacco-related infections. In this study, we investigated the role of smoking in increasing the risk of bacterial, fungal, viral, and parasitic infections. We also evaluated various mechanisms by which smoking increases the risk of tobacco-related infections.

Keywords: Smoking, Infection, COPD, CAP, Respiratory tract

©2022 The Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
the oral-respiratory tract but can also lead to antibiotic resistance. In addition, exposure to cigarette smoke was reported to be associated with the changes in the microbial flora of the body (8).

In summary, smoking is associated with a variety of changes in the functioning of the cellular and humoral immune systems. These changes include decreased levels of circulating immunoglobulins, decreased antibody responses to specific antigens, decreased CD4 + lymphocyte counts, increased CD8 + lymphocyte counts, decreased phagocyte activity, and decreased proinflammatory cytokine release (9). The effect of smoking on the immune system is not well known. Some researchers believe that there are antigens in cigarettes that can lead to the formation of antigen-antibody complexes. These complexes can cause pulmonary and environmental changes in the responses of the humoral and cellular immune systems (10). The antigen-antibody complexes may cause local changes in the immune status of the saliva and bronchoalveolar fluid and predispose individuals to respiratory infections (9). Cigarettes affect both innate and adaptive immunity and play a dual role in regulating immunity by intensifying pathogenic immune responses or weakening the immune system. Cigarette-affecte

**Tobacco-Associated Microorganisms**

Tobacco-related microbial elements include bacteria, bacterial spores, fungi, fungal spores, cell wall components (some glucans and flagella), and a variety of bacterial and fungal toxins. These microbial flora are associated with tobacco during the manufacturing process. In many reports, processed tobacco from various brands of cigarettes carries 15 different classes of bacteria and a broad range of potential pathogens such as *Serratia, Acinetobacter, Burkholderia, Bacillus, Clostridium, Staphylococcus,* and *Pseudomonas* species, as well as *Mycobacterium avium* (2,15).

**Reasons for Increased Risk of Infection in Smokers**

The nasopharyngeal flora of smokers contains fewer aerobic and anaerobic organisms and more pathogens such as *S. pneumoniae, H. pneumoniae,* Influenza virus, *Moraxella catarrhalis,* and *Streptococcus pyogenes* compared with that of non-smokers. The formation of microbial colonies in the upper respiratory tract can be the result of the effect of cigarette smoke on this system (16,17).

Evaluations have shown that bacterial colonies are seen in the lower respiratory tract of smokers, whereas such an environment was previously considered to be sterile. Although there is no noticeable difference between healthy smokers and non-smokers, serious differences are found in the microbiome of patients with advanced COPD. The number of bacteria belonging to *Lactobacillus* and *Burkholderia* species shows a significant increase in the lower respiratory tract of patients with COPD (1,18,19). Cigarette or tobacco smoke increases the risk of infectious diseases through the following mechanisms.

**Effect of Smoking on the Respiratory Tract**

Smokers and those exposed to sidestream smoke are at increased risk for viral and bacterial infections of the upper and lower respiratory tract. The most common bacteria that infect the respiratory tract are *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus, Legionella pneumophila,* and *Mycobacterium tuberculosis.* Smoking, as a mediator, has a direct role in strengthening the growth mechanisms of bacteria (1). The predominant viral infections are caused by rhinovirus, influenza, and varicella pneumonia. On the other hand, researchers believe that the mechanisms of susceptibility to infection in smokers may include changes in the structural, functional, and immunological defenses of the host, especially the mucociliary escalator and resident alveolar macrophages being vulnerable (14).

The role of smoking in increasing the risk of respiratory infections was investigated based on the following subjects:

1. Tobacco-associated microorganisms
2. Damage caused by smoke to the respiratory system

**Influence on Mucociliary Escalator**

Mucociliary escalator is a layer of hydration above the lung tissue that entraps and removes particles and pathogens from the lower airways. The mucociliary escalator is composed of mucus and the cilia in the respiratory epithelium. It removes particles and pathogens by the mechanical actions of cilia and cough. The ciliary dysfunction, excessive mucus secretion, and
the disruption of epithelial cells are the harmful effects of cigarette smoke that enable pathogens to descend into the lung. The upper respiratory tract has microbial flora while in the healthy lung, the lower airways are effectively sterile (1,20).

**Biofilm Formation**

Biofilms occur in 60% to 80% of all bacterial infections. Biofilms are communities of microbes embedded in an extracellular matrix of polymeric materials, mainly polysaccharides, proteins, and nucleic acids, that insulate potential pathogens against host defense and antibiotics (21). The function of the biofilm is to protect pathogens against the host’s defense system and antibiotics. Pathogens remain inactive within the biofilm, and when their environmental conditions are more favorable, they begin their destructive activity. Smoking leads to biofilm-associated diseases, such as community-acquired pneumonia (CAP), otitis media, vaginosis, and chronic periodontitis (22).

Studies show that exposure to cigarette smoke activates the ability for biofilm formation by some important human pathogens such as *Pseudomonas aeruginosa*, *Streptococcus mutans*, *Klebsiella pneumonia*, *S. aureus*, and *Porphyromonas gingivalis* (23).

**Cigarette and Antibiotic Resistance**

Antibiotic resistance is spreading rapidly around the world, affecting the health of millions of people and costing billions of dollars in the economy. Potential factors influencing the prescription of antibiotics, such as tobacco use, can significantly affect this public health crisis (21). Some studies have shown that the effectiveness of antibiotic therapies in smokers is limited. Biofilm formation due to smoking not only restricts the access of antibiotics to pathogens but also neutralizes the interactions between the host defense and antibiotics (21,24). The prevalence of opportunistic pathogens such as *H. influenzae*, *S. pyogenes*, *S. pneumoniae*, and *M. catarrhalis* in smokers is much higher than in non-smokers (25). Cigarette smoke has a devastating effect on the upper respiratory tract. Tobacco smoke is one of the factors leading to gingivitis and leads to enhanced colonization of pathogens in the subgingival area and among the patients with an infectious diagnosis, smokers had 20% to 30% higher odds of receiving antibiotics than non-smokers. Tobacco use can be associated with higher antibiotic use, which can increase antimicrobial resistance in the community (24).

**Infectious Diseases Related to Smoking**

Global estimates from 2017 indicate that there were approximately 490 million incident cases and 1.34 million deaths due to infectious respiratory diseases among adults aged 35 to 74 years. Of these, 22.5% (approximately 300,000 deaths) were attributed to smoking (26). Smoking is associated with infectious diseases that lead to increased prevalence and mortality and increases the risk of various infections through a dose-dependent mechanism. COPD is characterized by poorly reversible airflow obstruction and is associated with emphysema, fibrosis, mucus hypersecretion, and persistent colonization of the lower airways by opportunistic pathogens (2, 27). Patients with COPD have a stable but gradually deteriorating condition and suffer from periodic attacks due to infections. Smoking is a significant risk factor for pneumococcal pneumonia in patients with COPD. Although smoking and smoking-related diseases are associated with a higher risk of infection, most treatments are performed solely to reduce inflammatory parameters without considering the presence of persistently colonized microorganisms (3,28).

Acute respiratory tract infection (ARTI) and particularly CAP are the most important respiratory infectious diseases related to smoking, especially in patients with COPD (29). CAP is one of the leading causes of hospitalization, and its mortality rate is high. CAP-related pathogens include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *S. pneumoniae*, and respiratory viruses. *S. pneumoniae* is the most well-known pathogenic strain isolated from CAP patients, especially in invasive pneumococcal disease and septic shock (14,29). Norty et al have proven that smoking is one of the strongest independent factors leading to severe respiratory diseases (30). The risk of CAP in smokers is 4.1 times higher than in non-smokers (95% CI: 2.4 - 7.3). Additionally, the risk of CAP in secondary smokers is 2.5 times higher than in non-smokers (95% CI: 1.2 - 5.1). Smoking cessation will definitely reduce the risk of CAP. People who have quit smoking for 4 years have a much lower risk (OR = 0.39, 95% CI, 0.17-0.89 CI) than people who have quit for less than 1 year (31). ARTI is a major cause of morbidity and mortality worldwide. In a general analysis, 70%-80% of acute respiratory infections are caused by viruses. Rhinovirus, coronavirus, adenovirus, influenza and parainfluenza virus, and respiratory syncytial virus are the most important pathogens. The remaining 20-30% of these infections are attributed to bacteria. Numerous studies show that smoking increases the risk and recurrence rate of upper respiratory tract infections, while smoking cessation can reduce the incidence and severity of these infections (14). Exposure to second-hand smoke was found to be a significant risk factor for ARTI in children, which can increase the odds by 4.67 compared to children who were not exposed to second-hand smoke (32). Blake et al found that the risk of ARTI in non-smokers was 1.46 times lower than in smokers (33).

**Smoking and Bacterial Infection**

Active smokers and those exposed to second-hand smoke...
have a high risk for bacterial infections. Bacterial infections associated with tobacco smoking include pneumonia, nasopharyngeal and respiratory tract infections, cystic fibrosis, bacterial meningitis, Legionnaires’ disease, bronchitis, tuberculosis, otitis media, post-surgical and nosocomial infections, and *Helicobacter pylori* infections (25).

Smoking is one of the main causes of pneumococcal pneumonia, especially in patients with COPD. Pneumonia weakens mucosal tissue through the ethanolic mechanism. Studies show that cigarette smoke prevents phagocytosis through the alveolar macrophages, with the modulatory effect of complementary pneumonia. On the other hand, the excretion of non-opsonizing bacteria or macrophores with IgG coating does not change. As a result, the body's efficiency in repelling respiratory bacteria decreases. Many studies have provided ample evidence of a close link between smoking and various respiratory illnesses. Various pathogens such as *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae*, and several other respiratory viruses are involved in the development of CAP. Smoking in the elderly increases the risk of CAP by 2.3 to 3.1 times compared to non-smokers. Five years after quitting smoking, the risk of developing CAP in former smokers is about the same as in non-smokers.

Parental smoking increases the risk of bacterial infections such as otitis media, meningococcal meningitis, and lower respiratory tract infections in 2-year-olds, especially pneumonia caused by *S. pneumoniae* (8). The results of a cohort study showed that children under 5 years of age who had smoking parents were 2.5 times more likely to develop pneumonia and were 2.3 times more likely to develop other severe diseases (34).

*Helicobacter pylori* is a major pathogenic factor for gastroduodenal ulcer disease and gastric carcinoma. Smoking is significantly associated with increased *H. pylori* infection and decreased therapeutic efficacy. As the prolonged infection increases the risk of gastric cancer, the profound effect of smoking on this infection can be understood (35). In the study conducted by Namiot et al on 142 *H. pylori*-positive peptic ulcer patients, treated with OAT-omeprazole and amoxycillin, detailed information on smoking and drinking habits was obtained from all subjects. It was found that both smoking and drinking can affect the efficacy of *H. pylori* eradication. Smoking and alcohol consumption habits are important and noteworthy when the drugs for *H. pylori* eradication are selected (36).

**Smoking and Fungal Infections**

Many studies have introduced an association between smoking and the incidence of *Candida albicans* infection. Cigarette smoke exposure can lead to the pathogenesis of oral diseases such as *C. albicans* infection by suppressing host immune and antioxidative response (37). Smoking alone, or in combination with other factors, is not only a known risk factor for oral candidiasis but also a risk factor for invasive fungal infections, including *Cryptococcus neoformans* and *Aspergillus* spp. infections (38). The main risk factors for invasive fungal infections include HIV infection, primary immunodeficiencies, chronic kidney disease, neutropenia, diabetes mellitus, severe burns, influenza infection, and corticosteroid treatment. These people should implement smoking cessation strategies (38). In the case of cryptococcosis, there is a strong association between smoking and infection with *C. neoformans* and *Cryptococcus gattii* in HIV-infected smokers and at-risk individuals (39). Smoking is harmful to the general public, but it is a major risk factor for people with weakened immune systems, especially those with HIV infection. Smoking-induced pulmonary iron loading may predispose individuals with HIV-1 infection to an increased risk of infection caused by a range of obligatory or facultative intracellular pathogens, including *C. neoformans*. Therefore, people with HIV infection should be strongly advised to refrain from smoking (40). However, our previous studies showed that smoking had no significant effect on infections associated with diabetic foot ulcers. Additionally, it did not have a significant direct effect on AIDS and hepatitis C infections in the study conducted in Hormozgan province. Nevertheless, smoking was associated with higher rates of high-risk sexual behaviors that can have an indirect effect on the increase of infectious diseases such as AIDS and hepatitis C. However, these studies have been local and limited (41, 42).

**Smoking and Viral Infections**

Viral infections associated with tobacco smoking include common cold, acute respiratory syndromes (MERS, SARS, and COVID-19), influenza, human papilloma virus (HPV) infection, varicella, and human immunodeficiency virus (HIV) infection (9). Large epidemiological studies support the association between smoking and the prevalence of colds and lower respiratory tract symptoms. This century has seen pandemics of Middle East respiratory syndrome (MERS), H1N1 influenza virus, severe acute respiratory syndrome (SARS), and now coronavirus 2019 (COVID-19). If the current trend of smoking continues, these respiratory pandemics will add to the 1 billion predictable deaths from smoking in this century (26). Smoking increases the risk of death in patients with respiratory infectious diseases by exacerbating the symptoms of the disease. A meta-analysis of 16 studies found that smokers were 50% more likely to have more severe COVID-19 symptoms. Given some claims that smokers do not get COVID-19 or show milder symptoms, these scientific findings should be considered during the COVID-19 pandemic. Evidence from recent studies suggests that the association between...
COVID-19 and smoking will be approximately the same as previously observed in other infectious respiratory diseases (26).

COPD is a serious health threat affecting more than 1.1 billion smokers worldwide. The acute phase of the disease is mostly the result of viral and bacterial infections. The number of smoking parents of children with acute respiratory infections is higher compared to other populations. Exposure of children to tobacco smoke is an important risk factor for influenza and other respiratory infections. Quitting smoking can reduce the risk of infectious diseases (43).

In a prospective cohort study to assess the role of smoking in increasing respiratory infections, it was found that among a large group of US Army recruits (1230 soldiers), 22.7% of smokers compared with 16% of non-smokers had an upper respiratory viral infection. The results of this study showed that smoking increased the risk of respiratory infections (33). Cohen et al. showed that smoking impairs the host’s immune system, which inhibits virus replication, and also stimulates the production of inflammatory cytokines, thereby increasing the risk of infection (44).

**Smoking and Parasitic Infections**

Intestinal parasitic infections are still major health problems in the developing world, including Pakistan. To date, there is no estimate of parasitic infections of drug addicts in this country. Khan et al collected 450 stool samples from drug addicts, including cigarettes and marijuana. The samples were examined by direct wet mount method using normal saline and Lugol’s iodine preparation and concentration procedures using salt and formal-ether solutions. Of the total examined drug addicts, only 22.8% (n = 103/450) were found to be infected with single or various parasite species. Studies support the association between smoking and the prevalence of intestinal parasites (45).

Several studies have shown that smoking may be a risk factor for *Trichomonas vaginalis* and *Entamoeba gingivalis* infections in humans. There was a statistically significant correlation between the risk factors such as smoking of patients and the presence of these parasites. The prevalence of *E. gingivalis* and *T. tenax* in dental plaques and saliva samples is high. The reasons may be the reduced immunity in these patients and the presence of these parasites (46).

Eosinophilic lung diseases comprise a group of diffuse parenchymal lung diseases characterized by the prominent infiltration of the lung interstitium and the alveolar spaces by polymorphonuclear eosinophils, with conservation of the lung architecture. As a consequence, a common denominator of eosinophilic lung diseases is represented by a dramatic response to systemic corticosteroid therapy and treatment without any sequelae in most cases, despite significant impairment of lung function at presentation. Eosinophilic lung disorders can present as acute or chronic pneumonia or as the transient Loffler syndrome, which is most commonly of parasitic origin. The main causes contain exposure to drugs and fungal infection; however, acute eosinophilic pneumonia most often is related to tobacco smoking (47).

A study by Tompkins et al in 2014 examined the association between smoking status and *Trichomonas vaginalis* infection. In this study, smoking status was assessed based on self-reported data and serum cotinine levels. Examination of serum cotinine showed a 10-fold increase in *T. vaginalis* infection among active smokers, and active smokers were more likely to get infections and illnesses than those who did not have nicotine exposure. Therefore, based on the data obtained, smokers were more likely to develop *T. vaginalis* infection than non-smokers. Finally, we found that smoking status was an independent risk factor for *T. vaginalis* infection by measuring serum cotinine levels in smokers. Previous studies have shown an association between smoking status and STI, which was also found to be true for human papilloma virus and *Mycoplasma genitalium*. Recently, an association has been found between *T. vaginalis* infection and smoking in men in the United States. This may indicate the biological effect of smoking on the immune or local tissue level that affects the level of susceptibility to infection (48).

**Conclusion**

It has been demonstrated that smoking can dose-dependently increase the incidence and mortality of illnesses. Additionally, smoking is associated with a poor prognosis for lung cancer. Cigarette smokers are more likely to have a recurrence of illness or an infection that does not heal compared to nonsmokers. Smoking cessation may help lessen the harm caused by smoking and the risk of developing an infection. Active smoking cessation promotion and education are realistic and cost-effective therapies that can be used to minimize the risk of infection caused by smoking, as well as the incidence and mortality associated with the infection. Additionally, it is critical to encourage smokers to be vaccinated in order to avoid developing an infection. Vaccination is one of the most effective ways to fight against infectious diseases (49,50). External factors such as smoking alter the natural respiratory microbiota, affecting the host’s health and increasing the chance of acquiring chronic respiratory illnesses and infections.

While understanding host-pathogen dynamics is critical for creating effective treatments, it is equally essential to investigate how those dynamics are altered when the host is exposed to a variety of environmental stressors. Chronic respiratory infections should be treated by considering the presence of a microbial component, as such therapies may influence pathogen clearance and,
as a result, the course of chronic disease, either positively or adversely. Cigarette smoking is a significant public health issue in the United States due to the fact that it is the primary cause of numerous preventable diseases and accounts for a significant proportion of premature deaths. According to the majority of physicians, the most serious health effects of smoking include cancer, infection, atherosclerotic cardiovascular disease, and COPD. Infectious diseases may soon overtake cancer, heart disease, and COPD as the leading causes of morbidity and mortality associated with smoking. Smoking may increase the risk of infection as a result of anatomical changes in the respiratory tract and cause a decrease in immunological response, both systemically and locally within the lungs. Cigarette smoking significantly raises the risk of developing bacterial and viral infections. Significant associations between smoking and infection were also reported, indicating that smokers have a two- to four-fold greater risk of contracting invasive pneumococcal illness, a disease linked with a high fatality rate. Cigarette smokers are much more likely than nonsmokers to develop influenza infection, which is significantly more severe. Perhaps the greatest detrimental effect of smoking on public health is the increased incidence of tuberculosis. The poor and those living in developing nations are at higher risk of catching tuberculosis and dying from it. Smoking is prevalent among the poor in developed countries and is rapidly increasing in emerging economies. As a result, smoking is predicted to considerably contribute to the global disease burden associated with tuberculosis.

Acknowledgments
We are sincerely thankful to our counsellors in Clinical Research Development Center of Shahid Mohammadi Hospital.

Authors’ Contributions
KHA and PD conceived and designed the study. KHA, ZGH, HG, MH, and NA wrote the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures
The authors declare no competing interests.

Ethical Statement
Not applicable.

Funding/Support
There was no funding.

Informed Consent
Not applicable.

References
Ahmadi et al.


