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# Respiratory tract infections: Another reason not to smoke

## ■ ABSTRACT

Smoking is a risk factor for a number of pulmonary infections, probably because of its adverse effects on respiratory defenses. It is associated with increased morbidity and mortality from pneumonia and influenza, as well as more days lost from work from lesser respiratory infections. Patients who smoke need to be informed about their increased risk of respiratory infections and of the benefits of both being vaccinated and stopping smoking.

## ■ KEY POINTS

Smokers are more likely than nonsmokers to develop colds, influenza, pneumonia, tuberculosis, and varicella pneumonitis, which tend to be more severe.

Smokers should be targeted for influenza and pneumococcal vaccination: they are less likely than nonsmokers to be vaccinated.

For smokers who develop the typical rash of chicken pox, the authors advocate prompt treatment with oral acyclovir and careful observation for pneumonitis, which requires treatment with intravenous acyclovir.

**C**IGARETTE SMOKING is the leading cause of preventable death in the United States, and its association with lung cancer and chronic obstructive pulmonary disease (COPD) is well established. But smoking also affects the incidence, severity, and natural history of a number of other respiratory illnesses.<sup>1</sup>

Smokers need to be informed that they face a heightened risk of respiratory infections of all types: it's one more reason to try to give up the habit. We also ought to make sure they get their appropriate vaccinations against influenza and pneumonia.

This article discusses the effects of smoking on respiratory defenses and the impact of smoking on the common cold, influenza, pneumonia, tuberculosis, and varicella pneumonitis.

## ■ SMOKING WEAKENS RESPIRATORY DEFENSES

Smoking is believed to exacerbate respiratory diseases by harming respiratory defense mechanisms. Burning tobacco forms an aerosol of vaporized chemicals and particulates (approximately  $3 \times 10^9$  particles/mL of cigarette smoke) that include nicotine, multiple carcinogens, oxidants, and carbon monoxide.<sup>2</sup> The physical properties of cigarette smoke promote the deposition of particles in the lower airways, where they affect respiratory defense mechanisms at multiple levels. Specifically, smoking:

- Damages mucociliary function, which impairs clearance of inhaled substances even in smokers who have no respiratory symptoms.<sup>3</sup>
- Promotes bacterial adherence to airway



epithelial cells.<sup>4</sup> Even smokers with normal lung function have oropharyngeal flora colonizing the lower airways, a normally sterile environment.<sup>5</sup>

- Increases alveolar vascular and epithelial permeability.<sup>6,7</sup>
- Affects the composition, appearance, and function of pulmonary inflammatory cells. Smokers have several times more cells recovered by bronchoalveolar lavage and higher percentages of macrophages and neutrophils than do nonsmokers.<sup>8</sup> Alveolar macrophages are important both for clearing particles through phagocytosis and for regulating inflammation and cellular immunity. Smokers have larger alveolar macrophages than do nonsmokers, have intracytoplasmic inclusions not seen in the cells of nonsmokers, and may have impaired antigen-presenting function.<sup>9</sup>
- Reversibly depresses natural killer-cell function.<sup>10,11</sup>

### ■ SMOKERS GET MORE COLDS, WORSE COLDS

Cigarette smokers get more colds and worse colds than do nonsmokers. Several large retrospective cohort studies from the 1960s found that young smokers had more respiratory tract infections than their nonsmoking peers.<sup>12–14</sup>

Finklea et al<sup>15</sup> studied 1,848 military cadets over a 1-year period and found twice the rate of acute noninfluenzal lower respiratory tract infection in those who smoked more than one pack per day than in nonsmokers.

Aronson et al,<sup>16</sup> in a prospective study of young adults presenting with acute respiratory illness, found that compared with nonsmokers, smokers had more lower respiratory tract illnesses, a longer duration of cough, and more abnormalities heard by chest auscultation.

Women's Health Study participants who smoked 25 or more cigarettes per day had a significantly higher risk of developing prolonged colds, even after adjustment for chronic lung disease.<sup>17</sup>

Cohen et al<sup>18</sup> instilled a suspension of respiratory virus into the nares of 400 volunteers and found that smokers had higher rates of both documented viral infection and clinical colds than did nonsmokers (adjusted odds ratio 2.08).

Peat et al<sup>19</sup> found that, compared with children of nonsmokers, children of smokers have more childhood respiratory infections and hospitalizations for respiratory illness (odds ratio 2.0).

This increased incidence of colds probably contributes to reduced productivity due to acute respiratory illness in otherwise healthy adults.

### ■ SMOKING DOUBLES THE INFLUENZA RATE

Several studies have found that cigarette smokers have higher rates of influenzal infection than nonsmokers, and that the infections are more severe.

Rogot and Murray<sup>20</sup> studied a large cohort of US military veterans and found that smokers had a death rate that was 1.78 times higher than expected.

Finklea et al<sup>21</sup> prospectively studied college students during an influenza epidemic and found that cigarette smokers had a higher incidence of clinical infections and subclinical infections (as detected by antibody titers).

Kark et al<sup>22</sup> studied Israeli military recruits and found that smokers had a higher risk of developing clinical influenza (odds ratio 2.42) and that the influenza was more severe.

Finklea et al<sup>23</sup> found that levels of antibody to influenza wane more rapidly in smokers than in nonsmokers.

Nicholson et al<sup>24</sup> studied rates of influenza in an elderly immunized population and found no difference between smokers and nonsmokers. However, active smokers are less likely than nonsmokers to be vaccinated.<sup>24–26</sup>

### ■ SMOKING INCREASES THE RISK OF BACTERIAL PNEUMONIA

COPD is a well-recognized risk factor for bacterial pneumonia, and most cases of COPD are due to smoking. Because of the close relationship between smoking and COPD, it is challenging to separate the pneumonia risk related to smoking from that related to smoking-associated COPD.

Lipsky et al,<sup>27</sup> in a retrospective case-control study of patients with culture-proven

**Burning tobacco forms an aerosol that weakens defenses at multiple levels**

pneumococcal infection, found that current cigarette smoking was strongly associated with developing disease (odds ratio 4.00); however, the risk was not adjusted for whether COPD was present.

**Straus et al,**<sup>28</sup> in another case-control study, found that smoking was an independent risk factor for domestically acquired *Legionella* pneumonia (odds ratio 3.48). Cases and controls were matched for chronic pulmonary disease, but pulmonary function was not reported.

**Almirall et al,**<sup>29</sup> in a population-based, case-control study of 205 patients with community-acquired pneumonia, found a dose-response relationship between the level of smoking and the risk of pneumonia; people who ever smoked had twice the risk of non-smokers. Self-reported, previously diagnosed COPD was controlled for, but severity of lung dysfunction was not. Nearly one third of community-acquired pneumonia cases were attributable to cigarette smoking. Among patients without COPD, 23% of pneumonia cases were attributable to smoking. The risk of pneumonia declined after stopping smoking.

**Farr et al**<sup>30</sup> examined risk factors for community-acquired pneumonia in 178 patients admitted to the hospital and found that lifetime smoking history was an independent risk factor for pneumonia, after adjusting for self-reported chronic airway disease.

**Studies in patients with HIV infection.** Cigarette smoking is associated with an increased incidence of pneumonia in patients infected with human immunodeficiency virus (HIV).<sup>31,32</sup> However, the multicenter Pulmonary Complications of HIV Study<sup>33</sup> found an increased incidence of pneumonia only in the most lymphopenic subgroup of smokers, ie, those with CD4 counts of less than 200 per mm<sup>3</sup>.

Suppression of local lung defenses may contribute to the excess risk of pneumonia seen in HIV-infected smokers. Smoking depresses lung CD4 and CD8 cell counts, reduces lung CD4/CD8 cell ratios, and suppresses lung production of inflammatory cytokines (interleukin-1B and tumor necrosis factor- $\alpha$ ) in patients with HIV infection.<sup>34</sup>

## ■ SMOKING IS ASSOCIATED WITH TUBERCULOSIS

Smokers have higher rates of tuberculin skin test reactivity and conversion and of active tuberculosis. However, socioeconomic and demographic factors may be confounding variables.

**Nisar et al,**<sup>35</sup> in a cross-sectional study of 2,665 residents of homes for the elderly in the United Kingdom, found that compared with people who never smoked, more current smokers had positive skin test results (odds ratio 1.59). Ex-smokers had an odds ratio of 1.20.

**Anderson et al,**<sup>36</sup> in a case-control study of tuberculin skin testing in prison inmates, found that smokers were more likely to convert from negative to positive while they were incarcerated (odds ratio 1.78) than were non-smokers.

**McCurdy et al,**<sup>37</sup> in a cross-sectional study of California migrant farm workers, found that former smokers had a higher rate of tuberculin reactivity than people who never smoked (odds ratio 3.11). Current smokers had an odds ratio of 1.78. The authors speculated that the lower rate in current smokers than in former smokers may have been due to selection bias, as people with poorer respiratory health may be more likely to quit smoking.

**Adelstein and Rimington,**<sup>38</sup> in a longitudinal study of 76,589 volunteers undergoing mass miniature radiography, found a dose-response relationship between the number of cigarettes smoked per day and the rate of tuberculosis. In men older than 35 years, the rates (per 1,000) were:

- In nonsmokers: 0.53
- In light smokers (1–9 cigarettes per day): 1.13
- In medium smokers (10–19 cigarettes per day): 2.47
- In heavy smokers ( $\geq 20$  cigarettes per day): 3.17.

Women showed a similar pattern, and in women who were heavy smokers the rate was even higher than in men: 4.25.

**Gajalakshmi et al,**<sup>39</sup> in a case-control study in 30 villages in southern India, also found a dose-response relationship between smoking and the prevalence of pulmonary

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tuberculosis. Compared with nonsmokers, mild smokers (1–10 cigarettes per day) had an odds ratio of 1.75, moderate smokers (11–20 cigarettes per day) 3.17, and heavy smokers (> 20 cigarettes per day) 3.68. Duration of smoking was also associated with an increased risk of tuberculosis. The death rate from tuberculosis was about four times higher in those who ever smoked vs those who never smoked.

**Alcaide et al**<sup>40</sup> studied young adults who were close contacts of people with new cases of active tuberculosis and found a strong relationship between active smoking and the development of pulmonary tuberculosis after adjusting for confounding factors (odds ratio 3.8).

**Altet et al**<sup>41</sup> studied children living in households containing someone with active tuberculosis. Exposure to cigarette smoke (eg, passive smoking, as confirmed by urine cotinine levels) was a risk factor for developing active pulmonary tuberculosis (adjusted odds ratio 5.39).

## ■ SMOKERS HAVE A HIGHER RISK OF VARICELLA PNEUMONITIS

Chicken pox is a common childhood infection caused by the varicella zoster virus. Although generally benign, it can cause potentially fatal pneumonitis in susceptible individuals. Risk factors for developing varicella pneumonitis include conditions associated with compromised immunity, such as bone marrow and solid organ transplantation, cancer (especially Hodgkin lymphoma), and corticosteroid use.<sup>42</sup>

Chicken pox is more severe in adults than in children and causes a higher incidence of complications. Adults account for fewer than 2% of varicella cases but one fourth of deaths.<sup>42</sup> Most of the increased deaths in adults are attributable to varicella pneumonitis.

Pneumonia usually begins 1 to 6 days after the onset of the rash, with cough and dyspnea.<sup>43</sup> Chest radiographs typically show diffuse interstitial or nodular infiltrates, and patients may have significant hypoxia. The mortality rate of untreated varicella pneumonitis in adults is approximately 10%, although it approaches 50% in patients with respiratory failure.<sup>42</sup>

Smoking has been identified as a risk factor for varicella pneumonitis in otherwise-healthy adults. Ellis et al<sup>44</sup> found that pneumonitis occurred in 7 of 19 adult smokers hospitalized with varicella, but in none of the 10 nonsmokers in this study. In a larger study of adults hospitalized with varicella, smokers had a risk of pneumonitis 15 times that of nonsmokers.<sup>45</sup> In a retrospective review of 15 patients hospitalized for varicella pneumonitis, 12 (80%) had a history of cigarette smoking.<sup>46</sup>

The increased incidence of pneumonitis in smokers may be caused by enhanced primary viremia from nasal mucosal effects of smoking, abnormal pulmonary macrophage function, and smoking-induced changes in pulmonary vascular permeability, which may facilitate the entry of hematogenously disseminated varicella.

Acyclovir effectively treats varicella virus infection and is recommended for patients with complications or who are at risk of developing them.<sup>43</sup> Because smokers are more susceptible to pneumonitis, it is prudent to give oral acyclovir to all adult smokers with varicella, although this approach has not been validated in a clinical trial. Patients with respiratory complaints should be evaluated for pneumonia, and if it is present, it should be treated with intravenous acyclovir. In spite of appropriate and aggressive treatment, varicella pneumonitis can progress to fulminant respiratory failure.

## ■ SUMMARY

Smoking appears to be a risk factor for the acquisition of a number of different pulmonary infections. This link is likely mediated by smoking's adverse effects on respiratory defenses. Considering the high rates of morbidity and mortality from pneumonia and influenza, as well as the economic consequences of work days lost from lesser respiratory infections, the merits of smoking cessation are clear. The fact that smokers have been shown to be less likely than nonsmokers to undergo vaccination and yet are probably at higher risk for influenzal and pneumococcal infections highlights the importance of targeting this group for vaccination. Because of the high prevalence of pneumonitis among adult smokers with varicella, smokers presenting

**Risk of tuberculosis increases with number of cigarettes smoked**





with the typical rash of chicken pox should undergo prompt treatment with acyclovir, and those with respiratory complaints should be evaluated for pneumonia. Physicians should

educate their smoking patients about their increased risk of respiratory infections, the importance of appropriate vaccinations, and the benefits of smoking cessation.

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