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Cigarette Smoking and Lower Respiratory Tract Infection

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1. Introduction

Acute bronchitis, one of the most common diagnoses in ambulatory care medicine, accounted for approximately 2.5 million visits to U.S. physicians in 1998 (Slusarcick & McCaig, 2000). This condition consistently ranks as one of the top ten diagnoses for which patients seek medical care, with cough being the most frequently mentioned symptom necessitating office evaluation (Knutson & Braun, 2002; Saldías et al., 2007). The diagnosis is based on clinical findings, without standardized diagnostic signs and sensitive or specific confirmation laboratory tests (Oeffinger et al., 1997).

Acute bronchitis is usually caused by a viral infection, especially by influenza, parainfluenza and respiratory syncytial virus, it is also caused by adenovirus, coronavirus and rhinovirus (Marrie, 1998). When microbiological studies are performed, less than 10-20% of patients will have evidence of acute bacterial infection (Macfarlane et al., 2001). Thus, *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been clearly established as causes of acute bronchitis. But there is no clear evidence that *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* cause acute bronchitis in adults without underlying lung disease; studies have failed to distinguish between colonization and acute infection (Ramirez-Ronda et al., 1981; Treanor & Hayden, 2000). However, these bacteria are important causes of superinfections after acute viral respiratory illnesses (Hament et al., 1999; Peltola & McCullers, 2004).

The devastating health impact of cigarette smoking is well known (Kuper et al., 2002; Stewart et al., 2008). Despite ongoing efforts to reduce smoking prevalence, over 1.1 billion people continue to smoke, representing one-sixth of the world's population (Jha et al., 2002). Cigarette smoking is a major risk factor for premature mortality due to cancer, cardiovascular and cerebrovascular disease, and chronic obstructive pulmonary disease (Dye & Adler, 1994). About half of all smokers will develop a serious smoking-related illness, such as chronic obstructive pulmonary disease (COPD), which is characterized by irreversible airway obstruction, or cardiovascular disease. Furthermore, about 1-5% of smokers will develop a smoking-related malignancy, mostly lung adenocarcinoma or other epithelial cell tumours. But cigarette smoking also appears to be a major risk factor for respiratory tract infections (Marcy & Merrill, 1987). Both active and passive cigarette smoke exposure increase the risk of infections. Passive exposure to tobacco smoke in children

contributes significantly to morbidity and mortality (Cheraghi & Salvi, 2009). Children in particular, seem to be the most susceptible population for the harmful effects of environmental tobacco smoke (ETS). Exposure to ETS amongst children at homes have been reported to vary from 27.6% in Africa, 34.3% in South East Asia, 50.6% in Western Pacific, and up to 77.8% in Europe (Warren et al., 2008). The morbidity and mortality of infectious diseases associated to smoking are not widely appreciated by physicians. The mechanism of increased susceptibility to infections in smokers is multifactorial and includes alteration of the structural (Dye & Adler, 1994; Marcy & Merrill, 1987) and immunologic host defenses (Sopori et al., 1994; Sopori et al., 1998). We reviewed the epidemiology of smoking-related lung infections and the mechanisms by which smoking increases the risk of infection.

2. Mechanisms by which cigarette smoking may predispose to respiratory infections

The specific mechanisms by which cigarette smoking increases the risk of respiratory infections are incompletely understood (Saldías et al., 2007; Domagala-Kulawik, 2008). They are multifactorial and probably interactive in their effects. Mechanisms by which smoking increases the risk of infections include structural changes in the respiratory tract (Dye & Adler, 1994) and a decrease in immune response (Sopori et al., 1998).

2.1 Structural changes caused by smoking

The ciliated respiratory epithelium, the main target of most respiratory viruses, is the first line of defense against harmful environmental agents and protects by sweeping particles away in the overlying mucus gel layer, phagocytosing and killing some pathogens, maintaining a barrier through tight junctions and priming, activating and recruiting other immune cells. Cigarette smoke and many of its components produce structural changes in the respiratory tract. These changes include peribronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of the mucociliary clearance, changes in pathogen adherence, and disruption of the respiratory epithelium (Dye & Adler, 1994). These changes are thought to predispose to the development of upper and lower respiratory tract infections, which may amplify the cigarette smoke-induced lung inflammation. A number of components of cigarette smoke, including acrolein, acetaldehyde, formaldehyde, free radicals produced from chemical reactions within the cigarette smoke, and nitric oxide, may contribute to the observed structural alterations in the airway epithelial cells (Marcy & Merrill, 1987).

Smoke directly compromises the integrity of this physical barrier, increases the permeability of the respiratory epithelium and impairs mucociliary clearance (Dye & Adler, 1994; Jones et al., 1980; Burns et al., 1989). Although cigarette smoke has been shown to activate epithelial cells to produce pro-inflammatory mediators (Mio et al., 1997), it attenuates the *in vitro* production of pro-inflammatory mediators by epithelial cells following stimulation with pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide or double-stranded RNA (Laan et al., 2004; Bauer et al., 2008). Smoke also induces direct oxidative damage to membrane lipids and causes extensive single-strand DNA breaks, triggering repair and apoptotic cascades (Kim et al., 2004). Thus, cigarette smoke acutely suppresses the respiratory epithelium and chronically can cause damage, inflammation and may ultimately transform it.

2.2 Effect of cigarette smoke on the lung and systemic immunity

Cigarette smoke has been shown to affect a wide range of host defense mechanisms (Sopori et al., 1994). However, findings between studies can be controversial and sometimes contradictory, probably because of differences in smoking history, genetic susceptibility and socioeconomic status (such as exercise, nutrition, occupation and ambient air quality, which can modify disease). Similar issues apply to animal models and *in vitro* systems, in which parameters of smoke exposure, such as duration, frequency and mode vary markedly between studies (Domagala-Kulawik, 2008; Stämpfli & Anderson, 2009). Accordingly, as the patterns of smoke exposure are so varied individually and geographically, no single experimental smoke exposure system can replicate the diversity of human smoking patterns, and each experimental system probably reflects only facets of the overall picture.

2.2.1 Cell-mediated immune responses

White blood cell count and distribution in peripheral blood. Smokers usually exhibit an elevated peripheral white blood cell count, around 30% higher than that of nonsmokers (Friedman et al., 1973; Yeung & Buncio, 1984; Tollerud et al., 1989; Mili et al., 1991). It has been shown a significant relationship between the white blood cell count in smokers and the plasma concentration of nicotine (Taylor et al., 1986). It has been suggested that nicotine induced catecholamine release might be the mechanism for this effect (Friedman et al., 1973). Other studies support the hypothesis that cigarette smoking causes bone marrow stimulation (Van Eeden & Hogg, 2000). It has been suggested that proinflammatory factors released from alveolar macrophages, such as tumor necrosis factor α , interleukin (IL) 1, IL-8, and granulocyte-macrophage colony-stimulating factor, are probably responsible for the stimulation of bone marrow by cigarette smoking. It has been reported the same relationship between cigarette smoking and increased leukocyte count in adolescents, indicating that there appears to be a rapid effect of cigarette smoking on white blood cell count that is unlikely to be due to smoking induced chronic disease conditions as seen in adult smokers (Tell et al., 1985).

Reports of the effects of smoking on the different subsets of lymphocyte T cells are conflicting. Light to moderate smokers were reported to have a significant increase in CD3+ and CD4+ counts and a trend toward increased CD8+ lymphocyte count (Miller et al., 1982; Hughes et al., 1985; Tollerud et al., 1989; Mili et al., 1991). By contrast, studies of heavy smokers (over 50 pack-years) reported a decrease in CD4+ and a significant increase in CD8+ cell counts. Thus, the decrease observed in the ratio of CD4+ to CD8+ lymphocytes in heavy smokers was due predominantly to an increase of CD8+ cells (Ginns et al., 1982). These effects appeared to be reversible as soon as 6 weeks after smoking cessation (Miller et al., 1982). Other studies have reported no difference in the CD4+ and CD8+ lymphocyte counts among moderate smokers (Costabel et al., 1986). Since CD4+ cells facilitate B-cell proliferation and differentiation and immunoglobulin synthesis, the decrease in this subset observed in heavy smokers might contribute to the increased susceptibility to infections in this population.

Airways and lung parenchyma. Bronchoalveolar lavage studies have demonstrated a marked decrease in the absolute number of CD4+ cells, and an increase in CD8+ cells with a lower CD4+/CD8+ cell ratio in moderate smokers vs nonsmokers (Leatherman et al., 1984; Costabel et al., 1986; Wewers et al., 1998). No significant changes in these variables in the peripheral blood were found in this population of moderate smokers, in contrast with the

findings in heavy smokers discussed previously. Thus, changes in lymphocyte population in the bronchoalveolar lavage in smokers may disclose pathologic changes earlier than in blood. Moreover, these findings suggest that smokers have a deficit in cell-mediated immunity in the lung alveolus, a site critical in the first-line defense against infection.

The retention of CD8⁺ T cells in the lungs of chronic smokers warrants particular attention as it is a hallmark of COPD and it is known that these cells can activate alveolar macrophages to produce matrix metalloproteinase 12, a potent elastin-degrading enzyme that has been linked to emphysema (Hautamaki et al., 1997; Grumelli et al., 2004). Furthermore, CD8⁺ T cells are required for inflammation and tissue destruction in smoke-induced emphysema in mice (Maeno et al., 2007). Cigarette smoke has also been found to promote the retention of virus-specific CD8⁺ memory effector T cells, but to weaken their defensive ability (Gualano et al., 2008).

Smoking is also associated with significant increases in the percentage of macrophages in bronchoalveolar lavage fluid (Wewers et al., 1998). Owing to their strategic positioning within the alveolar space, alveolar macrophages have a key role in sensing and eliminating microbial agents early in the course of an infection. Cigarette smoking increases the number of alveolar macrophages (Sopori et al., 1998) and activates them to produce pro-inflammatory mediators, reactive oxygen species and proteolytic enzymes (de Boer et al., 2000; Russell et al., 2002), thereby providing a cellular mechanism that links smoking with inflammation and tissue damage. Similar to its effects on the respiratory epithelium, cigarette smoke compromises the ability of alveolar macrophages to phagocytose bacteria (King et al., 1988; Berenson et al., 2006) and apoptotic cells (Hodge et al., 2007) and to sense PAMPs (Drannik et al., 2004; Chen et al., 2007; Gaschler et al., 2008). Importantly, cigarette smoke may not simply suppress the function of alveolar macrophages as previously suggested, but instead might skew their inflammatory mediator profile. The nature of the skewing may be a determinant of disease susceptibility. Accordingly, one study reported a distinctive state of activation of alveolar macrophages in smokers that distinguished them from those in non-smokers (Woodruff et al., 2005). This highlights a key emerging concept – smoke may induce partial M1 deactivation or partial M2 activation of macrophages. The balance and intensity of this skewing has direct implications for the immune system and its response to disease because effective host defense requires a macrophage activation programme that is appropriate for the particular type of pathogen and because M1-type macrophages can cause marked lung damage (emphysema), whereas M2-type macrophages are linked to tumour progression. The molecular mechanisms of altered alveolar macrophage responsiveness and skewing are not presently understood but they are at least partially reversible by exposure to the reduced form of glutathione, which implicates oxidative damage of effector pathways. The infection risk is compounded by host deficiencies or polymorphisms in innate and adaptive immune response genes, in particular those encoding pattern recognition receptors, such as mannose-binding lectin, and their signal transduction intermediates (Becker & O'Neill, 2007).

In the lungs, dendritic cells (DCs), which are the most potent antigen-presenting cells and are indispensable for the initiation of T cell-mediated immune responses (Mellman & Steinman, 2001), are probably highly susceptible to smoke-induced effects because of their anatomical position (in the lumen and directly beneath the epithelium of the lung) (McComb et al., 2008). Although it is known that the DC-directed chemokine CX3CL1 is upregulated in emphysema (McComb et al., 2008), there are only a few studies assessing the

effects of smoking on lung DCs in humans and animal models (Tsoumakidou et al., 2008). Clinical studies suggest that the number of mature DCs is reduced in the large airways of patients with COPD who smoke (Jahnsen et al., 2006). Following smoking cessation, the numbers of mature DCs increase and are similar to non-smoking healthy controls. By contrast, the number of immature DCs is increased in the small airways of patients with COPD compared with individuals who have never smoked and individuals who smoke but do not have COPD (McComb et al., 2008). These data indicate that smoking behavior may affect DC numbers and maturity state.

Leukocytes function. Polymorphonuclear leukocytes from the peripheral blood of smokers exhibit depressed migration and chemotaxis compared with PMNs from nonsmokers (Noble & Penny, 1975; Corberand et al., 1979). The motility and chemotaxis of PMNs are depressed in the oral cavity of smokers compared with nonsmokers (Eichel & Shahrik, 1969; Noble & Penny, 1975). The whole cigarette smoke, its gas phase and the water-soluble fraction are potent inhibitors of PMN chemotaxis (Bridges et al., 1977). Of the water-soluble fraction of cigarette smoking, the unsaturated aldehydes (acrolein and crotonaldehyde) were the major contributors to the inhibitor properties. The non-volatile components of cigarette smoking also inhibit chemotaxis by a mechanism that differs from that of the unsaturated aldehydes present in the vapour phase of smoke (Bridges et al., 1977; Bridges & Hsieh, 1986). The non-volatile component did not inhibit migration. Nicotine had no effect on PMN migration and chemotaxis (Sasagawa et al., 1985). Macrophages from the lungs of smokers have a greater inhibitory effect on lymphocyte proliferation than macrophages from the lungs of nonsmokers. Thus, the immunosuppressive effects of the macrophages on cell-mediated immune response are increased in smokers (Holt, 1987). The release of cytokines (TNF α , IL-1, IL-2 and IL-6) from macrophages may also be altered in smokers (McCrea et al., 1994; Twigg et al., 1994; Ouyang et al., 2000; Hagiwara et al., 2001). Hydroquinone, the phenolic compound in cigarette tar, had the most potent inhibitory effect of these cytokines, whereas nicotine had little effect. The cytokines IL-1 and IL-6 are important in the host defense against infection (Smith, 1988; Luster et al., 1999). Animal studies have shown that depletion of these cytokines increases susceptibility to bacterial pneumonia. Since PMNs play a significant role in host defense against acute bacterial infections, an impairment of PMN functions by smoke may contribute to the increased susceptibility of smokers to systemic infections, including bacterial pneumonia.

Lymphocyte functions. Natural killer (NK) cell activity in peripheral blood has been reported to be reduced in smokers compared with nonsmokers (Ferson et al., 1979; Hughes et al., 1985; Tollerud et al., 1989; Nair et al., 1990). These alterations appear to be reversible, since NK activity in ex-smokers was similar to that of a never-smoking group compared with smokers (Silverman et al., 1975; Hersey et al., 1983). The recovery period was relatively short, as little as 6 weeks (Miller et al., 1982; Hughes et al., 1985). Since NK cells are important in the early surveillance response against viral infections and resistance against microbial infections (Herberman & Holden, 1978; Herberman, 1980), impairment of NK cell activity by cigarette smoking is a potential mechanism for the increased incidence of infections among smokers.

Mounting evidence suggests that natural killer cells have an important role in innate host defense against microbial agents and in protective antitumour immune surveillance. This is achieved by direct cytotoxicity through perforin and granzymes, CD95 ligand-induced apoptosis and pro-inflammatory cytokine and chemokine release (Tollerud et al., 1989;

Hamerman et al, 2005). Several studies have shown that NK cell numbers and activity are decreased in smokers compared with non-smokers (Swann et al., 2007). Exposure to cigarette smoke attenuates the cytotoxic activity and cytokine production of NK cells in humans and mice (Lu et al., 2006; Mian et al., 2008), thereby linking NK cell defects to increased infection risk and cancer.

Animal studies have shown that nicotine inhibits the antibody-forming cell response through impairment of antigen-mediated signalling in T cells and suppression of intracellular calcium response (Geng et al., 1995; Geng et al., 1996; Sopori et al., 1998). It has been suggested that nicotine through activation of protein tyrosine kinases and depletion of inositol-1,4,5-trisphosphate-sensitive calcium stores in T cells could be a major immunosuppressive component in cigarette smoking (Kalra et al., 2000).

2.2.2 Humoral immune system

Peripheral blood. The effects of cigarette smoking on humoral immunity have been studied extensively (Sopori et al., 1994; Sopori et al., 1998). Several studies have found that smokers had serum immunoglobulin levels (IgA, IgG, and IgM) 10% to 20% lower than those of nonsmokers (Dales et al., 1974; Ferson et al., 1979; Gerrard et al., 1980; Andersen et al., 1982). It has been shown that IgA, IgG, and IgM levels are higher among former smokers than current smokers and increased with duration of smoking cessation (Mili et al., 1991). This suggests that the effect is reversible, with a return toward the immunoglobulin levels of nonsmokers. It has been reported that three months after subjects stopped smoking, IgG and IgM but not IgA levels have increased compared with levels during smoking (Hersey et al., 1983).

Lung parenchyma. The IgG content of bronchial fluids was found to be twice higher in smokers than nonsmokers (Onari et al., 1978; Hersey et al., 1983). A selective increase in immunoglobulin levels could be explained either by stimulation of local immunoglobulin production or by exudation of plasma immunoglobulin into alveolar spaces in response to inhaled cigarette smoke (Warr et al., 1977). The availability of opsonic antimicrobial antibodies is essential for optimal function of phagocytes to take up and contain bacteria (Reynolds, 1988). The antibody response to a variety of antigens, such as influenza virus infection and vaccination is depressed in cigarette smokers (Finklea et al., 1971).

Autoimmunity has been proposed as a cause of smoke-induced lung disease. B cells are abundant in smoke-induced lung disease, and their roles, although obscure, are probably greatly underestimated. Cigarette smoke serves as an adjuvant, possibly because it is a potent inducer of granulocyte/macrophage colony-stimulating factor production in the lungs, which enhances the ability of DCs to present antigen and probably to induce TH₂ type-biased immune responses (Trimble et al, 2009).

3. Smoking and respiratory infections

Given the complex nature of the immune system, in which unaffected defense mechanisms may compensate for local deficiencies, it is difficult to predict how the impact of cigarette smoke on specific host defense pathways affects the overall responses to microbial agents (Domagala-Kulawik, 2008). Specifically, it is unclear whether the increased risk of infection observed in smokers is due to increased susceptibility to microbial agents, an inability to effectively clear infectious agents or exaggerated pro-inflammatory responses to microbial

agents (owing to changes in immune homeostasis), thereby evoking symptoms of infection. Similar considerations apply to acute exacerbations of COPD that are due to bacterial and viral infections (Sethi & Murphy, 2001; Wedzicha, 2004; Papi et al., 2006) and to microbial colonization of the airways, which occurs in approximately one third of patients with COPD (Patel et al., 2002).

3.1 Viral infections

Environmental tobacco smoke exposure increases significantly the risk of lower respiratory tract infections in children, especially maternal smoking (Table 1). Using mouse models, it has been investigated the effects of cigarette smoke on inflammatory processes, viral clearance and secondary immune protection following influenza virus infection (Robbins et al., 2006; Gualano et al., 2008; Kang et al., 2008). Cigarette smoke exposure was found to be associated with exacerbated pro-inflammatory responses to influenza virus, although neither the rate of viral clearance nor the development of influenza virus-specific memory responses were compromised. Hence, cigarette smoke mainly affects primary antiviral inflammatory processes, whereas secondary immune protection remains intact (Robbins et al., 2006). The heightened inflammatory response was associated with increased production of pro-inflammatory mediators and mortality. Furthermore, one study (Kang et al., 2008) showed that increased inflammation led to accelerated emphysema formation and airway fibrosis, providing evidence that altered responsiveness to viral agents may contribute to the pathogenesis of emphysema.

Common cold. Several epidemiological studies support the association between smoking and the prevalence of colds and lower respiratory tract symptoms. In a prospective cohort study that examined a large group of US Army recruits found an increased risk of upper respiratory tract infection in smokers (relative risk: 1.5; 95% confidence interval [CI], 1.1-1.8) (Blake et al., 1988). It has been reported that smoking status is predictive of the development of clinical colds when healthy volunteers are exposed intranasally to a low dose of respiratory viruses (Cohen et al., 1993). Viral suspensions were installed into the nares and infections were diagnosed on the basis of viral isolation, virus-specific antibody, and clinical findings. Smokers had a significantly higher incidence of acute infection (clinical cold) than nonsmokers (OR: 2.23; 95% CI, 1.03-4.82). Among virologically confirmed infected individuals, smoking was associated with a higher likelihood of symptoms leading to a clinical diagnosis (OR: 1.83; 95% CI, 1.00-3.36). The relationship between smoking and increased symptoms from viral respiratory infections could be explained by impairment of immune processes that limit viral replication or enhancement of inflammatory processes involved in the production of symptoms.

Influenza. Several studies have confirmed the relationship between cigarette smoking and the risk of influenza infections (Finklea et al., 1969). Influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers. Female smokers in the Israeli Army had increased risk of influenza (OR: 1.44; 95% CI, 1.03-2.01) and complications associated to influenza infection compared with nonsmokers (Kark & Lebiush, 1981). In another study, the incidence of influenza in healthy young male recruits was higher among smokers (OR: 2.42; 95% CI, 1.53-3.83) (Kark et al., 1982). Influenza was more severe among smokers, with a dose-related increase in rate: 30% in nonsmokers, 43% in light smokers, and 54% in heavy smokers ($p < 0.001$). Overall, 31.2% (95% CI, 16.5-43.1) of influenza cases were attributed to cigarette smoking.

Enhanced bacterial adherence has been documented for respiratory cells infected, with influenza A virus being responsible for viral-bacterial combination pneumonia (Hament et al., 1999). Studies have suggested that inflammatory activation of platelet-activating factor is an important factor in the attachment and invasion of cells by pneumococcal strains. Cigarette smoking alters platelet-activating factor metabolism and may contribute to the increased incidence of bacterial superinfection in people who develop influenza (Miyaura et al., 1992; Ichimaru & Tai, 1992).

Study	Design/Population	Sample size	Outcome
1) Jedrychowski & Flak.	Cohort study in children from Poland.	1,129	Maternal smoking during pregnancy and postnatal exposure to ETS increase risk of acute respiratory infections.
2) Li et al.	Meta-analysis study including 13 studies.		ETS exposure increases risk of serious LRTI at early life.
3) Gürkan et al.	Case control study in children from Turkey.	58	ETS exposure increases risk of respiratory syncytial virus bronchiolitis.
4) Boyce et al.	Retrospective cohort study in children from USA.	248,652	Increase risk for RSV bronchiolitis hospitalization at first year of life.
5) Pardo Crespo et al.	Case-reference study in children from Spain.	885	Maternal smoking increase the risk of hospitalization for LRTI.
6) Albernaz et al.	Nested case-control study in infants from Brazil.	5,304	Maternal smoking increase the risk of hospitalization for bronchiolitis.
7) Nielsen et al.	Retrospective case-control study in infants from Denmark.	1,252	Maternal smoking during pregnancy increase the risk of hospitalization for RSV infection.
8) Zlotkwaska & Zedja.	Cross sectional study in children from Poland.	1,561	ETS exposure increases risk of bronchitis, wheeze and attacks of dyspnoea.
9) Pattenden et al.	Cross sectional study in children from Austria.	53,879	Parental smoking increase wheeze, asthma, bronchitis and nocturnal cough.
10) Baker et al.	Cohort study in children from Czech Republic.	452	ETS exposure increases incidence of LRTI.
11) Keskinoglu et al.	Case control study in children from Turkey.	300	ETS exposure increases incidence of LRTI.
12) Chatzimicael et al.	Cross sectional study from Greece.	586	ETS exposure increases risk of upper and lower respiratory tract infections.
13) Friguls et al.	Cohort study in children from England and Spain.	1,611	Prenatal and post natal tobacco exposure increase risk of upper and lower respiratory tract infections.

References: 1) *Environ Health Prospect* 1997;105:302-6; 2) *Pediatr Pulmonol* 1999;27:5-13.; 3) *Eur J Epidemiol* 2000;16:465-8; 4) *J Pediatr* 2000;137:865-70; 5) *An Esp Pediatr* 2000;53:339-45; 6) *Rev Saude Publica* 2003;37:485-93; 7) *Acta Paediatr* 2003;92:1314-21; 8) *Eur J Epidemiol* 2005;20:719-27; 9) *Tob Control* 2006;15:294-301; 10) *Environ Health Perspect* 2006;114:1126-32; 11) *Eur J Pediatr* 2007;166:455-9; 12) *Indian J Pediatr* 2008;75:335-40; 13) *Arch Bronconeumol* 2009;45:585-90.

Table 1. The environmental tobacco smoke (ETS) exposure increases the risk of lower respiratory tract infections (LRTI) in children.

Although influenza was more severe in smokers, antibody levels to A(H1N1) antigen were not significantly higher than those of nonsmokers. Moreover, influenza antibodies wane more rapidly in smokers than in nonsmokers (Finklea et al., 1971). This finding suggests that smokers are not only at a high risk of influenza, but have an increased susceptibility to new attacks afterward (Kark et al., 1982). Influenza rates are similar in vaccinated smokers and nonsmokers. However, influenza vaccination can be considered to be more efficacious in smokers than nonsmokers because the infection rates are higher in unvaccinated smokers (Crujff et al., 1999).

Respiratory syncytial virus bronchiolitis. Respiratory syncytial virus (RSV) infection is very common in early life; over 95% of children have been infected by two years of age. RSV infections are responsible for over 100,000 hospital admissions in the United States annually, mostly affecting infants (Moler & Ohmit, 1999). Of RSV-related admissions, 7% to 21% will require ventilatory support because of respiratory insufficiency (Everard & Milner, 1992). Therefore, RSV infection imposes a significant burden on children early in life. Maternal smoking exposure has been shown to reduce lung function in children, and several studies suggest that this effect on lung function is attributable primarily to exposure during pregnancy (intrauterine cigarette smoke exposure) (Hofhuis et al., 2003). Maternal smoking during pregnancy may impair in utero airway development or alter lung elastic properties. It has been shown that maternal cigarette smoking, especially postnatal, increase the severity of RSV bronchiolitis infection in infants (Gürkan et al., 2000; Lanari et al., 2002; Bradley et al., 2005). As a preventive measure, it has been reported a protective effect of long-term breastfeeding on the risk of lower respiratory tract infection during the first year of life, especially in children exposed to environmental tobacco smoke (Nafstad et al., 1996).

Passive smoking and respiratory tract infections in childhood. A study in 1974 reported that infants of mothers who smoked had significantly more admissions for bronchitis or pneumonia than infants of non-smoking mothers (Harlap & Davies, 1974). The excess bronchitis and pneumonia increased with increased number of cigarettes smoked by the mother. This excess was mainly seen in infants aged 6 to 9 months. Another study (Colley et al., 1974), also found that the incidence of pneumonia and bronchitis in the first year of life was associated with parents' smoking habits; the incidence was lowest where both parents were non-smokers, highest where both smoked, and lay between these two levels where only one parent smoked. During the following three decades, a large number of investigations have reported associations between parental smoking and occurrence of lower respiratory tract illness in young children (Table 1). A systematic review (Strachan & Cook, 1997) of around 50 studies in children up to 3 years, including 38 studies used for quantitative analysis, has confirmed these findings. There was consistency in the findings between the community and hospital studies. Pooled ratios were found to be 1.57 for smoking by either parent and 1.72 for maternal smoking. The reviewers also found that there was a significantly increased risk from smoking by other household members in families where the mother did not smoke (odds ratio 1.29). In most of the studies also a dose-response relationship was evident, and the associations with paternal smoking were still present after adjustment for confounding factors. From earlier studies, it appeared that the risk was higher during the first 6 months of life, and gradually decreased to slightly above normal by age 3 years. However, later studies (Taylor & Wadsworth, 1987) have found similar relationships between maternal smoking and lower respiratory illness in

children up to 5 years of age. Exposure to passive smoking also seems to increase the risk for acute respiratory tract infections in older children (Jedrychowski & Flak, 1997). A dose-response between the degree of exposure to environmental tobacco smoke and acute respiratory infection was found in a cohort of 9-year-old children. Passive smoking combined with allergy nearly tripled the risk of acute respiratory tract infections (odds ratio 3.39).

3.2 Bacterial infections

Similarly, cigarette smoke exposure was also found to be associated with increased inflammation following challenge with bacterial agents such as *Pseudomonas aeruginosa* and non-typeable *H. influenzae* (Drannik et al., 2004; Gaschler et al., 2009), two pathogens that are associated with COPD exacerbations. Cigarette smoke was associated with increased bacterial burden in mice infected with *P. aeruginosa*, whereas bacterial burden was decreased in smoke-exposed animals following infection with non-typeable *H. influenzae*. Changes in the bactericidal activity of alveolar macrophages may contribute to increased bacterial burden (Drannik et al., 2004), but it is unclear how infection with non-typeable *H. influenzae* induces decreased bacterial levels; the mechanisms of this are currently being investigated. Preliminary data suggest that increased levels of immunoglobulins in the bronchoalveolar lavage of smoke-exposed animals might have contributed to this phenomenon. This finding provides evidence that compensatory mechanisms may outweigh certain deficiencies and help to explain why not all smokers suffer from severe chest infections. As discussed above, smoke affects all people who are exposed to it, but the degree and severity is modified by many susceptibility determinants.

Pneumococcal pneumonia. Cigarette smoking is a substantial risk factor for pneumococcal pneumonia, especially in patients with chronic obstructive pulmonary disease. However, even without chronic obstructive pulmonary disease, smoking is a major risk factor. In a population based surveillance study (Pastor et al., 1995), smoking was strongly associated with invasive pneumococcal disease in healthy young and middle aged adults, for whom pneumococcal vaccination is not currently recommended. Among such individuals with invasive pneumococcal disease, 47% were current smokers. The odds ratio (OR) for invasive pneumococcal disease was 2.6 (95% CI, 1.9-3.5) for smokers in the 24-to 64-year age group and 2.2 (95% CI, 1.4-3.4) for smokers 65 years or older. The attributable risk from smoking was 31% and 13% in these 2 groups, respectively.

A population based case-control study (Nuorti et al., 2000) showed that smoking was the strongest independent risk factor for invasive pneumococcal disease among immunocompetent adults. The OR was 4.1 (95% CI, 2.4-7.3) for active smoking and 2.5 (95% CI, 1.2-5.1) for passive smoke exposure in nonsmokers compared with nonexposed nonsmokers. The attributable risk in this population was 51% for cigarette smoking and 17% for passive smoking. The risk of pneumococcal disease declined to nonsmoker levels 10 years after cessation. In another case-control study, current smoking was associated with a nearly 2-fold risk of community-acquired pneumonia (OR: 1.88; 95% CI, 1.11-3.19), where 32% of the risk was attributable to cigarette smoking (Almirall et al, 1999). There was a trend toward a dose-response relationship: A 50% reduction in the OR was reported 5 years after cessation of smoking.

In vitro adherence of *Streptococcus pneumoniae* to buccal epithelial cells has been shown to be increased in cigarette smokers (Raman et al., 1983). This increased adherence may persist for

up to three years after smoking cessation. Since increased adherence of bacteria to surface cells is an established pathogenic step for bacterial colonization and infection in the lung, this may contribute to the increased risk of respiratory infection that exists in cigarette smokers.

Legionnaires disease. Legionnaires disease is a life-threatening lower respiratory tract infection responsible for 1% to 3% of community-acquired pneumonia. Diverse environmental factors have been identified, and cigarette smoking appears to be an independent risk factor (Doebbeling & Wenzel, 1987; Straus et al., 1996). The risk of legionnaires disease was significantly increased for smoking (OR: 3.48; 95% CI, 2.09-5.79), specially for persons without an underlying disease (OR: 7.49; 95% CI, 3.2-17.1) (Straus et al., 1996).

Otitis media and exposure to secondhand tobacco smoke. Long term tobacco smoke exposure is a risk factor for otitis media and bronchitis in children (Richardson, 1988). In a case-control study, children with recurrent otitis media more commonly had exposure to secondhand smoke (OR: 1.88; 95% CI, 1.02-3.49; $p=0.04$). A prospective follow-up of the case group showed no significant difference in the clinical course of the children who were exposed to secondhand smoke (Kitchens, 1995). In other study, passive smoking was a significant risk factor for otitis media with effusion and recurrent otitis media (Ilicali et al, 1999). But only maternal smoking was a significant factor ($p<0.001$). Moreover, in utero exposure to cigarette smoke was associated with an increased risk of otitis media. In a study (Stathis et al, 1999), acute ear infections were associated with the mother's consumption of 1 to 9 cigarettes (OR: 1.6; 95% CI, 1.1-2.5), 10 to 19 cigarettes (OR: 2.6, 95% CI, 1.6-4.2), and 20 or more cigarettes (OR: 3.3; 95% CI, 1.9-5.9) per day during pregnancy. For subacute ear infections, an association was present with the mother's consumption of 10 to 19 cigarettes (OR: 2.6; 95% CI, 1.4-5.0) and 20 or more cigarettes (OR: 2.8; 95% CI, 1.3-6.0). In utero exposure to 20 or more cigarettes per day was also associated with an increased risk of ear surgery by 5 years after delivery (OR: 2.9; 95% CI, 1.3-6.6).

Tuberculosis. Developing tuberculosis disease involves two distinct transitions, with their corresponding risk factors: the transition from being exposed to being infected and the transition from being infected to developing disease. Several studies have shown that smoking is a risk factor for tuberculin skin test reactivity, skin test conversion, and the development of active tuberculosis (Table 2). It has been reported an increased relative risk of development of tuberculosis for heavy smokers compared with nonsmokers (RR: 2.17; 95%CI, 1.29-3.63) (Yu et al., 1988). After adjusting for age and heavy drinking, smokers of 20 years' or greater duration had 2.6 times (95% CI, 1.1-5.9) the risk of nonsmokers for tuberculosis (Buskin et al., 1994). It has been found a strong association between active smoking and the risk of pulmonary tuberculosis (Alcaide et al., 1996). Both studies showed a dose-response relationship with the number of cigarettes consumed daily. In other study, current smokers had a nearly 2-fold increased risk compared with never-smokers (OR: 1.87; 95% CI, 0.73-4.80) (McCurdy et al., 1997).

A large case-control study in India examined smoking and tuberculosis in men between 35 and 69 years of age (Gajalakshmi et al., 2003). The tuberculosis prevalence risk ratio was 2.9 (95% CI, 2.6-3.3) for ever-smokers compared with never-smokers, and the prevalence was higher with a higher level of cigarette consumption. The authors found that the smoking attributable fraction of deaths from tuberculosis was 61%, greater than the fraction of smoking-attributable deaths from vascular disease or cancer. In a study among children living with a patient with active pulmonary tuberculosis, passive smoking confirmed by measurement of urinary cotinine levels was a strong risk factor for the development of active tuberculosis (OR: 5.39; 95% CI, 2.44-11.91) (Altet et al., 1996).

Study	Design/Population	Outcome
1) Yu GP et al.	Cross sectional study of risk factors associated to pulmonary TB diagnosis in adults, China.	RR of pulmonary TB for heavy smokers: 2.2 (95%CI 1.3-3.6).
2) Buskin SE et al.	Case-control study of risk factors for diagnosis of active TB among adults, USA.	OR for smokers ≥30 years: 2.6 (95%CI 1.1-5.9).
3) Alcaide J et al.	Case-control study investigating the impact of active and passive smoking on risk of developing active TB among infected young adults, Barcelona, Spain.	OR for young adults exposed to smoke: Active smoking: 3.6 (95%CI 1.4-9.2). Active and passive smoking: 5.1 (95%CI 1.9-13.2). Dose response: 1-20 cig/day: 3.0 (p<0.05). > 20 cig/day: 13.0 (p<0.001).
4) Altet MN et al.	Case-control study investigating the impact of passive smoking on risk of developing active TB among infected children, Barcelona, Spain.	OR for those exposed to passive smoke: 5.4 (95%CI 2.4-11.9). Dose response: 1-20 cig/day : 1.6 (95%CI 0.7-2.6). 21-40 cig/day: 4.0 (95%CI 1.5-9.8). > 40 cig/day: 7.8 (95%CI 3.4-17.6).
5) Tocque K et al.	Case-control study that investigates the impact of smoking on risk of pulmonary TB, Liverpool, England.	OR for smokers ≥ 30 years: 2.3 (95%CI 1.2-4.2).
6) Kolappan C & Gopi P.	Case-control study investigating the impact of smoking on diagnosis with pulmonary TB among men, India.	OR for smokers: 2.2 (95%CI 1.3-3.9) Dose response based on quantity and years smoked compared to non-smokers (p<0.0001).
7) Tekkel M et al.	Case-control study that investigates the risk factors for new diagnosis of pulmonary TB among individuals over age 15, Estonia.	OR of pulmonary TB diagnosis for smokers: Current smoker: 4.6 (95%CI 2.4-8.7) Former smoker: 2.3 (95%CI 1.0-5.1)
8) Leung CC et al.	Cross-sectional study to assess the impact of smoking on epidemiology and characteristics of TB, Hong Kong.	OR of developing TB among ever-smoker: 2.4 (95%CI 1.7-3.4).
9) Miguez-Burbano et al.	Case-control study that investigates the impact of long-term smoking on development of TB in HIV-1 infected patients, Miami, USA.	RR for long-term smokers (≥20 y): 3.0 (p=0.04).
10) Ariyothai N et al.	Case-control study investigating the impact of smoking (active and passive) on risk of pulmonary TB in HIV-negative individuals over age 15, Thailand.	OR for those exposed to tobacco smoke: Current active smokers: 2.7 (95%CI 1.0-7.0) Ever-active, >10 years 3.0 (95%CI 1.1-8.2) Ever-active, >10 cig/day: 4.0 (95%CI 1.3-12.6)
11) Crampin A et al.	Case-control study to examine risk factors for diagnosis with tuberculosis in individuals at least 15 years old, Malawi.	OR for smokers compared to never smokers: Ex-smokers: 1.6 (95%CI 0.7-3.2) < 5 cig/day: 0.9 (95%CI 0.5-1.7) ≥ 5 cig/day: 1.3 (95%CI 0.7-2.4)
12) Leung CC et al.	Prospective study of adults ≥65 years old to investigate the relationship between smoking and TB, Hong Kong.	Hazard ratios compared to never-smokers: Active tuberculosis: Current smoker: 2.6 (95%CI 1.9-3.7) Ex-smoker: 1.4 (95%CI 1.0-2.0)
13) Lienhardt C et al.	Case-control study to investigate host and environmental factors potentially associated with risk of developing smear-positive pulmonary tuberculosis in individuals >15 years, West Africa.	OR for smokers compared to never-smokers: Past smokers: 2.4 (95%CI 1.5-3.8) Current smokers: 3.1 (95%CI 2.4-4.2)
14) Tipayamongkhogul M et al.	Case-control study to examine risk factors associated with TB in BCG immunized children, Bangkok, Thailand.	Passive exposure to tobacco smoke was significantly associated with TB: OR: 9.31 (95%CI 3.14-27.58)

References: 1) *Tubercle* 1988;69:105-12 ; 2) *Am J Pub Health* 1994;84:1750-6; 3) *Tuber Lung Dis* 1996; 77:112-6; 4) *Tuber Lung Dis* 1996;77:537-44; 5) *Eur Respir J* 2001;18:959-64; 6) *Thorax* 2002;57:964-6; 7) *Int J Tuberc Lung Dis* 2002;6:887-94; 8) *Int J Tuberc Lung Dis* 2003;7:980-6; 9) *Addict Biol* 2003;8:39-43; 10) *Southeast Asian J Trop Med Public Health* 2004;35:219-27; 11) *Int J Tuberc Lung Dis* 2004;8:194-203; 12) *Am J Respir Crit Care Med* 2004;170:1027-33; 13) *Int J Epidemiol* 2005;34:914-23; 14) *Southeast Asian J Trop Med Public Health* 2005;36:145-50.

Table 2. Tobacco smoking and active tuberculosis (TB).

The biological basis by which tobacco smoking increases tuberculosis risk may be through a decrease in immune response, mechanical disruption of cilia function, defects in macrophage immune responses, and/or CD4+ lymphopenia, increasing the susceptibility to pulmonary tuberculosis (Rich & Ellner, 1994; Onwubalili et al., 1987).

4. Conclusion

Smoking appears to be an important risk factor for the acquisition of a lower respiratory tract infection (bronchitis, influenza, pneumonia, tuberculosis). This link is likely mediated by smoking's adverse effects on respiratory defenses (structural and immune system changes induced by smoking). Considering the high rates of morbidity and mortality from pneumonia, tuberculosis 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 influenza and pneumococcal infections highlights the importance of targeting this group for vaccination. The available epidemiological evidence, from studies worldwide, indicates a dose-response relationship between smoking and tuberculosis and that the association is likely to be a causal one. This provides a compelling reason for smoking cessation measures to be undertaken to combat the scourge of tuberculosis, particularly in developing countries. 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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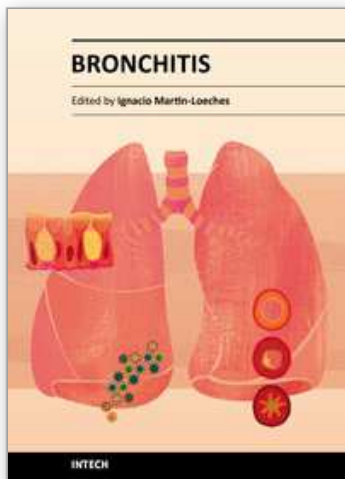
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Lung parenchyma has been extensively investigated. Nevertheless, the study of bronchial small airways is much less common. In addition, bronchitis represents, in some occasions, an intermediate process that easily explains the damage in the lung parenchyma. The main target of this book is to provide a bronchial small airways original research from different experts in the field.

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