Bacterial Infection and the Pathogenesis of COPD*

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Bacterial infection of the lower respiratory tract can impact on the etiology, pathogenesis, and the clinical course of COPD in several ways. Several recent cohort studies suggest that lung growth is impaired by childhood lower respiratory tract infection, making these individuals more vulnerable to developing COPD on exposure to additional injurious agents. Impairment of mucociliary clearance and local immune defense in smokers allows bacterial pathogens to gain a foothold in the lower respiratory tract. These pathogens and their products can cause further impairment of mucociliary clearance due to enhanced mucus secretion, disruption of normal ciliary activity, and airway epithelial injury, and thus persist in the lower respiratory tract. This chronic colonization of the lower respiratory tract by bacterial pathogens could induce a chronic inflammatory response with lung damage. Nontypeable *Haemophilus influenzae*, usually regarded as an extracellular mucosal pathogen, has been demonstrated to cause intracellular infections of the upper and lower respiratory tract respiratory tissue. Increased incidence of chronic *Chlamydia pneumoniae* infection of the respiratory tract has been associated with COPD. These chronic infections of respiratory tissues could contribute to the pathogenesis of COPD by altering the host response to cigarette smoke or by inducing a chronic inflammatory response. Application of newer molecular and immunologic research techniques is helping us define precisely the role of bacterial infection in COPD.

(CHEST 2000; 117:286S–291S)

Key words: bacterial infection; COPD; *Haemophilus influenzae*; pathogenesis

Abbreviations: CF = cystic fibrosis; IL = interleukin; LOS = lipo-oligosaccharide; NTHI = nontypeable *Haemophilus influenzae*; PCR = polymerase chain reaction

The precise role of bacterial infection in COPD has been a source of controversy for several decades.1,2 Several putative roles of bacterial infection in the etiology, pathogenesis, and the clinical course of COPD can be identified.3 These include the following: (1) childhood lower respiratory tract infection impairs lung growth reflected in a lower FEV\(_1\) in adulthood; (2) chronic colonization of the lower respiratory tract by bacterial pathogens induces a chronic inflammatory response with lung damage (the vicious circle hypothesis); (3) chronic infection of respiratory tissues by bacterial pathogens contributes to the pathogenesis of COPD by altering the host response to cigarette smoke or by inducing a chronic inflammatory response; (4) bacteria cause acute exacerbations of chronic bronchitis, which contribute significantly to the morbidity and mortality of COPD; and (5) bacterial antigens in the lower airway induce hypersensitivity that enhances airway hyperreactivity. With the availability of newer molecular and immunologic research techniques, the role of bacterial infection in COPD is being reevaluated. In this article, the first three putative roles of bacterial infection in either predisposing to COPD or contributing to its pathogenesis by causing a chronic infection of the lower airways will be discussed.

Childhood Infection and Adult Lung Function

Several recent studies have reported lung function (by spirometry) in cohorts of adult patients for whom reliable information is available regarding the incidence of lower respiratory tract infection (bronchitis, pneumonia, whooping cough) in childhood (<14 years of age; Table 1).3–6 All of these studies have shown a lower FEV\(_1\) and often a lower FVC among adults who experienced childhood lower respiratory tract infection.3–6 This association is seen after controlling for confounding factors such as tobacco exposure. The magnitude of this defect in FEV\(_1\) has varied among the studies and is greater in older cohorts. The defect in lung function is not obstructive with preservation of the FEV\(_1\)/FVC ratio, but is consistent with “smaller lungs,” suggesting impaired lung growth. The extent of decrease in FEV\(_1\) is unlikely to cause symptomatic pulmonary disease on its own, but could make the individual susceptible to the effects of additional injurious agents such as tobacco smoke.

Although the association between childhood lower respiratory tract infection and impaired lung function in adulthood is now well established, there is ongoing debate as to whether this association reflects a cause-effect relationship in which the infectious process damages a vulnerable lung undergoing rapid postnatal growth and maturation. If this was the case, then the effect of the infection on lung function should be seen only in the first 2 years of life during postnatal lung growth but not in later childhood (3 to 14 years). However, this has not been observed consistently in the studies to date.3–6 An alternative explanation for the observed association is that an undetermined genetic factor predisposes these individuals to lower respiratory tract infections in childhood as well as a lower FEV\(_1\) in adulthood. This explanation implies that impaired lung growth antedates the respiratory tract infection.

The etiology of childhood pneumonia and bronchitis was not established in these studies. Bacterial infection, especially by *Streptococcus pneumoniae* and *Haemophilus influenzae* is a common cause of severe pneumonia in children.7 The impact of childhood bacterial lower respiratory tract infection on the prevalence of COPD is likely to be greater in developing countries where there is a high incidence and inadequate treatment of these infections.
Vicious Circle Hypothesis

Tobacco smoking cannot be the sole factor responsible for the pathogenesis of COPD, as only a small proportion (15%) of smokers develop chronic bronchitis and an even smaller proportion go on to develop COPD. In the absence of underlying lung disease, the tracheobronchial tree is sterile. In patients with COPD, the tracheobronchial tree is chronically colonized with potential respiratory pathogens, predominantly nontypeable H influenzae (NTHI), S pneumoniae, and Moraxella (Branhamella) catarrhalis.8,9 Several years ago, we proposed a vicious circle hypothesis to explain how chronic bacterial colonization of the lower airways in patients with COPD can perpetuate inflammation and contribute to progression of the disease (Fig 1).1,10 Substantial supporting evidence for this hypothesis, both in vitro and in vivo, has now accumulated and is discussed below.

Vicious Circle Hypothesis Supporting Evidence

Central to the vicious circle hypothesis is the notion that once bacterial pathogens have gained a foothold in the lower respiratory tract from impaired mucociliary clearance due to tobacco smoking, they persist by further impairing mucociliary clearance (Fig 1). This impairment

Table 1—Association of Childhood Lower Respiratory Tract Infection With Level of Lung Function in Adults

<table>
<thead>
<tr>
<th>Study Authors/yr</th>
<th>n</th>
<th>Childhood Lower Respiratory Tract Infection</th>
<th>Age at Follow-up</th>
<th>Effect on FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker et al 3/1991</td>
<td>639 (all male subjects)</td>
<td>Bronchitis or pneumonia in first yr</td>
<td>59–67 yr</td>
<td>↓ 200 mL</td>
</tr>
<tr>
<td>Shaheen et al 4/1994</td>
<td>618</td>
<td>Pneumonia in first 2 yr</td>
<td>67–74 yr</td>
<td>↓ 650 mL (in male subjects with pneumonia)</td>
</tr>
<tr>
<td>Johnston et al 5/1998</td>
<td>1,392</td>
<td>Pneumonia in first 7 yr</td>
<td>34–35 yr</td>
<td>↓ 102 mL (with pneumonia)</td>
</tr>
<tr>
<td>Shaheen et al 6/1998</td>
<td>239</td>
<td>Pneumonia in first 14 yr</td>
<td>57.6 ± 4.3 yr</td>
<td>↓ 390 mL (with pneumonia in first 2 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchitis in first 14 yr</td>
<td></td>
<td>↓ 130 mL (with bronchitis in first 2 yr)</td>
</tr>
</tbody>
</table>

Vicious Circle Hypothesis
Initiating factors
e.g. smoking, childhood respiratory disease

Impaired mucociliary clearance

Airway epithelial injury

Progression of COPD

Bacterial colonization

Bacterial products

Inflammatory response

Altered elastase - anti-elastase balance

Increased elastolytic activity

Figure 1. Schematic diagram of the vicious circle hypothesis of the role of bacterial colonization in the progression of COPD.
of mucociliary clearance can be due to enhanced mucus secretion, disruption of normal ciliary activity, and airway epithelial injury. Experimental evidence demonstrates that respiratory tract pathogens and their products can cause all of these effects in vitro.

**Bacterial Infection and Chronic Mucus Hypersecretion**

Adler et al.\(^{11}\) examined the effect of cell free filtrates of broth cultures of NTHI, *S. pneumoniae*, and *Pseudomonas aeruginosa* on the secretion of mucous glycoproteins by explanted guinea pig airway tissue. Seven of 28 strains (25%) of NTHI, 10 of 26 strains (34%) of *S. pneumoniae*, and 12 of 18 strains (66%) of *P. aeruginosa* stimulated mucin secretion. This stimulation was a true secretory effect and not passive release of preformed intracellular macromolecules due to cellular damage, as ultrastructural assessment (by light, transmission, and scanning electron microscopy) demonstrated an absence of cytotoxicity. The *Pseudomonas* stimulatory products were 60- to 100-kd proteases. The NTHI and pneumococcal stimulatory exoproducts were 50 to 300 kd in size and did not possess proteolytic activity.

**Bacterial Infection and Mucociliary Clearance**

The tracheobronchial ciliary escalator is of paramount importance in maintaining sterility of the lower respiratory tract by transporting bacteria trapped in mucus toward the pharynx.\(^{12}\) Disruption of this ciliary activity is therefore likely to be very important in the establishment of a chronic colonization in the tracheobronchial tree. Wilson et al.\(^{13}\) measured using photometry the effect of cell-free supernatants of NTHI, *P. aeruginosa*, and *Staphylococcus aureus* on ciliary beat frequency of strips of human nasal ciliary epithelium. Rapid inhibition of ciliary beat frequency was seen with NTHI and *P. aeruginosa* but not with *S. aureus*. On direct examination, ciliary dyskinesia and ciliostasis were seen. Human neutrophil elastase inhibits ciliary activity and damages respiratory epithelium.\(^{14,15}\) Bacterial products in the airways may be a potent stimulus for neutrophil migration into the airways, and elastase released from these neutrophils can act synergistically with bacterial products and cause further inhibition of tracheobronchial ciliary function.

**Bacterial Infection and Airway Epithelial Injury**

An important component of the vicious circle hypothesis is the potentially damaging effects of bacteria and bacterial products on airway epithelial lining cells. Such epithelial injury in the large airways would contribute to bacterial persistence, and in the small airways could contribute to the respiratory bronchiolitis that causes progressive airways obstruction. In an *in vitro* tissue culture model of nasal turbinate epithelium, Read et al.\(^{16}\) have demonstrated that NTHI is capable of causing airway epithelial injury. They studied these epithelia after 30 min, 14 h, and 24 h of incubation with a NTHI strain. At 30 min, the airway epithelium and cilia were intact and the bacteria were found associated with the overlying mucus layer. At 14 h, patchy injury developed to the airway epithelium, with bacterial cells now associating with these damaged epithelial cells but not with intact epithelium. At 24 h, detached epithelial cells with adherent bacteria were seen.

The studies discussed above demonstrate that bacteria that colonize and infect the lower respiratory tract in COPD are capable of fostering in the tracheobronchial tree an environment in which they can persist, supporting the central tenet of the vicious circle hypothesis (Fig 1). Recently, more attention is being directed toward another portion of the vicious circle, the possible effects of bacterial products and the chronic inflammatory response it engenders on the elastase-anti-elastase balance in the lung. If bacterial products in the tracheobronchial tree could cause neutrophil influx and degranulation in the airways and lung parenchyma, they could contribute to chronic inflammation, parenchymal lung damage, and progressive small airway obstruction seen in COPD. Evidence to support the occurrence of such an effect of bacterial products in the lower respiratory tract is presented below.

**Bacterial Infection and Airway Inflammation**

The presence of bacteria in the lower airways in patients with stable COPD has been labeled colonization. However, this bacterial presence is definitely abnormal, as the lower respiratory tract in the absence of lung disease is normally sterile.\(^{8,9}\) This abnormal colonization of the tracheobronchial tree is not confined to the large airways. It has been shown to extend to the peripheral airways by bronchoscopic protected specimen brushings culture.\(^{17}\) Even during colonization, bacteria in these airways are likely to be in a constant state of turnover, releasing extracellular products, undergoing lysis with release of a variety of proteins, lipo-oligosaccharide (LOS) and peptidoglycan. LOS is a potent inflammatory stimulus; in fact, repeated instillation of LOS can lead to development of emphysema in hamsters.\(^{18}\) It is therefore quite likely that this colonization actually is a low-grade smoldering infection that induces chronic airway inflammation. In the large airways, such inflammation would contribute to mucus production; in the small airways, it could contribute to respiratory bronchiolitis and progressive airway obstruction. Direct evidence from patients with COPD that colonization of the airways induces inflammation is forthcoming.\(^{19,20}\) Indirect evidence includes *in vitro* experiments with NTHI LOS and from patients with cystic fibrosis (CF), another disease associated with airway bacterial colonization.

Khair et al.\(^{21}\) incubated explant cultures of human bronchial epithelium with NTHI LOS at two different concentrations, 10 μg/mL and 100 μg/mL. Epithelial permeability and intracellular adhesion molecule-1 expression, and release of interleukin (IL)-6, IL-8, and tumor necrosis factor-α into the culture medium were measured. IL-6 and tumor necrosis factor-α secretion and intracellular adhesion molecule-1 expression by the bronchial epithelial cells was significantly increased by only the
higher concentration of LOS (100 μg/mL), while IL-8 expression was stimulated by both 10 μg/mL and 100 μg/mL LOS. The levels of inflammatory mediators attained in the culture medium were adequate to increase neutrophil chemotaxis and adherence in vitro. There was no increase in epithelial permeability.

Konstan et al.22 compared airway inflammation in 18 adolescents or adults with mild CF (FEV₁ of 79 ± 4% predicted) with 23 healthy control subjects. The CF patients were free of symptoms of acute infection and were therefore presumed to have mucosal bacterial colonization with little inflammatory response or ongoing lung destruction. BAL was obtained in these subjects for quantitative bacterial culture, cell counts, Ig, and elastase measurement. *P. aeruginosa* was isolated from the BAL in 16 patients, *S. aureus* and NTHI in 6 patients each, while all the samples from the healthy control subjects were sterile. A marked inflammatory response was seen in the CF patients, with total (mean ± SEM) cell counts in the BAL of epithelial lining fluid of 68 ± 32 × 10⁶ cells/μL vs 5 ± 1×10⁶ cells/μL in healthy control subjects; differential cell count in the CF patients revealed an intense neutrophilia (57%) vs 3% in control subjects. IgG, IgA, and IgM were elevated 2.5- to sixfold in the patients demonstrating an active local immune response. Fifteen of 18 patients had free elastase in BAL, while none was present in the control subjects, and the concentrations measured were greatly in excess of the nanomolar quantity required to interfere with local host defenses, cause mucin secretion, and stimulate IL-8 release, etc. This shows that in CF there is an active inflammatory response in the lower airways to bacterial colonization.

**Chronic Bacterial Infection of Respiratory Tissues**

Bacterial pathogens implicated in COPD such as NTHI have always been regarded as extracellular pathogens that infect the airway lumen. Recently, NTHI infection of the respiratory tissue by has been demonstrated in both upper and lower respiratory tract.23,24 Whether chronic *Chlamydia pneumoniae* infection of the respiratory tract is associated with COPD has also been recently investigated.25 These studies have used detection techniques more sensitive than bacterial cultures for determining the presence of bacterial organisms in tissue and have made some very interesting and somewhat surprising observations.

**Intracellular NTHI Infection of Respiratory Tissues**

Forsgren et al.23 examined hypertrophied adenoid tissue removed at adenoidectomy from 10 children with nasal obstruction for the presence of intracellular NTHI. Three complementary techniques were used: in situ hybridization with a fluorescent-labeled probe specific for 16s ribosomal RNA of NTHI, transmission electron microscopy, and culture of the adenoid tissues after treatment with an aminoglycoside to kill extracellular bacteria. They detected NTHI in the adenoids of all 10 patients with in situ hybridization, mostly in the reticular crypt epithelium and in subepithelial locations. Transmission electron mi-

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**Figure 2.** Potential pathways by which infection-induced lung damage could contribute to the pathology of COPD.
Crosseyed these findings, and culture techniques showed that these intracellular bacteria were viable. The reservoir for these bacteria appeared to be large subepithelial mononuclear cells, likely macrophages, which contained up to 200 viable and actively dividing intracellular NTHI per cell. This was confirmed by enriching macrophages from the adenoid cell suspension and demonstrating high titers of bacteria on culture in these enriched cells.

Forty-nine explanted lungs from patients undergoing lung transplantation were examined for the presence of NTHI by Möller et al. The underlying lung disease was COPD in 16, CF in 16, bronchiectasis in 5, and noninfectious pulmonary diseases in 12 patients. The presence of NTHI was determined by staining tissue sections with a monoclonal antibody that binds to an epitope on the outer membrane protein P6 of NTHI and with polymerase chain reaction (PCR) for the same outer membrane protein with DNA extracted from the lung tissue as a template. NTHI was present in tissue sections by immunostaining and PCR in 24 of 49 (49%) patients overall. When classified by underlying disease, lung explants were positive for NTHI in 10 of 16 CF (62%), 8 of 16 COPD (50%), 2 of 5 bronchiectasis (40%), and 4 of 12 noninfectious diseases (33%) specimens. NTHI was present in a significantly greater proportion of tissue sections from patients with COPD and CF than from patients with bronchiectasis and noninfectious diseases (58% and 47% vs 33% and 29%, respectively; p < 0.0001). NTHI was found in subepithelial tissues and in macrophages, and were found with equal frequency in all parts of the lung, central and peripheral airways, and in the parenchyma.

These two studies demonstrate that NTHI resides intracellularly, especially in macrophages, and in the subepithelial zone in human respiratory tissues. These bacteria are protected from antibiotics and bactericidal antibodies, and may act as reservoirs of infection. Tissue infection by NTHI could also contribute to the pathogenesis of COPD directly or indirectly. Chronic low-grade infection could directly induce a chronic inflammatory response in the parenchyma and the airways of the lung that could be additive or synergistic to the inflammatory effects of tobacco smoke. Indirectly, such an infection could enhance the damaging effects of tobacco smoke on respiratory tissues. On the other hand, it is possible that this tissue infection is simply a marker of compromised local immunity. Whether tissue infection by NTHI is seen in early COPD and the effect of this infection in tissue models needs to be investigated.

**Chronic C. pneumoniae infection in COPD**

*C. pneumoniae* is an obligate intracellular atypical bacterial pathogen. Acute *C. pneumoniae* infection can cause bronchitis and pneumonia. Chronic infection with *C. pneumoniae* is being actively investigated as a cause of several systemic diseases, especially coronary artery disease. von Hertzen et al. studied whether the incidence of chronic *C. pneumoniae* infection is increased in COPD. Presence of chronic *C. pneumoniae* infection was determined by three different methods: serum antibodies to *C. pneumoniae* (IgG and IgA and circulating immune complexes), sputum IgA antibodies to *C. pneumoniae*, and PCR of sputum for *C. pneumoniae* DNA. Two of the three methods had to yield positive results in a patient to conclude that he or she had a chronic *C. pneumoniae* infection. Thirty-four patients with severe COPD, and 13 patients with mild to moderate COPD were compared with 23 patients with community-acquired pneumonia who served as control subjects. The incidence of chronic *C. pneumoniae* infection (as defined above) was 71% in patients with severe COPD, 46% in mild to moderate COPD, and 0% in the control group. Whether this chronic infection contributes to the pathogenesis of COPD as discussed above or is a reflection of compromised local immunity warrants further investigation.

**SUMMARY**

Figure 2 summarizes the known and proposed mechanisms by which bacterial infection of the tracheobronchial tree can produce the symptom complex, pathologic features, and pathophysiology of COPD. This model parallels in many respects the mechanisms by which tobacco smoking causes chronic bronchitis and airway obstruction. This proposed mechanism therefore emphasizes how tobacco smoking and tracheobronchial infection can synergistically induce this chronic disabling disease.

**Future Directions**

There are several unanswered questions regarding bacterial infection in COPD that can be exciting areas of investigation. Which bacterial products (eg, LOS, outer membrane proteins) are present in the lower airways in chronic bronchitis and at what concentration? What are the mechanisms by which these bacteria and their components incite airway inflammation? Is this airway inflammation correlated with progression of airway obstruction in these patients?

Answering such questions will enable us to place the role of bacteria in this chronic disabling disease in the correct perspective. If bacteria do play a role in progression of obstruction, then important new areas of therapeutic intervention open up, including vaccines and antimicrobial therapy to prevent persistent bacterial colonization.

ACKNOWLEDGMENT: The author thanks Adeline Thurston for secretarial assistance.

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Bronchial Inflammation*

Its Relationship to Colonizing Microbial Load and α₁-Antitrypsin Deficiency

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Neutrophil elastase is capable of generating many of the features of chronic bronchial disease. In patients with COPD, airways inflammation with neutrophil recruitment and elastase release is positively correlated with colonizing bacterial load in the stable clinical state (p < 0.0005). In addition, α₁-antitrypsin deficiency is associated with a greater neutrophil load, higher elastase activity, leukotriene-B₄ concentration, and serum protein leak than matched patients without deficiency (p < 0.005). These data confirm an effect of bronchial colonization on airways inflammation in COPD and indicate the role of α₁-antitrypsin in its modulation.

(CHEST 2000; 117:291S–293S)

Key words: α₁-antitrypsin deficiency; bacteria; COPD; inflammation

Abbreviations: α₁-AT = α₁-antitrypsin; LTB₄ = leukotriene B₄; MPO = myeloperoxidase; NE = neutrophil elastase; SLPI = secretory leukotriene inhibitor

The presence of bronchial disease is often a feature of patients with COPD. It is associated with inflammation, as indicated by the presence of increased numbers of neutrophils, ¹ a reduction in mucociliary clearance, mucus gland hyperplasia, and epithelial damage,² all of which may facilitate bacterial colonization.

Neutrophil elastase (NE) has been shown to produce many of the features of bronchial disease, including the

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