

## Canadian guidelines for the management of acute exacerbations of chronic bronchitis

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Acute exacerbations of chronic bronchitis (AECB) account for over 1.5 million physician visits annually in Canada and are a cause of significant morbidity and mortality. This document represents a joint effort between respirologists, microbiologists, infectious disease specialists and family physicians to update the Canadian AECB guidelines published in 1994. Treatment recommendations are graded on the strength of evidence in the published literature where possible. The role for oral corticosteroid therapy in preventing treatment failures, speeding up recovery and delaying the time to next exacerbation is discussed. Risk factors for treatment failure were used to stratify patients into risk groups to help guide antibiotic treatment recommendations. The importance of emerging antimicrobial resistance to current antibiotics is reviewed and strategies to prevent future AECB episodes are suggested.

**Key Words:** *Chronic bronchitis, Exacerbations, Antibiotics, Risk Stratification*

Acute exacerbations of chronic bronchitis (AECB) account for over 1.5 million physician visits annually in Canada and are a cause of significant morbidity and mortality. Canadian guidelines for the management of chronic bronchitis were published in 1994 (1). In that document, the pathophysiology of chronic bronchitis and emphysema and the pathology, risk factors, diagnosis and treatment of chronic bronchitis were discussed. AECB were dealt with in the major section of the document. A stratification system comprising five different patient groups was proposed, with antimicrobial recommendations made for each group. Many recent developments have forced a re-examination of these recommendations with respect to the risk stratification process and the specific antimicrobial recommendations. This document is an update from our original guidelines and is a joint effort by the Canadian Thoracic Society (CTS) and the Canadian Infectious Disease Society (CIDS).

### Lignes directrices canadiennes sur le traitement des exacerbations aiguës de bronchite chronique

Les exacerbations aiguës de bronchite chronique (EABC) motivent plus 1,5 million de consultations médicales chaque année, au Canada et sont cause d'une morbidité et d'une mortalité importantes. Le présent document est le fruit du travail de collaboration entre les pneumologues, les microbiologistes, les infectiologues et les omnipraticiens visant à actualiser les lignes directrices canadiennes en matière d'EABC, publiées en 1994. Les recommandations relatives au traitement ont été cotées, dans la mesure du possible, en fonction du degré de fiabilité des données trouvées dans la documentation. On y traite du rôle de la corticothérapie orale pour éviter les échecs de traitement, accélérer le rétablissement et repousser la prochaine exacerbation. Les facteurs de risque d'échec de traitement ont servi de critère à la classification des patients en groupes de risque pour aider à orienter les recommandations quant à l'antibiothérapie. Il est également question de l'importance d'un phénomène nouveau, soit de la résistance des bactéries aux antibiotiques actuels, et de stratégies pour prévenir les futurs épisodes d'EABC.

### METHODS

A needs assessment survey was sent out with the 1994 guidelines to representative family physicians across Canada early in 1999. The purpose was to obtain insight into the major challenges they faced in diagnosing and managing AECB. A committee was established that was composed of members from both the CTS and the CIDS, as well as two family physicians with strong interests in continuing medical education and AECB. The committee members were divided into four teams, each of which was responsible for one of four sections. These sections were as follows: epidemiology, risk factors, pathogenesis and pathophysiology; diagnosis and therapy excluding antibiotics; antimicrobial therapy; and resistance. The committee met for one day in Toronto, Ontario, in May 1999 to discuss key areas of interest and controversy. Subsequently, each team developed a draft of its section. These drafts were then circulated among all committee members and revised a number of times based on comments from committee members and outside reviewers.

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Relevant articles published between 1966 and July 1, 2002, were retrieved from Medline using the index terms 'chronic obstructive pulmonary disease', 'chronic bronchitis' combined with 'acute exacerbations', as well as specific terms relating to various interventions such as 'steroids', 'bronchodilators', 'anticholinergics', 'antibiotics' and 'mucolytics'. Articles published before 1966 were retrieved from the reference lists of later papers. The Cochrane control trials register until the end of the year 2001 was also searched. In addition, abstracts from the American Thoracic Society, American College of Chest Physicians, European Respiratory Society and International Conference on Antimicrobial Agents in Chemotherapy meetings from 1999 to 2002 were reviewed.

Treatment recommendations were graded on the strength of evidence similar to those used for the Canadian guidelines for the initial management of community-acquired pneumonia (2). Well-conducted, randomized, controlled trials constitute strong or Level I evidence; well-designed controlled trials without randomization including cohort and case-control studies constitute Level II or fair evidence; and expert opinion, case studies, and before and after studies are Level III or weak evidence. These ratings appear as roman numerals in parentheses after each recommendation in these guidelines.

### EPIDEMIOLOGY AND RISK FACTORS

Chronic obstructive pulmonary disease (COPD) is now the fifth leading cause of death in Canada and the prevalence is increasing (3). There have been several attempts in recent years to define COPD (4,5). Most definitions consider COPD to be a disease state characterized by air flow limitation that is not fully reversible. The air flow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to inhaled particles or gases. It is an umbrella term that includes the entities of chronic bronchitis and emphysema when associated with air flow limitation. Ordinarily, asthma, cystic fibrosis, bronchiectasis and bronchiolitis obliterans are excluded from this definition.

Chronic bronchitis can be defined clinically as a disorder with expectoration of sputum on most days during at least three consecutive months for more than two successive years, other causes of cough and sputum having been excluded (6). Chronic bronchitis is present in approximately 85% of patients with COPD. Chronic bronchitis frequently coexists with emphysema and small airways disease, the degree of each varying from person to person. It is essential to recognize that chronic bronchitis often occurs without airway obstruction; only a minority of patients with chronic bronchitis have evidence of COPD (7).

#### Epidemiology

Between 1951 and 1984, the mortality from COPD in Canada increased in both sexes, and by the mid 1980s, COPD was the sixth leading cause of death in men and the eighth leading cause of death in women (8). By 1995, COPD was the fifth leading cause of death in Canada and there had been an increase in total deaths from 4438 in 1980 to 8583 in 1995. During this period, the age-standardized mortality in men remained stable (around 45 per 100,000 population) while it doubled in women (8.3 per 100,000 in 1980 to 17.3 per 100,000 in 1995) (9). Review of data from the 1994 to 1995 Canadian National Health Survey indicated that about 750,000 Canadians had chronic bronchitis or emphysema

diagnosed by a health professional. The prevalence of COPD in Canada has been estimated to be about 5% in adults between the ages of 55 and 75 and approximately 7% in the over 75 age group. In 1993 to 1994, there were 55,782 hospital separations in which COPD was the primary discharge diagnosis; this was increased from 42,102 in 1981 to 1982. The average in-hospital length of stay for patients admitted with COPD was 9.6 days in 1981 to 1982 and 8.3 days in 1993 to 1994 (9). These data clearly demonstrate that COPD is a disorder with enormous morbidity and mortality, and puts a very significant burden on health care resources.

COPD appears to have a similar prevalence in other Western countries. The Cardiovascular Health Study (10) in the United States, in which spirometry was performed on 5201 elderly individuals, demonstrated that 5% of adults over the age of 65 reported a diagnosis of one of the COPDs (asthma, chronic bronchitis and emphysema). In this study, undiagnosed airway obstruction was noted in 7% of individuals and was most likely to occur in current and former smokers, women, lower income groups and individuals with chronic cough. This still may be an underestimate with reports of as many as 20% of the population having COPD in the United States, where it is the fourth leading cause of death (11,12). The prevalence of COPD in Europe varies from approximately 4% in Denmark and Norway (13,14), to 6% in Spain and Sweden (15,16). Data from the Asia Pacific area appear to be in the same range (17). In some communities, the prevalence of chronic bronchitis is much higher, and this may reflect the local environment and smoking habits. In Nepal, the prevalence of chronic bronchitis is 18% with similar frequency in men and women, and this may relate to exposure to wood smoke for cooking with inadequate or absent ventilation (18).

#### Risk factors

Smoking, some occupational exposures and alpha-1 antitrypsin deficiency are well-established risk factors for the development of COPD. There is good evidence that a number of other risk factors are also important including air pollution, environmental tobacco smoke, respiratory infections, airway hyperresponsiveness and genetic factors.

Cigarette smoking is undoubtedly the most common cause of chronic bronchitis, and there is well-established evidence that cigarette smoking is associated with increased mortality from COPD, increased prevalence of symptoms of COPD and increased prevalence of lung function abnormalities. The degree of abnormality is proportional to the amount smoked and is not specific for cigarettes, because both pipe and cigar smokers also have an increased morbidity and mortality from COPD. Although many smokers have some degree of cough and sputum production, only approximately 15% will develop significant COPD (19-21). In Western society, cigarette smoking accounts for 80% to 90% of the overall COPD burden (22).

A number of occupations have been associated with the development of COPD, and there is good evidence that chronic exposure to cadmium, silica, minerals and grain dusts can result in the development of airway disease. Workers involved in mining, furnace work, farming, metal work, wood and paper work, and cement workers are all at increased risk. Grain workers and cotton workers also have an increased risk of COPD (23,24).

Alpha-1 antitrypsin deficiency is a well-recognized cause of COPD but is responsible for less than 1% of all cases. Only a

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few nonsmokers with alpha-1 antitrypsin deficiency develop emphysema; most never develop symptoms. Some alpha-1 antitrypsin-deficient smokers never develop obstruction (25). Some families appear to have an increased risk of COPD and it is probable that other genetic factors may increase susceptibility to COPD (26).

Individuals with increased airway hyperresponsiveness who smoke appear to be at increased risk for the development of COPD. It is difficult to determine whether bronchial hyperresponsiveness is a true risk factor for COPD or whether it follows as a result of the development of smoking-related airway disease and the decrease in lung function. The Lung Health Study demonstrated a strong correlation between increased bronchial hyperresponsiveness and accelerated decline in forced expiratory volume in one second ( $FEV_1$ ) (27). This finding confirmed earlier work that showed that both smokers and exsmokers with less nonspecific hyperreactivity had a slower decline in  $FEV_1$  (28).

Ongoing exposure to environmental tobacco smoke and secondhand smoke appears to be a risk factor for the subsequent development of chronic bronchitis (29); 4197 never smokers aged between 18 and 60 years in eight separate geographic areas of Switzerland were surveyed and it was found that there was an increased prevalence of respiratory symptoms that was directly proportional to the increased dose and duration of exposure to secondhand cigarette smoke (30).

There appears to be a causal relationship between early childhood infections and respiratory symptoms and reduced lung function in adult life. Over 800 children in East Boston were observed for 13 years, and it was found that respiratory illness before two years of age and two or more lower respiratory tract illnesses during a single surveillance year were associated with lowered lung function in adulthood (31). The causal relationship between pneumonia in early childhood and COPD in late adult life has been further supported in a study of 618 subjects with a mean age of 70 years in whom parish records were available for their first two years of life. It was found that pneumonia before the age of two was associated with a lower  $FEV_1$  in late adult life (32). Adenoviral infections are responsible for many childhood respiratory illnesses and the adenovirus is known to persist in a latent form. Latent adenoviral DNA was more commonly found in individuals with COPD than in those without (33). These data suggest that the developing airways are vulnerable to the effects of infection, and that latent adenoviral infections may contribute to the pathogenesis of COPD in adults. The role of acute respiratory infections in adults is less clear, although there is a good theoretical argument to support the "vicious circle" hypothesis of Cole and Wilson (34) that ongoing chronic bacterial infection may result in ongoing airway damage.

Air pollution appears to be a significant risk factor for COPD. The risk appears to be related to the nature and intensity of the air pollution. Exposure to particulates less than 10 microns was strongly correlated with the development of cough and sputum production and mortality in the Utah valley (35). More recently, a direct association between exposure to particulates in the air in Switzerland and symptoms of chronic phlegm production and cough was demonstrated in a large population study (36). Levels of air pollution have fallen considerably in most developed countries but are still high in many cities in developing countries, and levels of indoor air pollution can be very high in these countries – in particular,

where wood is burned to cook and heat the home. A recent case-control study in Colombia found wood smoke to be more highly associated with the development of COPD in women than either tobacco use or passive smoking (37).

There is currently no good evidence that race, socioeconomic class, education and dietary factors can be linked definitively as independent risk factors to the development of COPD. Recent data suggest that female sex may be an independent risk factor, although this has not been clearly established (38). It appears that women have a higher prevalence of airway hyperreactivity than men (39). Whether this alone explains their apparent increased susceptibility to the harmful effects of cigarette smoking remains to be determined.

## PATHOGENESIS, PATHOLOGY AND PATHOPHYSIOLOGY

The past few years have brought with them new interest into the basic mechanisms contributing to chronic bronchitis. A detailed review of this topic is outside the scope of these guidelines and the interested reader is referred elsewhere (40,41). This section reviews some basic tenets regarding the pathogenesis, pathology and pathophysiology of chronic bronchitis, particularly as it relates to acute exacerbations of the disease.

The pathological lesions of chronic bronchitis involve both the large and the small airways. The walls of the airways of affected patients contain a prominent inflammatory cell infiltrate. In the large airways, this inflammatory process is associated with metaplasia of both the columnar and the goblet cells lining the epithelium, an increase in the size of the mucous-secreting glands (42), an increase in the amount of smooth muscle and connective tissue in the bronchial wall (43) and degeneration of the airway cartilage (44). The Reid index, a ratio of gland to bronchial wall thickness, is the pathological marker of the excess cough and sputum production that defines the disease (39). However, there is no relation between this index and the degree of air flow obstruction, which appears to correlate better with the presence of inflammation in the small airways (45). Smooth muscle hyperplasia in chronic bronchitis is not related to bronchodilator responsiveness or bronchial hyperreactivity as occurs in asthma. However, bronchial hyperreactivity can be seen in up to 50% of patients with chronic bronchitis, occasionally making it difficult to exclude an asthmatic component to the illness. Part of the reason for the finding of bronchial hyperreactivity in chronic bronchitis may be due to the fact that these patients are starting with a lower  $FEV_1$ . The lower the  $FEV_1$ , the greater the response to an inhaled bronchoconstrictor. Therefore, the relevance of this finding remains unclear.

Two separate hypotheses have been put forward to explain the pathogenesis of chronic bronchitis and COPD. The "Dutch hypothesis" (46) postulated that airway hyperresponsiveness and atopy were markers of a basic genetic disturbance predisposing to the development of chronic lung disease characterized by the presence of cough, sputum production and air flow limitation. This suggests that asthma and chronic bronchitis are variations of the same disease. The "British hypothesis" (47,48) proposed that chronic obstructive bronchitis develops as a result of bronchial irritation and subsequent hypertrophy of mucous-secreting glands due to smoking, pollution and recurrent infections. The development of cough was hypothesized to lead to progressive airway obstruction, disability and death. A major criticism of this hypothesis was the

lack of evidence linking chronic cough and sputum production to progressive air flow limitation (49-51). However, recent studies have shown a consistent association between chronic mucous hypersecretion and both an accelerated decline in FEV<sub>1</sub> and an increased risk of subsequent hospitalization (52-54). In addition, exacerbation frequently appears to be correlated with FEV<sub>1</sub> decline (55), particularly in patients who continue to smoke (56). Thus, it appears that components of both of these hypotheses are likely to be correct. This would make it easier to explain the pathogenesis of such a heterogeneous disease.

The inflammatory cell infiltrate affects both the central airways and the peripheral airways, the sites responsible for the air flow limitation in smokers. So called 'small airways disease', a chronic inflammatory process of the small airways, has been demonstrated in virtually all young smokers (57). In addition, increased peripheral airway inflammation distinguishes the airways of smokers with obstruction from those without obstruction (58). However, only 15% to 20% of heavy smokers go on to develop clinically significant or measurable airway obstruction (48,59). Therefore, factors other than cigarette smoking alone must contribute to the development of air flow obstruction. There are most likely genetic factors influencing the susceptibility to the effects of cigarette smoking or the development of the airway inflammatory response to various stimuli (60,61). The association of mucous gland enlargement and goblet cell hyperplasia with the intensity of the inflammatory cell infiltrate in airway walls also suggests that inflammation is of central importance in the pathogenesis of chronic bronchitis. However, the cells, cytokines and mediators involved in the airway inflammation of chronic bronchitis are quite different from those found in asthmatic airways, perhaps explaining the differences in clinical presentation and responses to treatment of these diseases.

The neutrophil is the predominant cell found in the airways of patients with chronic bronchitis. Bronchial lavage fluid from patients with chronic bronchitis contains a significantly higher percentage of neutrophils than lavage fluid from asymptomatic smokers or normal control subjects (62). In addition, the potent neutrophil chemotactic factors, interleukin (IL)-8 and leukotriene B<sub>4</sub> (LTB<sub>4</sub>), and the neutrophil activation products myeloperoxidase (MPO) and elastase, are elevated in chronic bronchitis (63-65). There is evidence that the bacteria that colonize the airways of patients with chronic bronchitis and that are involved in many of the exacerbations of the disease secrete products that contribute to this neutrophil-driven inflammation (66). A higher percentage of neutrophils was found in the airways of smokers who developed airway obstruction over a 15-year period than those who did not (67). In addition, the annual decline in FEV<sub>1</sub> over the 15-year period was related to the degree of induced sputum neutrophilia implying cause and effect (68). Patients with more severe air flow obstruction have a higher percentage of neutrophils in both induced sputum and bronchial lavage (62,68,69). Finally, neutrophils in induced sputum are higher in COPD patients with severe air flow obstruction than nonobstructed smokers, nonsmoking control subjects and asthmatics (69).

Macrophages and activated T lymphocytes are also increased in the airways of patients with chronic bronchitis (70). The T cells are of the CD8<sup>+</sup> variety, differentiating the type of inflammation from that seen in asthma (71). Eosinophils, which are the predominant inflammatory cells in

the airways of asthmatics, do not seem to play a prominent role in the stable chronic bronchitic patient, although there have been reports of elevated bronchial lavage and biopsy eosinophils in some studies (64,65,72). The eosinophil may have a more prominent role in the pathogenesis of acute exacerbations (73).

#### Airway inflammation during AECB

Patients with chronic bronchitis are prone to recurrent exacerbations of their disease. Evidence is beginning to emerge that these exacerbations are associated with increased airway inflammation. In addition, there appears to be an association between the degree of inflammation and the severity and frequency of the exacerbations. Both the absolute number and the proportion of neutrophils in bronchoalveolar lavage (BAL) increase during AECB (74). In addition, cytokines and mediators known to reflect neutrophil infiltration and activation rise during AECB. Levels of IL-8, MPO and LTB<sub>4</sub> in induced sputum all rise during AECB (75-78). Patients with higher baseline cytokine levels have more frequent exacerbations (76). Patients with severe AECB requiring hospitalization have evidence of more severe neutrophilic inflammation during exacerbations (75).

Eosinophils, which do not appear to play a significant role in the pathogenesis of chronic bronchitis, may be important during AECB. There are increased numbers of eosinophils in induced sputum and BAL during AECB (74). In addition, bronchial biopsies taken from the airways of mild chronic bronchitics during an acute exacerbation have revealed marked increases in mucosal and submucosal eosinophils, as well as evidence of increased cellular activation (73,79).

#### Role of bacteria in chronic bronchitis and AECB

The normal tracheobronchial tree is sterile. In patients with chronic bronchitis, the lower airways are chronically colonized with bacteria, predominantly *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* (80-82). The role that these bacteria play in causing progressive lung disease remains controversial, but a clearer understanding of their interaction with damaged airways is emerging.

Cigarette smoking leads to the loss of ciliated epithelium and more viscous airway secretions, compromising the local defenses of the respiratory tract. The delay in mucociliary clearance allows inhaled bacteria to colonize the normally sterile airways (83). Once bacteria adhere to mucin or epithelial cells in the lower airway, they persist by further impairing mucociliary clearance. There are several mechanisms whereby bacteria may damage the lower airways. *H influenzae*, *S pneumoniae* and *Pseudomonas aeruginosa* have all been shown to stimulate mucus secretion (84). These same bacteria produce substances that impair ciliary function (85,86). In addition, there is some evidence that *H influenzae* can directly cause airway epithelial injury (87). Finally, bacteria residing in the lower airway secrete enzymes that break down local immunoglobulins, and also demonstrate antigenic heterogeneity to avoid immune surveillance and can form microcolonies surrounded by polysaccharide gel to decrease their clearance (88).

It is becoming clear that bacteria colonizing the lower airways of patients with chronic bronchitis are capable of stimulating the secretion of various inflammatory mediators and cytokines that contribute to airway inflammation. Lipopolysaccharide (LPS) is the major glycolipid in the outer

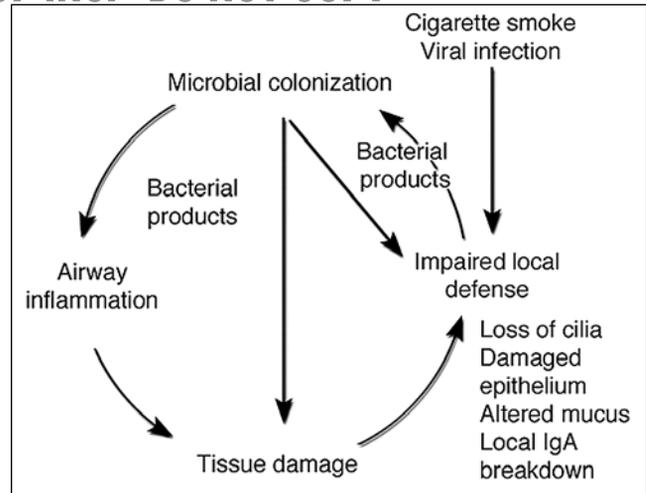
membrane of Gram-negative bacteria. Bacteria colonizing the airways are in a constant state of turnover to avoid recognition by the host inflammatory response. As they turn over, bacteria release extracellular products as well as LPS from their cell walls. LPS is a very potent inflammatory stimulus. *H influenzae* expresses an LPS molecule that lacks the long repeating polysaccharide side chains that are typical of this molecule in other Gram-negative bacteria. Therefore, the endotoxin of *H influenzae* is more commonly referred to as a lipo-oligosaccharide (LOS). LOS is a potent secretagogue for a variety of inflammatory mediators. It can increase epithelial cell permeability and can lead to the release of IL-6, IL-8 and tumour necrosis factor (TNF) (89).

Evidence has accumulated suggesting a correlation between levels of inflammatory mediators and cytokines and bacterial colonization of the lower airways. Soler et al (90) performed BAL and compared quantitative cultures of bacteria in the lower airways with the levels of various cytokines. They demonstrated that bacterial colonization of the lower airways was associated with significantly more neutrophils and TNF-alpha when compared with airways that did not have significant amounts of bacteria. In addition, there was a trend toward higher levels of IL-8 in the BAL of patients colonized with bacteria. Interestingly, bacterial colonization and increased inflammatory cells and cytokines occurred in patients with chronic bronchitis whether or not they had associated air flow obstruction. Bresser et al (91) performed similar experiments using expectorated sputum in patients with both obstructive and nonobstructive chronic bronchitis. They found similar correlations between the levels of certain cytokines and infection with *H influenzae*. Of interest, they also found differences in levels of TNF-alpha in patients with obstructive lung disease when compared with patients with nonobstructive chronic bronchitis. This is of interest because the TNF-alpha has been implicated in the pathogenesis of chronic airway obstruction (69,92).

To summarize, initial damage to the airways, most commonly caused by cigarette smoking, impairs mucociliary clearance and weakens host defences, allowing the normal sterile airways to become colonized with bacteria. Once the bacteria colonize the airways, they contribute to the airway inflammation and impaired mucociliary clearance allowing their persistence in the airways and, perhaps, contributing to progressive airway obstruction. This is referred to as the "vicious circle" hypothesis (Figure 1) (34,93).

#### Lower airway bacterial colonization during the stable state

Initial studies examined the presence of bacteria in the sputum of patients with stable chronic bronchitis. *H influenzae* was present in the sputum of up to 60% of such patients (94). More recently, bronchoscopic techniques have been used to examine pathogens residing in the airways during stable chronic bronchitis. Cabello et al (95) found colonization of the lower airways in 83% of COPD patients. They claimed that only a minority of these bacteria were potentially pathogenic. However, nonpotentially pathogenic bacteria may still contribute to lower airway inflammation and risk of recurrent infections with other species. In addition, our view as to what is a pathogenic microorganism changes with time. For example, *M catarrhalis* was considered a commensal for many years but is now thought to be a pathogenic species in AECB. A similar debate revolves around *Haemophilus parainfluenzae* (96). Zalacain et al (97), using a protected specimen brush, found



**Figure 1)** The role of cigarette smoke and viral infection in initializing and perpetuating the "vicious circle" of impaired local defenses. IgA Immunoglobulin A Source: Recommendations on the Management of Chronic Bronchitis: A Practical Guide for Canadian Physicians. Reprinted from Supplement to CMAJ 15 November 1994; 151:7-23 by permission of the publisher, © 1994 Canadian Medical Association (1)

significant bacterial growth in 40% of patients with stable COPD and in none of the control subjects. Monso et al (98) found significant bacterial growth in 22% of patients with stable COPD using similar methods. Nontypeable *H influenzae* was the most common isolate in both studies, which is consistent with virtually all studies done using sputum from patients with chronic bronchitis. Monso et al (98) reported that current smoking was the most important predictor of bacterial colonization, whereas Zalacain et al (97) determined that air flow obstruction and smoking were independent predictors of airway bacterial colonization. Recent studies have confirmed the association between the degree of air flow obstruction and the type of bacteria colonizing the lower airways. Individuals with chronic bronchitis and an FEV<sub>1</sub> less than 50% of predicted have a six-fold higher risk of being colonized by virulent Gram-negative bacteria such as *P aeruginosa* and *Enterobacteriaceae* species than do patients with an FEV<sub>1</sub> above 50% of predicted (99,100). Whether this is an effect of worsening air flow obstruction or, more likely, an effect of more frequent episodes of AECB with subsequent use of antibiotic therapy in patients with poor lung function remains to be determined.

The location of bacteria within the airways may be important in terms of both inducing inflammatory responses and protecting the bacteria from local defense mechanisms. Nontypeable *H influenzae* not only binds to human epithelial cells in the airways but is able to penetrate the epithelial cell layer where they may be protected from both antibiotics and antibody mediated bactericidal activity (101,102). Moller and colleagues (103) found *H influenzae* not only in the epithelium and submucosa of the bronchi, but also in the interstitium and alveolar epithelium of patients with end-stage lung disease undergoing lung transplantation. These bacteria residing in tissues may act as a reservoir for recurrent infections or induce chronic low-grade infection that continues to enhance the host inflammatory response as described by the vicious circle

**TABLE 1**  
Prevalence of bacterial pathogens from sputum in acute exacerbations of chronic bronchitis

	Fogarty et al (106)	Eller et al (99)	Wilson et al (107)	Shah et al (108)	Langan et al (109)	Georgopoulos et al (110)	Habib et al (111)	Chodosh et al (112)	DeAbate et al (113)
Year	2000	1998	1999	1999	1999	2001	1998	1998	1997
Patients, n	548	211	750	832	802	395	373	624	492
Patients with isolates, n	403	112	287	547	400	219	192	290	301
Total isolates, n	498	150	342	577	513	275	181	379	346
Bacterial isolates, %									
<i>Haemophilus influenzae</i>	18	14	31	36	36	35	25	18	17
<i>Moraxella catarrhalis</i>	9	7	15	16	12	13	14	21	14
<i>Streptococcus pneumoniae</i>	5	17	25	18	11	3	8	7	6
<i>Staphylococcus aureus</i>	13	13	5	3	9	3	7	20	10
<i>Pseudomonas</i> species	NR	15	1	8	NR	3	13	NR	5
<i>Haemophilus parainfluenzae</i>	28	NR	5	2	27	NR	12	6	15
<i>Enterobacteriaceae</i> species	NR	25	5	5	NR	33	19	NR	8

NR Not reported

hypothesis. Finally, there is evidence that there may be antigenic drift in nontypeable *H influenzae* species so that recurrent infections may actually be by new strains of the bacteria in some individuals (102,104,105).

#### Isolation of bacteria during an AECB

Bacteria have been isolated from sputum in up to 60% of AECB. The most common organism isolated include *H influenzae*, *H parainfluenzae*, *S pneumoniae*, and *M catarrhalis* (Table 1) (99,106-113). Some studies have found higher numbers of *Staphylococcus aureus*, *Pseudomonas* species and members of the *Enterobacteriaceae* family. It is not always clear whether these more virulent organisms are found in patients with more severe air flow obstruction, more frequent exacerbations treated with antibiotics, or are due to different culture techniques. Finding a bacterial pathogen within the airways of somebody during an AECB does not necessarily implicate that species as the trigger for the exacerbation. A number of studies have shown a similar incidence of bacterial isolation from sputum during periods of clinical stability and AECB (114,115). More recently, investigators have turned toward the use of bronchoscopy using protected specimen brushes or BAL sampling of the lower airways with subsequent quantitative cultures to determine the importance of bacteria during episodes of AECB. Four studies have now been published using these methods and all have shown evidence for significant bacterial infection of the distal airways in approximately 50% of patients experiencing an AECB (116-119). Two of these studies were performed in outpatients and demonstrated significant bacterial growth more frequently in patients during an episode of AECB than at baseline (117,119). Although many of the bacteria found in the airways were similar during periods of clinical stability and exacerbations, the colony counts were significantly elevated during episodes of AECB.

Sputum, bronchial washings and bronchial brushings may underestimate the presence of bacteria, particularly if the latter have penetrated the epithelial cell layer. Bandi et al (102) found nontypeable *H influenzae* in only 26% of bronchial washings or brushings from clinically stable patients with chronic bronchitis, and in only 7% of patients with AECB. However, intracellular nontypeable *H influenzae* were demonstrated in bronchial biopsies from 87% of patients

with AECB, 33% of stable patients with chronic bronchitis and from no healthy controls.

Sethi and colleagues (46) used molecular typing to identify new strains within a bacterial species in sputum isolates collected during an AECB. Exacerbations were associated with 33% of visits in which new strains were identified, versus only 15% of visits in which no new strains were found ( $P < 0.001$ ). These findings support an important role for bacteria in AECB.

If bacteria are important in inducing exacerbations and contributing to worsening airway inflammation, there should be a correlation between measures of airway inflammation and sputum culture results during an episode of AECB. Sethi et al (77) followed a group of COPD patients at regular intervals and cultured either spontaneously expectorated or induced sputum from individuals who had evidence of an AECB. The sputum specimens were also assayed for IL-8, TNF-alpha and neutrophil elastase, which were used as surrogate markers for neutrophilic inflammatory responses to acute bacterial infection in the airways. These investigators showed that there were significantly higher levels of markers of airway inflammation in pathogen-positive exacerbations than in pathogen-negative exacerbations, supporting a role for these pathogens in AECB.

One of the arguments against the importance of bacteria in AECB has been that many patients recover without antibiotic therapy. Up to this point, there have been no characteristic markers separating a bacterial exacerbation from a nonbacterial exacerbation, making the study of potential beneficial effects of antibiotics in AECB very difficult. Anthonisen et al (120) suggested that antibiotics benefit patients with AECB who have a triad of increased sputum volume, sputum purulence and worsening dyspnea. It was only in patients with all three of these symptoms that antibiotics seemed to have a statistically significant and clinically relevant advantage over placebo. Some studies purporting to show no additional benefits of antibiotics compared with oral corticosteroids alone included many patients who had underlying asthma, and no effort was made to document the presence of bacterial infection (121). More recently, Stockley et al (122) compared the presence of purulent sputum with the results of bacterial cultures. During periods of exacerbation, a positive bacterial culture was obtained from 84% of patients if their sputum was purulent, whereas positive cultures were obtained in only 38% of patients with mucoid sputum. In addition, when the patients

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were restudied in a stable state between exacerbations, the incidence of a positive bacterial culture was similar in both groups, approximating 40%. Overall, they felt that the presence of purulent sputum was 94.4% sensitive and 77% specific in predicting the yield of a high bacterial load in culture and in identifying the group most likely to benefit from antibiotic therapy. In a follow-up to this study, the same authors correlated the presence of sputum purulence with the levels of certain inflammatory markers including MPO, IL-8 and LTB4 (123,124).

The role of viruses and atypical organisms, such as *Mycoplasma* and *Chlamydia* species, is becoming clearer. There are three separate mechanisms whereby these organisms may have a role in COPD and AECB. First, infection with certain agents at a young age may make airways more susceptible to the effects of cigarette smoking and increase the risk of chronic bronchitis later in life. This has been suggested both with adenoviral infections in childhood (33) and with *Chlamydia pneumoniae* infection (125). Second, these organisms can cause AECB in their own right. Up to one-third of AECB are related to viral or *Mycoplasma* infections (82,114,126-128). *C pneumoniae* is thought to account for only 5% to 10% of acute exacerbations of COPD (129,130), although one recent study suggested that it may be involved either alone or as a cofactor in up to 22% of AECB (131). The third mechanism whereby viruses and atypical organisms may be involved in AECB would be by causing a primary infection that worsens lower airway inflammation, which enables a secondary increase in bacterial proliferation that would then play a role in the exacerbation (131,132). There is evidence that respiratory virus infections are associated with more severe and frequent AECB and may contribute to chronic infection in COPD (128). Rhinovirus infection had been shown to be involved in precipitating AECB (133) and a recent study suggests that rhinovirus infection leads to an elevation of lower airway IL-6 levels (134). This worsening of lower airway inflammation may theoretically enhance bacterial proliferation, leading to secondary bacterial involvement in these episodes of AECB as well.

### AECB

Like the disease itself, exacerbations of chronic bronchitis are defined clinically. It has become traditional to use some combination of the following three criteria originally described by Anthonisen and colleagues (120) to define AECB: increased cough and sputum, sputum purulence and increased dyspnea over baseline. Unfortunately, there are no characteristic laboratory or radiographic tests to make the diagnosis of AECB, so the definition of an exacerbation remains problematic. Seemungal and colleagues (134) have proposed major and minor criteria to define an exacerbation. The major criteria are the three proposed by Anthonisen. Minor criteria include wheezing, sore throat, cough and symptoms of a common cold such as nasal congestion or discharge. They defined an exacerbation as the presence of at least two major symptoms, or one major and one minor symptom, for at least two consecutive days. It is clear that the incidence of AECB will vary depending on which definition is used. Using the Anthonisen criteria, the typical patient with COPD will average two to three AECB episodes annually. Other causes of deterioration include congestive heart failure, pneumonia, pulmonary emboli, pneumothorax, inappropriate oxygen administration and drugs such as tranquilizers.

Approximately 50% of exacerbations, particularly those meeting the Anthonisen criteria, are believed to result from infection, but exposure to allergens, pollutants or irritants (cigarette smoke, dust) may all precipitate a worsening of chronic bronchitis. Exacerbation rates are an important determinant of disease-specific health status as measured by a standard quality of life questionnaire (135). Exacerbations may lead to hospitalization, which carries with it a 4% short term mortality rate for patients with mild to moderate disease (136), but as high as 24% if admitted to an intensive care unit with respiratory failure (137-140). This latter group of patients with severe disease have one-year mortality rates of up to 46% (137-139). Many patients requiring hospitalization for AECB will require subsequent readmissions because of persistent symptoms (137,140,141). In addition, they will experience at least a temporary decrease in their functional abilities (142).

There are no characteristic physical findings in AECB. Although some authors have suggested that severe exacerbations of chronic bronchitis are associated with a body temperature of higher than 38.5°C (143), this idea is not widely accepted. In fact, a study of patients hospitalized because of a severe AECB found that the mean temperature on admission was 36.4°C (137). The presence of an elevated body temperature should suggest a viral infection (128) or underlying pneumonia as a cause of an AECB. The lack of a clear definition of AECB has hampered investigation into appropriate therapy of the disorder.

Chest roentgenograms are not helpful in making the diagnosis of AECB, although they should be considered if there is a possibility of pneumonia or congestive heart failure contributing to the presentation. An exception to this general rule should be made for patients seen in emergency rooms or admitted to hospital. In these settings, routine chest roentgenograms have been shown to reveal abnormalities that lead to changes in management in 16% to 21% of patients (144-146).

Sputum Gram-stain and culture have a very limited role in the investigation of the etiology of AECB because, for reasons discussed above, the airways of patients with chronic bronchitis are chronically colonized with bacteria. Therefore, the finding of a particular organism does not necessarily imply a causal relationship to the AECB. Sputum analysis should be reserved for patients with frequent exacerbations or chronic purulent sputum in whom the presence of more virulent and/or resistant bacteria is more likely (Level III evidence).

Objective measurements of lung function are necessary to confirm the presence of air flow obstruction. There is a poor correlation between chronic symptoms of dyspnea and measurement of FEV<sub>1</sub> (147). In addition, there is a very poor correlation between the amount of sputum produced and the degree of air flow limitation (43,148). However, FEV<sub>1</sub> remains the best predictor of mortality (149) and has been shown to be important in predicting need for admission to the intensive care unit (150). There is also evidence that FEV<sub>1</sub> is highly predictive of clinical outcomes during AECB (151). Despite this there is continued evidence that spirometry is being underutilized in the patient group at risk of developing chronic bronchitis (152-154). The continued reliance on clinical indicators as a basis for obtaining spirometry leads to the underdiagnosis of COPD and other causes of air flow obstruction. Despite this, strong argument in favor of screening spirometry in high-risk individuals, there is little evidence to suggest that spirometry has a role in evaluating an AECB. Measurement of FEV<sub>1</sub> may not be possible

in a patient with a severe AECB. In addition, it is not clear that there is a correlation between transient falls in lung function and the severity of the exacerbation as defined by the Anthonisen criteria (120). Therefore, although it is helpful to know the premorbid FEV<sub>1</sub> as a predictor of adverse outcome during an AECB, it is not necessary that spirometry be performed during the actual exacerbation (Level III evidence). However, the development of an AECB should be a motivating factor to obtain objective measurements of pulmonary function after recovery in patients who had not previously had spirometry (Level III evidence). The use of peak expiratory flow rates (PEFR) is not recommended as a substitute for spirometry because it is much more effort-dependant, has not been demonstrated to predict outcome in COPD and should not show variability in a disease defined as having fixed air flow obstruction.

### Management of AECB

Chronic bronchitis is a clinical entity related to chronic/intermittent mucous hypersecretion. It represents a diagnostic category within the spectrum of COPD in which chronic air flow limitation may or may not be present. AECB are by definition associated with increases in the quantity and/or purulence of the sputum, with or without increased dyspnea. The large body of literature focusing on the treatment of AECB is, in most cases, focused on antimicrobial therapy.

The phrase 'exacerbation of COPD', on the other hand, typically refers to increases in dyspnea in association with increases in the degree of air flow limitation, with or without clinical manifestations of respiratory infection. Increased sputum volume and/or purulence may be present, but are not necessary for the diagnosis of COPD exacerbation.

The problem that becomes apparent in reviewing the COPD literature is that the majority of studies regarding treatment of exacerbations beyond antibiotics (oxygen, bronchodilators, corticosteroids, etc) are focused on exacerbations of COPD; hence, results are generally extrapolated, perhaps inappropriately, to the management of AECB.

Treatment of AECB should provide symptomatic relief, prevent transient loss of pulmonary function that may lead to hospitalization and lead to a re-evaluation of the disease in a particular patient to determine if the risk of future exacerbations can be reduced. Patients should be removed from any source of irritants that may worsen lower airway inflammation, including dust, pollutants and first- and second-hand smoke. Pharmacological therapy aims at decreasing the work of breathing, reducing airway inflammation, reducing the bacterial burden in the lower airways and treating any accompanying hypoxemia.

### Bronchodilator therapy

Bronchodilator therapy should be employed for the treatment of dyspnea accompanying an exacerbation. The majority of the studies examining the role for inhaled bronchodilators in exacerbations of COPD have been done in patients presenting to the emergency room or hospitalized because of the exacerbation. Therefore, it is not clear whether the results of these studies are applicable to the much larger population of AECB patients treated at home. In addition, the endpoint most commonly measured is FEV<sub>1</sub>, and this may not be the most relevant parameter because it may not change much in a single AECB episode. Some of the studies comparing anticholinergics to short-acting beta-agonists have combined asthmatics with

COPD patients. Nonetheless, certain general statements can be made based on the available literature (155).

Most studies comparing short-acting beta-agonists with inhaled anticholinergic agents show no appreciable difference between the two in terms of effects on pulmonary function (156-159). There may be fewer side effects with ipratropium than salbutamol (160). Most studies examining the effects of combination therapy do not report any added benefit of adding a second agent (156,160-162). One study demonstrated a greater improvement in FEV<sub>1</sub> with combination therapy than with a beta-agonist alone (163), while another showed shorter emergency room stays for the group on combination therapy (164). None of these studies are well standardized in terms of dose of medication or dosing frequency. Therefore, it is difficult to make specific recommendations. Some patients clearly benefit from combination bronchodilator therapy and there does not appear to be a significant increase in side effects with this combination (Level III evidence). Although there has been recent interest in the role of long-acting beta-agonists in the chronic therapy of COPD, these agents have not been studied in AECB and are not recommended for treatment of this condition at the present time. A number of studies have compared the use of metered dose inhalers (MDIs) to nebulized bronchodilators. These studies are occasionally flawed by using much larger doses of nebulized medications. Nonetheless, as supported by a meta-analysis of studies in patients with either asthma or COPD, there does not appear to be any difference in pulmonary function outcomes between delivery systems (165). Therefore, the choice of delivery system should be based on cost and the patient's ability to use MDIs with a spacer. In most situations, MDIs with an appropriate spacer would be preferred (Level II evidence).

There does not appear to be a role for the initiation of therapy with methylxanthines in AECB. The addition of aminophylline to inhaled bronchodilators has not been shown to lead to improved FEV<sub>1</sub> but does increase frequency of side effects (166,167). For patients who are already on an oral methylxanthine product, it is reasonable to continue the medication during an AECB. However, one must keep in mind possible drug interactions with antibiotics (eg, ciprofloxacin, clarithromycin) and adjust the dose accordingly (Level III evidence).

### Oxygen therapy

Patients with chronic bronchitis are at risk of developing hypoxemia during an exacerbation. This can lead to hypoxic pulmonary vasoconstriction with subsequent right heart strain and possible cor pulmonale. In addition, hypoxemia can increase the risk of myocardial ischemia in the elderly COPD population and can have neuropsychiatric side effects. Low-flow oxygen should be administered if hypoxemia is present (168-171). Excess use of oxygen should be avoided as this may lead to progressive hypercapnia, either by decreasing hypoxic ventilatory drive or by worsening ventilation-perfusion mismatching within the lung (172,173). The goal of therapy with supplemental oxygen should be to maintain a partial pressure of oxygen in arterial gas at or just above 60 mmHg. Decisions regarding long term need for supplemental oxygen should not be made during an AECB, because up to 50% of patients requiring oxygen during an exacerbation will no longer meet the criteria for home use if reassessed one to three months later (174-176).

**TABLE 2**  
**Randomized trials of corticosteroids in chronic obstructive pulmonary disease exacerbations**

Study (Reference)	Year	Sample size	Intervention	Outcomes	P*
Emerman et al (190)	1989	96	Methylprednisolone 100 mg × 1 dose	FEV <sub>1</sub> at 3 and 5 h Admission	NS NS
Albert et al (371)	1980	44	Methylprednisolone 0.5 mg/kg q6h × 72 h	Pre- and postbronchodilator FEV <sub>1</sub> tid × 72 h	<0.001
Thompson et al (191)	1996	27	Prednisone 30 mg × 3 days, 40 mg × 3 days, 20 mg × 3 days	Improvement in PO <sub>2</sub> Improvement FEV <sub>1</sub> Decreased treatment failures	0.002 0.006 0.002
Davies et al (192)	1999	56	Prednisolone 30 mg od × 2 weeks	FEV <sub>1</sub> postbronchodilator Length of hospitalization	<0.0001 0.027
Niewoehner et al (193)	1999	271	Methylprednisolone 125 mg q6h × 72 h followed by prednisone 60 mg od × 4 days tapered over 2 versus 6 weeks	Treatment failure Length of hospitalization Increased FEV <sub>1</sub> days 1-3	0.04 0.03 <0.05
Maltais et al (201)	2002	199	Prednisolone 30 mg q12h × 3 days Budesonide 2 mg q6h × 3 days	Postbronchodilator FEV <sub>1</sub>	<0.05 versus placebo NS budesonide versus prednisolone

\*Steroids versus placebo. FEV<sub>1</sub> Forced expiratory volume in 1 s; NS Not significant; PO<sub>2</sub> Partial pressure of oxygen

### Mucous clearing strategies

Expectorants or cough suppressants are not effective during exacerbations of chronic bronchitis. Pharmacological therapy to enhance mucous clearance has not been shown to improve lung function or hasten the clinical recovery in AECB (177-179), although it may produce a subjective improvement (177). There is no beneficial effect of chest physiotherapy on the time to recover from an AECB (180,181). There is even some suggestion of worsening pulmonary function and gas exchange with this form of therapy (182,183). Therefore, we do not endorse the use of mucolytic agents or chest physiotherapy during AECB (Level II evidence). Patients should be kept adequately hydrated to prevent excessive mucous viscosity but increased fluid intake should be avoided except by patients who are clearly dehydrated (Level II evidence).

### Miscellaneous therapies

At this point, there is no evidence supporting the use of leukotriene receptor antagonists in AECB.

The use of noninvasive ventilation (NIV) in acute exacerbations of COPD has been demonstrated to reduce mortality and decrease the need for intubation and mechanical ventilation (184,185) (Level I evidence). Overall, NIV also reduces morbidity and hospital or intensive care unit length of stay (186). Factors predicting success include good level of consciousness at the start of the trial, higher pH and lower partial pressure of carbon dioxide in arterial gas (PaCO<sub>2</sub>), and improvements in pH and PaCO<sub>2</sub> within 1 h of NIV initiation (187-189). Poor outcomes are associated with decreased adherence to NIV protocol, presence of pneumonia and poor nutritional status.

### Corticosteroid therapy

Since our first set of guidelines was published in 1994, a number of randomized, placebo-controlled trials have been published confirming the value of oral and/or parenteral corticosteroids in the therapy of AECB. These trials are summarized in Table 2. These studies demonstrate that systemic steroids lead to a faster improvement in pre- and postbronchodilator FEV<sub>1</sub>, more rapid recovery of partial pressure of oxygen, decreased treatment failures and shorter hospitalization rates. The one study that failed

to show a benefit of parenteral steroids during an exacerbation of COPD used only a single dose of methylprednisolone 100 mg in the emergency room and measured FEV<sub>1</sub> outcomes 1 h and 3 h following this bolus (190). The follow-up interval may not have been sufficient to detect a significant improvement because it is generally felt that steroids take at least 6 h to have a beneficial effect.

There are a number of limitations to these trials. All but one study (191) were performed in emergency rooms or hospital wards, so that the results may not be applicable to outpatient populations. The severity of the underlying lung disease was quite variable, although the majority of patients enrolled had moderate to severe underlying disease. Finally, the dose and duration of corticosteroid therapy varied widely among studies, making it virtually impossible to provide specific treatment recommendations. One must carefully weigh the pros and cons of higher dose and more prolonged corticosteroid therapy in this elderly group of individuals. In the studies quoted, the major side effect in the steroid-treated group was hyperglycemia (192,193).

Systemic therapy may have additional beneficial effects aside from speeding up recovery from an AECB. A retrospective study performed in an emergency room setting demonstrated that steroid-treated individuals had a significantly reduced likelihood of relapse compared with the group not getting steroids (194). Seemungal and colleagues (134) followed a cohort of 101 COPD outpatients over 2.5 years during which a total of 504 exacerbations were recorded. It was up to the individual treating physician to choose whether to add steroids to the treatment plan for any patient. Patients receiving prednisolone had more severe exacerbations as reflected by larger falls in PEFR and a longer recovery time for symptoms and PEFR. However, the rate of recovery of PEFR was faster in the group given prednisolone. Of greater interest, steroids prolonged the time to the next exacerbation from a median of 60 days in the group not receiving prednisolone to 84 days in the treated group (P=0.037). In contrast, antibiotic therapy had no effect on recovery time or time to next exacerbation.

The mechanism(s) through which corticosteroids speed up recovery in AECB remain(s) unclear. Steroids are effective in terms of reducing airway edema and mucus hypersecretion,

both of which play a role in the pathogenesis of AECB. Airway eosinophilia and activation have been demonstrated in some patients with AECB (79,134) and steroids are very effective at reducing eosinophil migration into the airways and preventing degranulation. Steroids are capable of increasing secretory leukoprotease inhibitor (SLPI) in airway epithelial cells in vitro and in airway secretions measured in induced sputum (195,196). SLPI has antiviral and antibacterial activity (197) and sputum SLPI levels are lower in COPD patients with more frequent exacerbations (124). Therefore, their effect on reducing the frequency of exacerbations may be on the basis of both decreased airway inflammatory effects and decreased risk of mucosal infections. However, this hypothesis will need to be tested in the future.

There is good evidence to support the use of oral or parenteral steroids for most patients with moderate to severe AECB (Level I evidence). The exact dose and duration of therapy should be individualized and more specific recommendations must await further evidence. It appears that 10 days of therapy is more effective than three days, but no other comparisons have been made (198). We recommend treatment for periods of five to 14 days (Level III evidence). Whether patients with mild disease (FEV<sub>1</sub> 60% to 70% greater than predicted) also benefit from a course of oral steroids during AECB is unknown at the present time. There are significant health consequences to the use of continuous oral corticosteroids in COPD and similar deleterious effects may occur in patients treated with frequent short courses (199).

The role for inhaled steroids in AECB has not yet been defined. Although some studies have failed to demonstrate a role for inhaled steroids in speeding up symptom resolution in AECB, these trials have not been designed to answer this question (200). A recently published prospective, randomized trial comparing high dose nebulized budesonide (2 mg every 6 h for 72 h) versus prednisone (30 mg twice daily for 72 h) demonstrated no difference between active treatments, with both being superior to placebo in terms of recovery of FEV<sub>1</sub> (201).

### ANTIBIOTIC THERAPY

Despite many decades of therapeutic trials, the role for antimicrobial therapy in AECB treatment remains controversial. There are a number of reasons for this. Most comparative antimicrobial trials demonstrate equivalence (1). These trials are mainly performed for registration purposes. Accordingly, they are powered to demonstrate equivalence only as required by the licensing authorities, and intrinsic superiority such as improved in vitro activity or excellent pharmacokinetics and/or pharmacodynamics cannot be demonstrated. Complicated patients with pretreatment-resistant pathogens or with comorbid conditions that might interfere with the activity or assessment of the antimicrobial agent are usually systematically excluded. Most clinical studies do not capture subtle outcome differences between agents such as speed of recovery, microbiological eradication rates and time to next occurrence. As currently designed, these studies demonstrate the efficacy of the antimicrobial but cannot demonstrate effectiveness (performance in real life circumstances). This part of the document will emphasize data supporting the use of antibiotics in AECB. Emerging concepts regarding antimicrobial resistance will be discussed. Finally, the data to support a simpler risk stratification scheme will be presented and specific antimicrobial recommendations for each risk category will be offered.

The controversial role of antibiotics has been somewhat clarified by more recent studies. Randomized, placebo-controlled antimicrobial trials conducted in previous decades were inconclusive (202-207) (Table 3). Many of the earlier studies were not powered to reach a definitive conclusion, but more recent well-designed studies have concluded that antibiotics are effective. Anthonisen and coworkers (120), in a landmark study, developed a classification system to identify patients likely to be infected with bacterial pathogens based on presenting clinical symptoms. A type I exacerbation was defined as a patient presenting with increased dyspnea, increased sputum volume and sputum purulence. A type II exacerbation referred to a patient with two of these symptoms, while a type III exacerbation occurred when a patient had only one symptom. Patients exhibiting a type I or type II exacerbation had a demonstrable benefit from antimicrobial therapy (more likely to resolve in 21 days, more rapid recovery of peak flow, shorter clinical illness, fewer patients exhibiting deterioration after the first 72 h) implying a bacterial etiology, while those with a type III exacerbation did not differ from patients receiving placebo. Allegra and coworkers (208), in another well-designed, randomized trial involving a large number of patients, demonstrated the superiority of amoxicillin/clavulanate to placebo. A more recent randomized, double-blind, placebo-controlled study in 93 mechanically ventilated patients with an exacerbation demonstrated that the use of fluoroquinolones compared with placebo was associated with a reduction in mortality, duration of hospital stay and time on mechanical ventilation, and a decrease in the need for additional antibiotics (209). A conflicting study purporting to show no benefit of antibiotic therapy is flawed by including patients with relatively mild disease and/or asthma, with the latter group undoubtedly improving due to the oral steroids that the patients were given (121).

Although the Anthonisen classification is helpful in predicting an antimicrobial response, it had only a sensitivity of 59% and a specificity of 60% in predicting a bacterial exacerbation (210). While this is an improvement, this would suggest that this particular classification system is only moderately successful in predicting a bacterial etiology and confirming the role of antimicrobials. The presence of green (purulent) secretions in a patient with a history of COPD was 99.4% sensitive and 77.0% specific for the yield of high bacterial load, and may identify a clear subset of patients likely to benefit from antibiotic therapy (122). It should be pointed out that the patients in this study all had increased dyspnea, so that they were all at least Anthonisen Type II. In a meta-analysis examining placebo-controlled trials in AECB, antibiotic therapy improved clinical outcomes and hastened clinical and physiological recovery (211).

Traditionally, older antibiotics such as ampicillin, tetracycline or trimethoprim/sulfamethoxazole (TMP/SMX), have been the standard treatment choices for AECB. The development of resistance of primary respiratory pathogens to these antibiotics, the recognition of more virulent Gram-negative organisms especially among patients with significant impairment of lung function, and the development of more potent, broad spectrum agents with improved coverage of the major respiratory pathogens has forced a re-examination of antimicrobial choices.

A failure rate that varies from 13% to 25% can be expected after treatment with traditional first-line antibiotics

**TABLE 3**  
**Randomized trials of antibiotics in acute exacerbations of chronic bronchitis**

Comparators	Patients (n/n)	Outcome of therapy	Reference
Placebo versus oxytetracycline	37/37	Treated patients lost half as much time from work and exacerbations were shorter	Elmes et al, 1957 (202)
Placebo versus oxytetracycline	27/26	Treated patients recovered sooner and deteriorated less often	Berry et al, 1960 (203)
Placebo versus ampicillin	28/28	No significant difference in clinical response	Elmes et al, 1965 (204)
Placebo versus physiotherapy versus chloramphenicol	10/10/9	No significant differences	Peterson et al, 1967 (205)
Placebo versus chloramphenicol versus tetracycline	86/84/89	Antibiotic therapy superior to placebo but no differences between antibiotics	Pines et al, 1972 (206)
Placebo versus tetracycline	20/20	100% versus 100% clinical response	Nicotra et al, 1982 (207)
Placebo versus either co-trimoxazole, amoxicillin or doxycycline	180/182	55% versus 68% success (P<0.01)	Anthonisen et al, 1987 (120)
Placebo versus co-amoxiclav	179/190	50.3% versus 86.4% success (P<0.01)	Allegra et al, 1991(208)
Placebo versus ofloxacin	47/46	Absolute risk reduction of 45.9 in death or need for additional antibiotics in ventilated patients (P<0.0001)	Nouira et al, 2001(209)

(amoxicillin, TMP/SMX, tetracycline, erythromycin) (212-214). This initial treatment failure may be associated with enormous additional expenditures, especially among patients with significant compromise of lung function. These patients may require hospitalization and are at risk for the development of respiratory failure (214). Resistance to  $\beta$ -lactam antibiotics such as ampicillin can be expected in 20% to 40% of isolated strains of *H influenzae* and in greater than 90% of strains of *M catarrhalis* (215,216). There are no clinical features that can predict the presence of  $\beta$ -lactamase-producing bacteria, except that patients with these organisms tend to have more courses of antibiotics (217). Penicillin resistance is now found in greater than 35% of *S pneumoniae* isolates in some studies and is increasing worldwide (218). Penicillin resistance in Canada has been reported as high as 30% (216). Penicillin resistance is also a marker for resistance to other classes of antibiotics including the cephalosporins, macrolides,  $\beta$ -lactam/ $\beta$ -lactamase inhibitors, TMP/SMX and tetracyclines (219). Whereas antibiotic resistance and widespread clinical failure in lower respiratory tract infections have not been linked at this time, this may only be a reflection of the rapidly changing antimicrobial environment. Most 'resistant' organisms demonstrate low levels of penicillin resistance (minimal inhibitory concentration [MIC] of 2  $\mu$ g/ml or less). Because the doses of  $\beta$ -lactams usually prescribed achieve high levels in blood, these levels of resistance may be overcome. If levels of resistance continue to increase, however, the value of many classes of antibiotics including  $\beta$ -lactams, cephalosporins, macrolides, tetracyclines and trimethoprim-sulfonamide combinations may diminish. Antibiotic overprescribing for nonbacterial infections is a major factor in the emergence of bacterial resistance. Attention must be paid to improving antibiotic use as well as to identifying those patients who would benefit from aggressive broad spectrum therapy. One advantage of a risk stratification system is that patients not requiring antimicrobial therapy can be identified as well as those requiring more aggressive therapy.

**$\beta$ -Lactam resistance:** There are three major mechanisms of  $\beta$ -lactam resistance: alteration of the antibiotic target sites (penicillin binding proteins [PBPs]), inactivation of the drug by enzymes produced by the bacteria ( $\beta$ -lactamases), and reduction of drug permeability into or out of the cell (220). Efflux

and bypassing a blocked pathway do not play a role in this class. **Target modification:** Target modification is the only mechanism of resistance of *S pneumoniae* to  $\beta$ -lactams. Reduced susceptibility of *S pneumoniae* to the  $\beta$ -lactams has been the result of the remodelling of the PBPs so that there is decreased binding affinity. Pneumococci for which the MIC of penicillin is less than 0.1  $\mu$ g/ml are defined as penicillin-susceptible, those for which the MIC is 0.1  $\mu$ g/mL to 1.0  $\mu$ g/mL are defined as penicillin-intermediately resistant and those for which the MIC is greater than 1.0  $\mu$ g/mL are defined as penicillin-resistant (221) (Table 4). Penicillin-nonsusceptible *S pneumoniae* (PNSP) are those that have an MIC of 0.1  $\mu$ g/mL or greater.

**Resistance trends and clinical significance:** The prevalence of PNSP continues to increase worldwide. Rates of resistance vary from 20% to 80% (216,222-228). Jacobs et al (225) in a United States surveillance study found that penicillin-resistant strains were more frequent than intermediately resistant ones (32.5% versus 18%). Zhanel et al (223) found in a cross-Canada surveillance study that penicillin-intermediately resistant and resistant strains occurred at rates of 14.8% and 6.4%, respectively.

Despite the widespread prevalence of nonsusceptible pneumococci, the clinical impact of using a  $\beta$ -lactam to treat a patient with a respiratory tract infection due to such a strain is uncertain (229-231). The *S pneumoniae* breakpoints for penicillin were established to predict efficacy in infections such as meningitis, where levels might barely reach the 2  $\mu$ g/mL level established for penicillin resistance. In contrast to antibiotic concentrations in the cerebrospinal fluid (CSF), peak serum and tissue concentrations of intravenously administered  $\beta$ -lactam antimicrobials may be considerably higher than the MICs of intermediate or resistant pneumococci. In the setting of pneumococcal bacteremia and/or pneumonia, current levels of penicillin resistance have not had any significant impact on mortality in adults. Pharmacokinetic/pharmacodynamic data suggests that bacteremic and respiratory tract infections due to pneumococci will only result in clinical failures when treated with a  $\beta$ -lactam when the penicillin MIC is 4  $\mu$ g/mL or higher (230). Less than 2% of pneumococcal isolates have MICs of 4  $\mu$ g/mL or higher (Table 4) (232).

The increasing prevalence of penicillin-resistant pneumococci may have a greater impact on the activity of the oral

**TABLE 4**  
**In vitro activities of 16 antimicrobials against 2245 isolates of *Streptococcus pneumoniae* collected from across Canada during 2000 (372)**

Antimicrobial	Minimal inhibitory concentration (µg/mL)														
	0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Penicillin		586*	1233	147	75†	18†	18†	38†	92	38	–				
Amoxicillin		84*	1153	734	73	37	46	74	33	10†	1				
Ceftriaxone			1824*	60	41	40	126	109†	43	1	1				
Ciprofloxacin					2*	63	892	1188	68†	7	7	6	9	3‡	
Levofloxacin					1*	19	832	1355	16	2†	5	12	3		
Gatifloxacin			1*	19	548	1612	40	4	3†	14	3	1			
Moxifloxacin			25*	449	1675	74	1	0	12†	8	1				
BMS-284756	44*	294	1533	344	9	4	10	6	1						
Gemifloxacin	588*	1214	401	20	3	11	6	1	1						
Doxycycline§								1960*	10	91	72	10	–		
Chloramphenicol										2198*	2	45†			
Erythromycin					1984*	9	3†	10	28	42	28	18	12	24	87‡
Clindamycin						2118*	3†	0	4	4	2	5	6	13	90‡
Telithromycin		2016*	59	49	37	23	40	19	2	–					
ABT-773		2102*	49	40	39	12	2	1	–						
Linezolid§					–	29	966	1054	94	–					
Trimethoprim/sulfamethoxazole						1501*	254	149†	87†	85	144	24	0	0	1‡

\*Less than or equal to; †Intermediate category where applicable; ‡Greater than or equal to; §Only 2143 isolates tested

cephalosporins. Oral cephalosporins have a disproportionate loss of activity against strains of PNSP. Therefore, as penicillin resistance rates increase, not only do the rates of cephalosporin resistance increase, but also the degree of resistance increases. Reports of clinical failures of cephalosporin treatment of pneumococcal infections caused by strains of *S pneumoniae* highly resistant to penicillins are rare. However, the numbers of penicillin-resistant pneumococci causing disease in prospective studies designed to evaluate the impact of resistance have been small (229).

In January 2002, the NCCLS published new susceptibility interpretive criteria for cefotaxime and ceftriaxone for non-meningeal isolates of *S pneumoniae* (233). Previously susceptibility interpretive breakpoints were less than or equal to 0.5/equal to 1/greater than or equal to 2 µg/mL for susceptible/intermediate/resistant, respectively. However, these breakpoints were derived largely from considerations in the treatment of meningitis. The Subcommittee on Antimicrobial Susceptibility Testing of NCCLS reviewed surveillance susceptibility data, pharmacokinetic-pharmacodynamic data in animal models of infection, clinical data and a simulated trial evaluating the probability of attaining target serum levels relative to various MICs. As a result of this review, the NCCLS has agreed to publish new interpretive criteria for nonmeningeal isolates of *S pneumoniae*. The changes are largely designed to clarify the efficacy of these drugs in nonmeningeal infections due to *S pneumoniae* strains with MICs of 1 µg/mL or less. Thus, new interpretive criteria for susceptibility of cefotaxime and ceftriaxone for *S pneumoniae* in nonmeningitis are less than or equal to 1/equal to 2/greater than or equal to 4 µg/mL for susceptible/intermediate/resistant, respectively (233).

Previous interpretive standards for cefuroxime categorized isolates of pneumococci with a cefuroxime MIC of 2 µg/mL or greater as resistant (221). However, pharmacokinetic/pharmacodynamic data based on a dose of cefuroxime of

15mg/kg twice a day suggests that pneumococcal MICs of 4 µg/mL or greater may be required before clinical failures occur. The most recent NCCLS guidelines categorize isolates of pneumococci with a cefuroxime MIC of 4 µg/mL or greater as resistant (233). Using breakpoints, which were the same as those in the new NCCLS guidelines, Doern et al (216) found that of the 41% of pneumococci that were PNSP, in a 1997 North American antimicrobial resistance surveillance program, 61% and 41% were resistant to cefixime and cepodoxime, respectively. As the prevalence of PNSP continues to increase, we may see an increase in the number of clinical failures associated with oral cephalosporin therapy of pneumococcal respiratory tract infections.

#### Antimicrobial inactivation

β-lactamase destroys penicillins and cephalosporins by hydrolysis and is the single greatest cause of resistance to these antimicrobials. β-lactamases account for greater than 99% of β-lactam resistance in *H influenzae* and *M catarrhalis* (224,234). Among the various β-lactamase enzymes, the TEM-1 and TEM-2 enzymes, which hydrolyze ampicillin and amoxicillin, are the enzymes most commonly seen in *H influenzae* (235). *M catarrhalis* produces ROB-1 and ROB-2 enzymes, which also hydrolyze ampicillin and amoxicillin, but have no effect on cephalosporins (236).

Studies done in the late 1990s have found rates of β-lactamase positivity in *H influenzae* between 30% and 40% in North America and about 20% in Europe (224,225,237-239). β-lactamase resistance in *M catarrhalis* rose very rapidly to over 90% in most countries of the world and has remained stable at that rate (224,225,237-239). Although there are no NCCLS breakpoints for *M catarrhalis*, the degree of activity of all the antimicrobials used to treat AECB, with the exception of amoxicillin, have excellent activity against this pathogen (239).

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Despite the widespread prevalence of  $\beta$ -lactamase-positive *H influenzae* and *M catarrhalis*, the clinical impact of using a  $\beta$ -lactam such as amoxicillin to treat a patient with AECB due to such a strain is unknown.

## Macrolide resistance

Resistance to the macrolide antibiotics occurs primarily by target site modification and active efflux (240-242). Acquired macrolide resistance has not been described in *H influenzae* and *M catarrhalis*. *H influenzae* appears to have inherent resistance to erythromycin. Azithromycin and clarithromycin are considerably more active (243). Clarithromycin is metabolized to 14-OH-clarithromycin, which is two to four times more active than clarithromycin itself; thus, in vitro susceptibility testing with only the parent drug inaccurately reflects in vivo sensitivity. Clarithromycin and 14-hydroxy-clarithromycin have additive effects against 82% of *H influenzae* isolates and are synergistic against 8%.

**Target site modification:** Resistance due to target site modification is mediated by one of a number of *erm* (erythromycin resistance methylase) genes that modify the ribosome target sites by methylation. The ensuing conformational change results in reduced affinity between the macrolides, clindamycin and streptogramin B antibiotics and the ribosome, thereby conferring the MLSB phenotype. This accounts for about 40% of the macrolide resistance in *S pneumoniae* in North America (244). In *S pneumoniae*, the *erm* gene is usually constitutive (244,245).

Resistance due to efflux has been described in *S pneumoniae* and is encoded for by the *mefE* gene (246). It confers erythromycin, clarithromycin and azithromycin resistance only (M phenotype) (242,247-249). Macrolide resistance due to efflux accounts for up to about 55% of the macrolide resistance of *S pneumoniae* (244).

Approximately 2% of pneumococcal isolates displaying macrolide resistance have both *erm* and *mef* genes. Approximately 1% to 2% of macrolide-resistant isolates have neither the *erm* nor the *mef* gene. A new mechanism of macrolide resistance has been described with structural changes that conceivably may become more common in the future (250).

**Resistance trends and clinical significance:** In the United States, resistance rates of pneumococci to the macrolides vary from 19% to 30% (225,251). In Canada, macrolide resistance rates have remained below 10% (216,223).

Resistance due to target site modification (RTSM) results in high levels of resistance to both clindamycin (MICs 8  $\mu$ g/mL or greater) and erythromycin (MICs 64  $\mu$ g/mL or greater). Strains resistant on the basis of efflux are susceptible to clindamycin (MICs 0.25  $\mu$ g/mL or less) and typically have erythromycin MICs of 1 to 32  $\mu$ g/mL (251). This has begged the question as to whether a patient infected with an efflux-mediated macrolide-resistant strain would more likely be successfully treated with a macrolide than if the infection was due to a strain that was macrolide-resistant on the basis of RTSM (251,252). Currently, there are no clinical data to determine whether the type of macrolide resistance affects the outcome.

Despite widespread macrolide resistance in *S pneumoniae*, there has been sparse clinical data to support that this correlates with clinical failure (253). A possible explanation may be the pharmacokinetic/pharmacodynamic properties of the macrolides (252). The concentrations of macrolides in the

alveolar macrophages and extracellular lining fluid of the alveolus are several fold higher than the serum concentrations and the MICs of macrolide-resistant strains (254).

## Fluoroquinolone resistance

Fluoroquinolones directly inhibit DNA synthesis. Inhibition appears to occur by interaction of the drug with complexes composed of DNA and either of the two target enzymes, DNA gyrase and topoisomerase IV. These enzymes are structurally related to each other, both being tetrameric with pairs of two different subunits. The GyrA and GyrB subunits of DNA gyrase are respectively homologous with the ParC and ParE subunits of topoisomerase IV. Both enzymes act by breaking both strands of DNA segment, passing another segment through the break, and then resealing the break. Fluoroquinolones appear to trap the enzyme on DNA during the topoisomerization.

**Target modification:** One mechanism of resistance is the alterations in target enzymes, which are generally localized to specific domains of each subunit type, the quinolone resistance determining region (QRDR). These alterations arise from spontaneous mutations in the genes encoding the enzyme subunits and, thus, can exist in small numbers (1 in 10<sup>6</sup> to 1 in 10<sup>9</sup> cells) in large bacterial populations.

Fluoroquinolone resistance has been associated most frequently with alterations in the *gyrA* and/or *parC* genes. In *S pneumoniae*, low-level fluoroquinolone resistance to ciprofloxacin and levofloxacin has been associated with mutations in the QRDR of *parC*. However, high-level resistance requires additional mutations in the QRDR of *gyrA* (255-259).

**Decreased accumulation:** Acquired fluoroquinolone resistance due to active efflux in *S pneumoniae* has been shown to be due to increased levels of expression of efflux pumps mediated by the *pmrA* gene (260). Efflux pumps of this type have broad substrate profiles and mediate resistance including chloramphenicol and hydrophilic quinolones such as ciprofloxacin, norfloxacin and ofloxacin. The activity of hydrophobic quinolones such as levofloxacin, gatifloxacin and moxifloxacin are less affected (260).

**Resistance trends and clinical significance:** Emergence of resistance to the fluoroquinolones has already been described in Canada, Spain, Hong Kong and Ireland. In Canada, Chen et al (261) found that the prevalence of ciprofloxacin-resistant pneumococci (MIC 4  $\mu$ g/mL or greater) increased from 0% in 1993 to 1.7% in 1997 to 1998 (P=0.01).

Reports of fluoroquinolone resistance in *H influenzae* and *M catarrhalis* are rare (262-266). These have occurred in patients with chronic or recurrent respiratory infections, which emphasizes the risk of the development of fluoroquinolone resistance in this type of patient.

Despite the marginal activity of ciprofloxacin against *S pneumoniae*, clinical failures of ciprofloxacin treatment of pneumococcal respiratory tract infections are rare (223,269-270). This may be explained in part by the fact that fluoroquinolones, including ciprofloxacin, are relatively concentrated in lung tissue (lung concentrations exceed serum concentrations by 1.5 to four fold) (271,272). Although there are no recommended ciprofloxacin susceptibility breakpoints for pneumococci, pharmacokinetic/pharmacodynamic data suggest that an isolate with a MIC of 2  $\mu$ g/mL or greater should be considered resistant to ciprofloxacin used at a dose of 500 mg twice a day (273,274). Therefore, as resistance emerges

and the MIC values increase above the MICs of wild type organisms, therapeutic levels of ciprofloxacin may not be achievable, even in the lung (275).

Reports of treatment failures in AECB due to ciprofloxacin-resistant pneumococci have started to emerge (276).

### TMP/SMX resistance

Biosynthesis of several amino acids and purines depends on the availability of tetrahydrofolic acid (THF). In addition, THF is a prerequisite cofactor for essential thymidylate synthesis. In contrast to human cells, which use dietary folates, most bacteria are unable to take up preformed folic acid derivatives and must synthesize THF. The sulfonamides and trimethoprim are structural analogues for intermediaries in THF synthesis.

Resistance to trimethoprim (TMP) and/or sulfamethoxazole (SMX) can be the result of chromosomal mutations or the acquisition of genetic elements, which bypass the TMP and/or SMX blockade (277,278). This has been found in *S pneumoniae* and *H influenzae* (279,280). TMP/SMX resistance in pneumococci is now very high. More than 90% of TMP/SMX resistant isolates are also resistant to penicillin (281). Conversely, increasing levels of resistance to  $\beta$ -lactams corresponds with increasing resistance to TMP/SMX. For example, Thornsberry et al (224) found that 40% of pneumococci that were highly resistant to penicillin were resistant to TMP/SMX, whereas only 3% of penicillin-susceptible pneumococci were. Therefore, overall rates of TMP/SMX resistance will reflect the prevalence of PNSP.

Thornsberry et al (224) found that 16% of  $\beta$ -lactamase-positive *H influenzae* were TMP/SMX resistant versus 7% of  $\beta$ -lactamase-negative isolates. In recent studies from North America, 10% to 16% of isolates of *H influenzae* were TMP/SMX resistant (224,239). As noted previously, *M catarrhalis* remains fully susceptible to TMP/SMX (226,241). There are no clinical data to show that TMP/SMX resistance is associated with clinical failures.

### Tetracycline resistance

The tetracycline group of antibiotics are either naturally occurring (tetracycline) or semisynthetic (doxycycline, minocycline) products. The bacteriostatic activity of tetracycline is associated with reversible inhibition of protein synthesis.

In both Gram-negative and Gram-positive bacteria, efflux of tetracycline is an important cause of high-level resistance. All efflux pumps confer resistance to tetracycline but not to minocycline (minocycline is much more hydrophobic than tetracycline).

A cytoplasmic protein produced by the resistant organism interacts or associates with the ribosome, making it insensitive to tetracycline inhibition (282). These ribosomal protection proteins, which are encoded by *tetM*, *O*, *P*, *Q*, and *S*, protect the ribosome from the action of tetracycline, doxycycline and minocycline. Ribosomal protection is the only mechanism of tetracycline resistance found in *S pneumoniae* (283).

Thornsberry et al (224) found that 51% of penicillin-highly resistant pneumococci were resistant to tetracycline, whereas only 4% of penicillin-susceptible pneumococci were. In Canada, approximately 10% of pneumococci are tetracycline resistant, whereas in the United States, 17% are resistant (223,224). Tetracycline resistance rates for both *H influenzae* and *M catarrhalis* are less than 1%.

There have been no clinical studies that have addressed the issue of the impact of tetracycline resistance on clinical outcome.

### Conclusion

Despite the increasing prevalence of resistance in the most common respiratory pathogens responsible for AECB, there is very little published clinical information, showing that in vitro susceptibility results predict clinical outcome. This may be in part due to the fact that clinical trials carried out for registration purposes are designed to show equivalency and do not include patients that are infected with a pathogen that is resistant to the study drug. In addition, it is only recently that the prevalence and degree of resistance have increased dramatically. As the prevalence of more highly resistant strains increases, we are now seeing cases of clinical treatment failures (276) and we suspect that these will increase in frequency.

### RISK FACTORS FOR TREATMENT FAILURE

Published failure and relapse rates for AECB in the literature vary from 17% to 32% depending on the definition used (Table 5). Identification of patients at risk of failing standard antimicrobial therapy with the usual first-line agents might lead to improved antimicrobial prescribing. Ball et al (212) enrolled 471 patients with AECB characterized by increased dyspnea, sputum volume and purulence. The median number of AECBs in the previous year was three, and one-third of the patients had cardiopulmonary disease (ischemic heart disease with/without cor pulmonale). Clinical features at presentation and antibiotic therapy did not predict recovery. However, an increased number of chest infections in the previous year and coexistent cardiopulmonary disease were predictors for returning to the physician with a chest problem. Patients with more than four treated exacerbations in the previous year were 2.11 times more likely to fail initial management than patients without this risk factor. The presence of coexistent cardiopulmonary disease increased the odds of failure by 2.3 times. The presence of cardiovascular comorbidity and more than four exacerbations in the previous year had a sensitivity of 75% and specificity of 47% in predicting return to the prescribing physician for further treatment.

In a retrospective study, Dewan and colleagues (284) reviewed the clinical experience with 107 patients in a University Veterans Administration clinic over a 24-month observation period. They observed a 14.7% failure rate within four weeks of observation among COPD patients mainly treated with first line antibiotics. More than one-half of the patients with exacerbations who failed initial treatment required hospitalization. Independent host factors that were associated with treatment failure included severe impairment of lung function, use of home oxygen, frequent exacerbations, history of previous pneumonia and use of maintenance corticosteroids. Using a stepwise logistic regression analysis, the necessity for home oxygen and frequent exacerbations correctly classified failures in 83% of the patients. In this study, age, the presence of comorbidity, and the choice of antibiotics did not affect treatment outcome.

In another retrospective study, Miravittles and colleagues (285) identified risk factors for relapse after ambulatory therapy of AECB. Baseline characteristics of coexisting ischemic heart disease, degree of dyspnea and frequency of visits to the family physician for respiratory problems in the past year were strongly

related to risk of relapse. The severity of AECB, as measured by the Anthonisen criteria, was not a risk factor for relapse. It appears that the Anthonisen criteria help to predict outcome in placebo-controlled trials (120) but not in trials where the majority of patients are given antibiotics (212,284-286).

### RISK FACTORS FOR HOSPITALIZATION

Patients are admitted to hospital following an inadequate response to outpatient management, an inability to perform the activities of daily living due to increased dyspnea or the development of respiratory failure, often in association with comorbidities or inadequate home care resources. Knowledge of risk factors for hospitalization might allow interventions to prevent this and other unfortunate outcomes (Table 6).

Ball and colleagues (212) demonstrated that the presence of significant ischemic heart disease or cor pulmonale was the only predictor of referral to hospital for further management of AECB. Patients suffering from chronic bronchitis for a greater number of years were less likely to be referred to hospital. This is in contrast to the findings of Grossman et al (287), who determined that severity of underlying COPD (using FEV<sub>1</sub> criteria) and duration of disease were the best predictors of hospitalization. Patients with severe chronic bronchitis were more than four times more likely to be admitted to hospital than patients with mild to moderate disease and the risk was similar for patients with disease for more than 10 years. If both risk factors were present, the risk of hospitalization increased almost 20-fold. Kessler et al (288) identified low body mass, a limited six-minute walk test, significant gas exchange impairment and pulmonary hemodynamic worsening as predictors of hospitalization. Multivariate analysis indicated that carbon dioxide retention (PaCO<sub>2</sub> higher than 44 mmHg) and pulmonary hypertension (mean pulmonary artery pressure at rest higher than 20 mmHg) were the best predictors of hospitalization. Age, comorbidity and smoking habit were not predictive of hospitalization. Vestbo and colleagues (52) demonstrated in the Copenhagen City Heart Study that chronic mucous hypersecretion was associated with an excess decline in FEV<sub>1</sub> and an increased risk of subsequent hospitalization because of COPD. This relationship continued to be significant even after adjusting for age, smoking and FEV<sub>1</sub>. Garcia-Aymerich and colleagues (289) found that after adjusting for a wide range of potential risk factors, only three or more admissions in the previous year, lower FEV<sub>1</sub> and underprescription of long term oxygen therapy were independently associated with a higher risk of admission for COPD exacerbation.

Miravittles and colleagues (290) found that the presence of ischemic heart disease, frequent exacerbations, chronic mucous hypersecretion, severe impairment of lung function and advanced age were all risk factors for hospitalization. Antonelli-Incalzi et al (291) found that the presence of comorbidities and advanced age increased the risk of mortality during an exacerbation.

### RISK STRATIFICATION

A group of high-risk patients in whom the cost of clinical treatment failure is high may be identified by simple clinical criteria. Patients with significant cardiac disease, frequent purulent exacerbations of COPD, generalized debility, malnutrition, chronic corticosteroid administration, use of supplemental oxygen, long duration of COPD, chronic mucous

**TABLE 5**  
**Risk factors for treatment failure**

Risk factor	Reference
Frequency of exacerbations	Ball et al, 1995 (212)
	Dewan et al, 2000 (284)
	Seemungal et al, 1998 (135)
Severity of FEV <sub>1</sub> impairment	Miravittles et al, 2001 (285)
	Dewan et al, 2000 (284)
Ischemic heart disease/congestive heart failure	Miravittles et al, 2000 (290)
	Ball et al, 1995 (212)
	Miravittles et al, 2001 (285)
Increasing age	Adams et al, 2000 (286)
	Antonelli-Incalzi et al, 1997 (291)
Maintenance steroids	Miravittles et al, 1999 (100)
Use of home oxygen	Dewan et al, 2000 (284)
Chronic mucous hypersecretion	Dewan et al, 2000 (284)
	Miravittles et al, 2000 (290)

FEV<sub>1</sub> Forced expiratory volume in 1 s

hypersecretion and severe underlying lung function abnormalities tend to fail therapy with usual antimicrobial therapy and have early relapse or hospitalization. These patients may be infected with difficult-to-treat organisms such as *Klebsiella pneumoniae* or *P aeruginosa*, particularly in the presence of severe impairment of lung function (99). Frequent exacerbations, chronic use of oral steroids and poor underlying lung function increase the risk for pseudomonas infection (99,100,118). Frequent courses of antibiotics increase the risk of infection with  $\beta$ -lactamase-producing bacteria (217). Treatment directed toward resistant pathogens with potent antimicrobial drugs might lead to improved clinical outcomes and overall lower costs, particularly if hospital admissions and respiratory failure can be prevented. Therapeutic failure leads to increased cost of care due to extra physician visits, further diagnostic tests and repeated courses of antibiotics. It may also lead to more hospitalization and prolonged absence from work. This greatly increases the cost of AECB treatment (292,293). Stratification of patients into risk categories may allow the physician to select targeted antimicrobial therapy to prevent some of these consequences.

Our proposed, simplified classification system divides patients into four groups (Table 7). It is important to point out that this stratification scheme has not been prospectively validated and represents a consensus from our group based on the evidence available (Level III evidence).

Group 0 patients present with the acute onset of cough associated with sputum production often in association with a preceding coryzal illness and fever. While smokers may be included in this group, these patients have no underlying lung disease and do not meet the definition for chronic bronchitis. These patients have acute tracheobronchitis that is usually viral in origin. The presence of purulent sputum in this previously healthy group of patients is not predictive of a bacterial infection, unlike the evidence in patients with chronic bronchitis. Because there is no underlying lung disease in this group, the illness is usually self-limited and runs a benign course. Most placebo-controlled trials have failed to support a role for antibiotic therapy in this group of patients, although meta-analyses of these trials gave conflicting results (294-296). However, none of these meta-analyses demonstrated a positive impact of antibiotics on duration of illness, limitation of

**TABLE 6**  
**Risk factors for hospitalization**

Reference	Variable	Odds ratio	Confidence interval (95%)
Ball et al, 1995 (212)	Cardiopulmonary disease	8.89	1.73–45.6
Kessler et al, 1999 (288)	PaCO <sub>2</sub> > 44 mmHg	2.1	1.4–3.1
	Ppa > 18 mmHg	2	1.3–3.1
Grossman et al, 1998 (287)	Duration of disease	4.6	1.6–13.0
	Severity of disease	4.3	0.8–24.6
	Duration and severity of disease	19.8	3.2–120.8
Vestbo et al, 1996 (52)	Mucous hypersecretion (men)	2.4	1.3–4.5
	Mucous hypersecretion (women)	2.6	1.2–5.3
	Ischemic heart disease	1.97	1.25–3.14
Miravittles et al, 2000 (290)	FEV <sub>1</sub> (% predicted)	0.72 for each 10% drop	0.58–0.888
Garcia-Aymerich et al, 2001 (289)	COPD admissions > 3 /past year	6.21	1.60–24.07
	FEV <sub>1</sub> (% predicted)	0.96 (per percentual unit)	0.93–0.98
	Underprescription of long term oxygen	22.64	2.31–221.88

COPD Chronic obstructive pulmonary disease; FEV<sub>1</sub> Forced expiratory volume in 1 s; PaCO<sub>2</sub> Partial pressure of carbon dioxide in arterial gas; Ppa Pulmonary arterial pressure

activities or return to work. Therefore, the routine use of antibiotics in patients with uncomplicated acute tracheobronchitis is not justified (297). Antibiotic overprescribing for trivial illnesses is a major factor in the emergence of bacterial resistance. Therefore, efforts at decreasing the use of antibiotics in group 0 patients may have a positive societal effect. Giving patients a written leaflet explaining why they do not require an antibiotic has been shown to reduce use of antibiotics (298). Patients in group 0 might benefit from one to weeks of inhaled beta-agonist bronchodilator therapy to reduce the severity and duration of cough, particularly if wheezing is heard on physical examination (297).

A small number of patients have a more protracted course. *Mycoplasma pneumoniae* and *C pneumoniae* are known etiologic agents for acute tracheobronchitis and may be responsible for those patients not demonstrating a rapid clinical improvement. Treatment with a macrolide or doxycycline might be considered for patients in whom the cough does not improve after 10 to 14 days (Level III evidence). There is no evidence supporting a positive response to this therapy even in the presence of documented infection with an atypical organism. Up to 20% of adults with a cough lasting more than three weeks have serological evidence of pertussis. Unfortunately, there are no clinical features that predict infection aside from exposure to someone with documented pertussis.

Group I patients have chronic bronchitis defined as having chronic cough and sputum production for at least three months for two consecutive years. During an exacerbation of this illness, they demonstrate worsening cough and increased production of purulent sputum. However, in general, they have only mild to moderate impairment of lung function (FEV<sub>1</sub> greater than 50% predicted value), have less than four exacerbations per year and have no significant cardiac disease. In this group of patients, the usual pathogens including *H influenzae*, *S pneumoniae* and *M catarrhalis* are present, although viral infection often precedes bacterial superinfection. Antibiotics have been demonstrated to shorten the clinical illness. Treatment with virtually any antibiotic is usually successful and the prognosis is excellent. Despite the presence of resistance to  $\beta$ -lactams, outcomes, in general, are acceptable. Until a prospective pharmaco-economic or clinical study demonstrates some advantage for more potent agents

among this group of patients, the recommendation for simple therapy such as an aminopenicillin, doxycycline or TMP/SMX is justified. However, the majority of studies showing beneficial results from the use of these agents were performed more than 10 years ago, before current concerns regarding emerging antimicrobial resistance. Given current knowledge about increasing *S pneumoniae* and *H influenzae* resistance to these older agents, therapy with selected second- or third-generation cephalosporins or a second-generation macrolide may be preferable (Level III evidence).

In the face of a treatment failure, alternative therapies such as a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor or fluoroquinolones can be used. However, there is no data demonstrating that these failures are due to resistant organisms or even due to antibiotic failure.

Group II patients have risk factors for treatment failure such as poor underlying lung function (FEV<sub>1</sub> less than 50% predicted). Alternatively, they may demonstrate only moderate impairment of lung function (FEV<sub>1</sub> between 50% and 65% predicted) but have significant comorbidity (ischemic heart disease, congestive heart failure) and/or experience four or more exacerbations per year. *H influenzae*, *S pneumoniae* and *M catarrhalis* continue to be the predominant organisms. Several studies have indicated that, with declining lung function, enteric Gram-negative organisms may be isolated from pulmonary secretions. Treatment with medications directed at resistant organisms, such as a fluoroquinolone or amoxicillin-clavulanic acid should perform better than amoxicillin or other traditional first-line agents. In addition, there is increasing evidence suggesting that the enhanced bacterial eradication associated with fluoroquinolones leads to faster symptom resolution and results in more prolonged disease-free intervals compared to cephalosporins and extended spectrum macrolides (Level II evidence) (vide infra).

It is unclear how group II patients who fail to respond to antimicrobial therapy or who quickly relapse should be treated. Again, it is unclear as to whether failures are due to antimicrobial failure or some other factor. It makes sense to treat therapeutic failures or recurrences within three months of antibiotic therapy with another class of antibiotic, but this has never been studied. A significant number of patients with an FEV<sub>1</sub> less than 50% predicted are infected with *Pseudomonas* species (99,100,118). Whether this occurs only

**TABLE 7**  
**Risk classification and suggested antimicrobial therapy**

Group	Basic clinical state	Symptoms and risk factors	Probable pathogens	First choice	Alternatives for treatment failure
0	Acute tracheobronchitis	Cough and sputum without previous pulmonary disease	Usually viral	None unless symptoms persist for > 10 to 14 days	Macrolide or tetracycline
I	Chronic bronchitis without risk factors (simple)	Increased cough and sputum, sputum purulence and increased dyspnea	<i>Haemophilus influenzae</i> , <i>Haemophilus</i> spp, <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i>	Second-generation macrolide, second- or third-generation cephalosporin, amoxicillin, doxycycline, trimethoprim/sulfamethoxazole	Fluoroquinolone, $\beta$ -lactam/ $\beta$ -lactamase inhibitor
II	Chronic bronchitis with risk factors (complicated)	As in group I plus (at least one of): FEV <sub>1</sub> < 50% predicted > 4 exacerbations/year Cardiac disease Use of home oxygen Chronic oral steroid use Antibiotic use in the past 3 months	As in group I plus <i>Klebsiella</i> spp + other Gram-negatives Increased probability of $\beta$ -lactam resistance	Fluoroquinolone, $\beta$ -lactam/ $\beta$ -lactamase inhibitor	May require parenteral therapy  Consider referral to a specialist or hospital
III	Chronic suppurative bronchitis	As in group II with constant purulent sputum; Some have bronchiectasis FEV <sub>1</sub> , usually < 35% predicted, or Multiple risk factors (eg, frequent exacerbations and FEV <sub>1</sub> < 50%)	As in group II plus <i>Pseudomonas aeruginosa</i> and multi-resistant <i>Enterobacteriaceae</i>	Ambulatory patients: Tailor treatment to airway pathogen <i>P aeruginosa</i> common (ciprofloxacin) Hospitalized patients: Parenteral therapy usually required.	

FEV<sub>1</sub>, Forced expiratory volume in 1 s

in the subset of patients with frequent exacerbations remains to be clarified. It is reasonable to get sputum samples, if possible, from these patients with multiple risk factors to help guide subsequent treatment.

Group III patients suffer from chronic bronchial infection with daily production of purulent secretions. They are subject to frequent exacerbations characterized by increased sputum production, increased sputum purulence, cough and worsening dyspnea often accompanied by hemoptysis. Some of these patients have bronchiectasis on high resolution computed tomography scanning. In addition to the usual respiratory organisms, other Gram-negative organisms including *Enterobacteriaceae* and *Pseudomonas* species should be considered as potential pathogens, particularly in patients treated chronically with oral steroids. Ciprofloxacin is the oral agent with the most activity against these species and should be considered the agent of choice when they are identified. As discussed in the previous paragraph, there is some overlap between patients in group II, with multiple risk factors, and those in group III.

### CLINICAL STUDIES

The next section will summarize clinical studies demonstrating the efficacy of different classes of antimicrobial agents. The approach used will review studies with various study designs to develop definitive recommendations for antimicrobial therapy.

#### Modelling studies

Backhouse et al (299) used a decision analytic model, comparing amoxicillin, amoxicillin/clavulanic acid, ciprofloxacin and cefaclor, to determine the most cost effective therapy in high-risk patients with AECB. They concluded that the cheapest

product is not always the most cost effective, and in their study, found amoxicillin/clavulanic acid to be the most cost effective. Clinical opinion was used to provide essential data regarding antimicrobial efficacy rates. They called for prospective clinical trials to reach a definitive answer.

Wool et al (300) compared four antibiotics – amoxicillin/clavulanic acid, ciprofloxacin, clarithromycin and rifloxacin – in the management of AECB. They reviewed 19 published studies to calculate pathogen eradication rates and used Italian costing data to estimate overall costs. They concluded that amoxicillin/clavulanic acid had the lowest drug acquisition cost and rifloxacin had the highest efficacy rate. Less cost effectiveness was calculated for ciprofloxacin and clarithromycin.

In a similar decision analytic model, van Barlingen et al (301) compared macrolides, fluoroquinolones, penicillins and cephalosporins in the outpatient treatment of AECB. The key cost drivers were the clinical success and failure rates of first-line treatment and the cost of hospitalization. They divided their theoretical patient population into two groups – those with mild to moderate AECB and those with more severe disease. For patients with less severe disease, they concluded that the differences among the antibiotic classes were not great but slightly favoured the macrolides and fluoroquinolones. For patients with more severe AECB, they concluded that the fluoroquinolones were the most cost effective. The experts selected to adjudicate clinical success rates for the various classes of antibiotics did not include the penicillins as appropriate therapy for patients with a severe AECB.

Pechere and Lacey (302) reviewed 12 studies of patients with AECB and demonstrated a strong correlation ( $r=0.91$ )

between eradication failure rates and clinical failure rates following treatment with macrolides, penicillins, cephalosporins, TMP/SMX or fluoroquinolones.

These studies concluded that the antibiotic class with the lowest acquisition cost was not necessarily the most cost effective. First-line clinical success rate is the most important factor in reducing overall costs. The studies reached different conclusions regarding which class of antimicrobial was the most cost effective because of the different assumptions used to create the models.

#### Database analysis

LeLorier and Derderian (303) examined the role of ciprofloxacin in the treatment of serious lower respiratory tract infections. Following the introduction of ciprofloxacin in the province of Quebec, they noted a decrease in the rate of hospitalizations for asthmatic bronchitis. This association was not found in the province of Saskatchewan, where ciprofloxacin usage was severely restricted. There was a statistically significant correlation between increased ciprofloxacin prescriptions and the differences between predicted and observed hospitalization rates. However, ecological correlations are poor models to establish cause-effect relationships, so these results must be viewed with caution.

Adams et al (286) demonstrated that patients severe enough to present to an emergency department and subsequently treated with ampicillin had higher recurrence rates of COPD exacerbations than patients who received other antimicrobial therapies. The recurrence rate with ampicillin was 54%, but was 13% if the patient received any other antibiotic from among choices that included cephalosporins, TMP/SMX, second-generation macrolides, ciprofloxacin or amoxicillin/ clavulanic acid ( $P < 0.001$ ). This would suggest that high-risk patients (presumably anyone requiring emergency department treatment for an AECB) benefit from aggressive therapy directed at resistant pathogens.

A retrospective study by Destache and colleagues (214) demonstrated that the use of newer antibiotics, when compared with the usual first-line antibiotics in the treatment of AECB, reduced both the hospitalization rate and the failure rate. While the acquisition cost of the newer antibiotics (cephalosporins, macrolides and fluoroquinolones) was higher, the overall costs of the treated patients given these drugs were lower. In particular, the group receiving amoxicillin/clavulanate, azithromycin or ciprofloxacin had the lowest hospitalization rate, lowest clinical failure rate and lowest costs compared with cephalosporins or first line therapy.

A recent population-based, retrospective cohort study was done in Ontario to determine the association between outpatient use of an oral antibiotic and 30-day all-cause mortality (304). In patients over 65 years of age hospitalized for COPD, the use of an antibiotic was associated with a significant reduction in short term mortality.

The previously discussed study by Adams and colleagues (286) also revealed a significant reduction in relapse rates for patients treated in the emergency room for AECB with antibiotics when compared with those not receiving antibiotics. This beneficial effect of antibiotics was not seen with amoxicillin.

In a retrospective analysis of their study that demonstrated a beneficial effect of amoxicillin/clavulanate versus placebo in AECB, Allegra and colleagues (305) demonstrated that

patients with the greatest impairment in lung function and/or more frequent exacerbations benefited the most from antibiotic therapy.

#### Prospective randomized trials

The hypothesis that aggressive antibiotic therapy should be offered to high-risk patients was tested in a recent, prospective health economic study. Patients with at least three treated exacerbations in the past year were randomly assigned to receive either ciprofloxacin or any nonquinolone-based therapy for their next AECB (306). Clinical endpoints (days of illness, hospitalizations, time to next exacerbation) were blended with quality-of-life measurements (Nottingham Health Profile, St George's Hospital Respiratory Questionnaire, Health Utility Index) and total respiratory costs from a societal perspective. While the overall results indicated no preference for either treatment arm, in patients with multiple risk factors (severe underlying lung disease, more than four exacerbations/year, duration of bronchitis greater than 10 years, elderly, significant comorbid illness), the use of ciprofloxacin led to improved clinical outcome, higher quality of life and less costs. However, due to the smaller number of patients in this post hoc analysis, this improvement did not reach statistical significance.

In a series of double-blind crossover studies, Chodosh (309) determined that ampicillin 0.5 g to 1 g four times daily was associated with a low failure rate and an infection-free interval ranging from 117 to 302 days. These studies were conducted in the 1970s when there was no  $\beta$ -lactamase-producing *H influenzae* or *M catarrhalis*. Ciprofloxacin 750 mg twice daily gave comparable results. Tetracyclines, TMP/SMX and especially cefaclor were associated with higher failure rates and a shorter infection-free interval. Two recently published studies compared ciprofloxacin 500 mg twice daily with clarithromycin 500 mg twice daily and cefuroxime axetil 500 mg twice daily in group II patients (307,308). These studies demonstrated similar clinical outcomes but ciprofloxacin had superior bacterial eradication rates. In addition, the time to the next exacerbation was shortest for clarithromycin (a poor outcome), although this did not reach statistical significance. A number of other studies have consistently demonstrated significantly superior bacterial eradication rates with fluoroquinolones compared to cefuroxime or clarithromycin (107-109).

In the recently completed GLOBE (Gemifloxacin Long-term Outcomes in Chronic Bronchitis) trial (309), gemifloxacin 320 mg once daily for five days was compared with clarithromycin 500 mg twice daily for seven days. While short term clinical outcomes were similar, gemifloxacin had a significantly better bacteriological eradication rate and demonstrated faster eradication of *H influenzae*. Gemifloxacin was superior to clarithromycin in preventing further exacerbations (71.0% versus 58.5% for no further exacerbations,  $P = 0.016$ ) and reduced the number of patients hospitalized for respiratory tract infection over the next six months of follow-up (0.023% versus 0.0625%,  $P = 0.059$ ). This is the first well-designed clinical trial to demonstrate clinical superiority of a more potent antimicrobial on clinically relevant outcomes. In a more recent study comparing moxifloxacin with amoxicillin, clarithromycin or cefuroxime, use of the fluoroquinolone resulted in higher clinical and bacteriological success rates and a subsequent reduced need for additional antibiotics (310).

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Despite this preliminary evidence that fluoroquinolones may be a superior choice in terms of bacterial eradication and delaying time to next relapse, there is not enough evidence to warrant their use in all cases of AECB. One must carefully balance the potential benefits of these powerful antibiotics with the risk of developing resistance. There is recent evidence to suggest that frequent use of fluoroquinolones leads to the emergence of resistant strains and that COPD patients are a major reservoir for these resistant organisms (311).

## SUMMARY OF EVIDENCE REGARDING ANTIBIOTIC THERAPY FOR AECB

1. Antimicrobial therapy is warranted for patients with an AECB if they fall into the Anthonisen type I or type II categories (Level I evidence, two randomized, large scale double-blind trials, one meta-analysis).
2. Antimicrobial therapy is not warranted for patients with a type III exacerbation (Level I evidence).
3. Patients can be stratified according to their risk of treatment failure (Level III evidence).
4. A high-risk group of patients can be identified on clinical grounds, and the major clinical features are significant impairment of lung function ( $FEV_1$  50% or lower than predicted), frequent exacerbations (four or more per year), long duration of disease, significant comorbidity, use of supplemental oxygen and chronic oral corticosteroid use (Level II evidence).
5. Risk group 0 patients (acute tracheobronchitis) should not be treated with antibiotics unless symptoms persist beyond 10 to 14 days (Level I evidence).
6. For risk group 0 patients with persistent symptoms, a macrolide or tetracycline is recommended since *M pneumoniae*, *C pneumoniae*, or *Bordetella pertussis* may be pathogens (Level III evidence).
7. Although resistant *H influenzae* and *M catarrhalis* may be pathogens, traditional 'first-line' agents (aminopenicillins, doxycycline, TMP/SMX) continue to be efficacious and are recommended for patients without risk factors for treatment failure (Level II evidence). Second-generation macrolides and some second- and third- generation cephalosporins (cefuroxime, cefprozil, cefixime) may be better choices given concerns regarding emerging antimicrobial resistance (Level III evidence).
8. There are no data to demonstrate that, among group I patients (low risk for treatment failure), there is any clinical or economic benefit derived from using more potent, broader spectrum agents (Level I evidence).
9. Broad spectrum potent agents such as fluoroquinolones or amoxicillin/clavulanate are recommended for group II patients (Level III evidence).

10. There is some evidence that fluoroquinolones perform better than other agents for group II patients (Level II evidence).
11. Group III patients at risk for *P aeruginosa* infection (frequent antimicrobials, structural lung damage and chronic corticosteroids) should be treated with an anti-pseudomonal agent (ciprofloxacin). Alternative agents currently must be given parenterally (Level III evidence).
12. Patients presenting with a relapse or recurrence of AECB, within three months of previous antibiotic therapy, should be treated with a different class of antibiotics (Level III evidence).

## PREVENTION OF AECB

Cigarette smoking remains the primary risk factor for the development of chronic bronchitis. Although only 15% of smokers will develop air flow obstruction, more than one-half will develop chronic cough and sputum production with subsequent increased risk for bacterial colonization and recurrent episodes of AECB. Unfortunately, in 1999, there were slightly more than six million smokers in Canada, representing 25% of the population age 15 years and older (312). Any intervention that slows the rate of decline in  $FEV_1$  is likely to have a major impact on survival in patients with chronic bronchitis. Smoking cessation has clearly been shown to reduce the rate of decline of  $FEV_1$  (313). The benefits in terms of decline of lung function are seen even in those over the age of 60 years (314). In addition, cessation of smoking has been shown to confer a survival advantage (Level II evidence) (315). Smoking cessation leads to dramatic symptomatic benefits for patients with chronic bronchitis (Level III evidence). Coughing stops in as many as 77% of patients who quit smoking and improves in another 17%. When coughing stops, it does so within four weeks in 54% of patients (316). Evidence is lacking that this decrease in cough and sputum production will lead to a subsequent decline in the frequency of AECB. It is known that patients with chronic cough and sputum production have increased numbers of AECB episodes compared to similarly matched smoking control patients so the hope is that smoking cessation will lead to fewer exacerbations. Nonetheless, this enthusiasm must be tempered by the fact that there is evidence for ongoing airway inflammation even in patients with COPD who do not currently smoke (317,318). A recent analysis of patients in the Lung Health Study (56) revealed that recurrent lower respiratory infections hastened the decline in  $FEV_1$  in current smokers but not in ex-smokers.

A detailed discussion of smoking cessation can be found elsewhere (319). No single technique to encourage smoking cessation is successful in all groups of patients; however, recent studies using a combination of behavioural counselling, nicotine replacement and pharmacological therapy to decrease the desire to smoke revealed one-year abstinence rates of as high as 35.5% (320). A discussion of smoking behaviour and the setting of a specific cessation date should be part of every physician-patient encounter (Level III evidence).

Patients with chronic lung disease have a higher risk for complications from influenza infection. By virtue of its ability

to further damage airway epithelial cells, influenza infection can lead to secondary bacterial proliferation and an increase in the frequency of AECB. Serological evidence of influenza A or B infection has been found in up to 28% of patients with AECB (126,321,322). In addition, COPD patients infected with influenza have a significant risk of requiring hospitalization (323). Perhaps this is related to the transient decline in pulmonary function caused by influenza in a group of patients with less pulmonary reserve (127). Annual influenza vaccination reduces morbidity and mortality of influenza in the elderly by 50%. In addition, it reduced the incidence of hospitalization for acute and chronic respiratory conditions by as much as 39% (324,325). Therefore, the use of an annual influenza vaccine for all patients with chronic bronchitis is strongly recommended (Level II evidence). The role for either oral or inhaled neuraminidase inhibitors, which are effective against strains of both influenza A and B, are currently being studied in terms of preventing AECB during influenza outbreaks in high-risk patients. Therefore, no current evidence-based recommendations can be made. However, high-risk patients who have not been vaccinated should receive prophylaxis during an outbreak (Level III evidence).

The value of pneumococcal vaccination in patients with chronic bronchitis is less well established. At least two meta-analyses looking at efficacy of a 17-valent or less vaccine resulted in opposite conclusions (326,327). Since 1983, a 23-valent vaccine has been available in Canada and this covers 85% of the serotypes responsible for invasive pneumococcal infection. Use of this vaccine in elderly patients with chronic lung disease revealed a significant lower risk for pneumonia, hospitalization and death, and direct medical care cost savings (329). However, AECB is a mucosal infection and it is unclear whether this vaccine can reduce the incidence of this complication of chronic bronchitis. Some reports state that the vaccine has up to a 65% efficacy in patients with COPD but do not specifically comment on AECB (329). It is generally agreed that pneumococcal vaccination is safe and can reduce invasive pneumococcal infection leading to current recommendations for vaccinations in all patients with COPD at least once in their lives. In addition, consideration should be given to repeating the vaccine in five to 10 years in high-risk patients (330) (Level III evidence).

Over the past two decades, attempts have been made to use oral administration of bacterial antigens in the hope of upregulating antigen-specific antibodies in the bronchial mucosa, thereby decreasing the frequency of AECB. Initial studies using an oral vaccine against *H influenzae* revealed a decrease of approximately 50% in use of antibiotics and days lost from work in patients with chronic bronchitis (331). A recent meta-analysis of six trials using this vaccine showed a decrease in the number of episodes of bronchitis at both three and six months in treated patients and a decrease in antibiotic use at six months but not at three months in treated patients (332). Problems with this meta-analysis include the fact that some patients with recurrent episodes of acute bronchitis and without underlying chronic bronchitis were included. In addition, a six-month follow-up only was obtained, so it is unclear whether there will be a continued benefit at one or two years after vaccination. More recent studies have used a preparation called OM-85, which is a lyophilized powder made from cultures of eight different bacterial pathogens responsible for AECB (*H influenzae*, *S pneumoniae*, *M catarrhalis*, *K pneumoniae*,

*Klebsiella ozaenae*, *S aureus*, *Streptococcus pyogenes* and *Streptococcus viridans*). The use of this preparation in institutionalized elderly patients with chronic bronchitis led to a 30% reduction in respiratory tract infections (333). However, a more recent multicentre study failed to demonstrate any reduction in the frequency of AECB (334). Nonetheless, patients treated with the vaccine had a 30% reduction in hospitalization related to respiratory problems and a 55% reduction in total number of days in hospital. A more recent analysis of this study suggested that use of this oral immunostimulating agent was cost effective (335). If available in the future, the use of oral immunostimulating agents would be recommended in Canada (Level II evidence).

The use of inhaled corticosteroids in chronic bronchitis and COPD has been the subject of great interest over the past decade. There are two potential mechanisms whereby inhaled steroids might have a role in chronic bronchitis. First, by decreasing the annual rate of decline in FEV<sub>1</sub> which is the major predictor of mortality from COPD. Second, by decreasing airway inflammation via an effect on either mucus hypersecretion or on inflammatory cytokines and mediators. Theoretically, this effect should decrease the risk of exacerbations. Studies examining the effects of inhaled steroids on airway inflammation have been conflicting. There is some evidence that therapy with higher doses of inhaled corticosteroids reduces visible bronchial inflammation and epithelial fluid albumin (336), airway neutrophilia (337) and markers of neutrophilic inflammation such as IL-8 and MPO (338). A similar number of studies failed to demonstrate any effect of inhaled steroids on airway neutrophilia, epithelial permeability or airway mediator and cytokine levels (339-341). Patients in studies showing a beneficial response tended to be treated for somewhat longer periods of time (six to eight weeks versus four weeks), but it is unclear whether this is a sufficient explanation for the different outcomes.

The past two years have brought with them the publication of long awaited trials of the effects of inhaled corticosteroids in slowing the rate of annual decline of FEV<sub>1</sub> in patients with COPD. These studies examined the effects of different inhaled steroids (budesonide, fluticasone propionate, triamcinolone) versus placebo for 3 to 3.5 years with a total of over 3000 patients completing the trials (342-345). Overall, there was no benefit seen in terms of rate of decline in lung function in patients treated with inhaled steroids versus those getting placebo. In addition, patients receiving inhaled steroids had a higher percentage of skin bruising (342), a decrease in bone density of the lumbar spine and femur (345) and a small decrease in mean cortisol concentrations, although this was not associated with any clinical effects (344).

The Inhaled Steroids on Obstructive Lung Disease in Europe (ISOLDE) study (344) revealed a 25% reduction in the median exacerbation rate from 1.32 per year on placebo to 0.99 per year for patients on fluticasone propionate. Another study examining the effects of fluticasone 500 µg twice daily versus placebo over the course of six months also showed a significant reduction in both moderate and severe exacerbations in the steroid-treated group compared with the placebo group (86% versus 60%, P<0.001) (346). Available data do not allow specific recommendations to be made regarding the use of inhaled steroids in patients with COPD. The risks versus the benefits of this therapy must be individualized. Patients with severe impairment in FEV<sub>1</sub> and those

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with frequent exacerbations requiring the use of oral corticosteroids should be considered for therapy with inhaled corticosteroids (Level III evidence). Supporting this recommendation is a recent cohort study performed in Ontario. Data were collected regarding filling of prescriptions for inhaled steroids in 22,620 patients over the age of 65 years hospitalized with COPD, and one-year prognosis was measured according to whether they received a prescription for an inhaled steroid within three months of their admission. Prescription of an inhaled steroid led to a 10% one-year reduction in readmission and/or death (347). After adjusting for age, sex, comorbid conditions, concomitant medications and visits for COPD in the preceding year, the reduction in mortality was 29% (95% CI, 22% to 35%) and reduction in risk of readmission was 24% (95% CI, 22% to 29%) (347).

There is little evidence to suggest a benefit of regular therapy with oral corticosteroids in patients with COPD. Although two retrospective, long term studies (348,349) claimed to demonstrate a beneficial effect over 20 years in patients with COPD, this effect was most apparent in patients with the most rapid rate of decline in FEV<sub>1</sub> and no comments were made on the frequency of AECB. The same group showed no benefit with the addition of 5 mg of prednisolone daily to inhaled corticosteroids in patients with relatively mild COPD in terms of decreasing the frequency or duration of AECB over a two-year period (350). This, combined with the recognition of the significant complications of chronic oral corticosteroid therapy (351,352) including a dose-dependent increase in mortality (353), argues against chronic use of systemic steroids in COPD (Level II evidence). It appears that even patients on chronic oral corticosteroids can be weaned off this medication without any adverse effects on pulmonary function, quality of life or frequency of AECB (354).

Long-acting beta-agonists have been shown to be beneficial in some patients with COPD. Some evidence exists that salmeterol is effective in reducing damage to the epithelium caused by *H influenzae* or *P aeruginosa* in vitro (355,356). Theoretically, this may lead to less epithelial damage caused by bacteria and reduce the frequency or severity of AECB. There is some early clinical evidence that this may be true with patients on salmeterol having a longer time to first AECB compared to placebo or ipratropium (357). A similar delay in time to next exacerbation has recently been demonstrated in patients prescribed tiotropium (358,359). Further investigations will be necessary before long-acting beta-agonists or long-acting anticholinergics can be recommended for this purpose.

A meta-analysis published in 1998 suggested that oral mucolytic agents such as N-acetylcysteine or iodinated glycerol reduced the frequency of AECB, disability days and antibiotic use (360). The greatest effects were seen in patients who had a large number of exacerbations. Oral mucolytic agents reduced exacerbations by 22% in patients who had an average of 5.5 exacerbations per year. However, a more typical chronic bronchitic patient with two to three exacerbations per year would expect to reduce exacerbations by less than one by taking mucolytic agents daily for two to three years. No effect on rate of decline of FEV<sub>1</sub> was seen. A more recent meta-analysis on the effect of oral N-acetylcysteine revealed similar results in terms of a decrease in AECB in patients treated for 12 to 24 weeks (361). In addition, a recently published update of Poole's Cochrane analysis confirmed the

beneficial results of N-acetylcysteine and determined that the number of patients needed to treat for one patient to have no exacerbations during the study period was six (362). A study in Switzerland suggested that therapy with N-acetylcysteine was cost effective (363). The mechanism by which N-acetylcysteine reduces AECB is unclear but may be related to enhancing macrophage activity, which would help defend against mucosal infections (364). N-acetylcysteine therapy should be considered in patients with more than five exacerbations per year (Level I evidence).

Hyaluronan is a high molecular weight glycosaminoglycan that is found naturally in the body. It has a role in enhancing neutrophil function. It has been shown to significantly decrease the frequency of AECB and reduce the need for antibiotics in this group of patients (365). It has to be given by subcutaneous injection weekly, making it somewhat impractical. In addition, cost effectiveness of this form of therapy remains to be proven. At this point, its use cannot be endorsed to prevent AECB (Level III evidence).

Numerous trials dating back to the mid-1950s have been carried out to determine whether antibiotic prophylaxis reduces the frequency of AECB (93,366,367). Murphy and Sethi (93) identified nine prospective, placebo-controlled, randomized trials in each of which at least 25 patients were studied. In five of these trials, no reduction in the frequency of exacerbations was achieved; however, in two of these, significantly less time was lost from work by the antibiotic-treated groups (368,369). In four studies, the frequency of AECB was significantly reduced in groups treated with antibiotics compared with those receiving placebo. Similar to studies using other agents that decrease airway inflammation, antibiotic prophylaxis seemed to benefit patients who suffered the largest number of exacerbations over the course of the year. Therefore, patients in group III may benefit from prophylaxis with antibiotic agents to which their colonizing bacteria are sensitive. It should be pointed out that each of these studies regarding antibiotic prophylaxis was done with older generations of antibiotics and there is a need for current studies with newer antibiotics, particularly given the emerging bacterial resistance problems. Nonetheless, the effects of the antibiotics may be anti-inflammatory rather than antimicrobial. This is suggested by a recent study looking at the effects of erythromycin versus placebo in preventing AECB and hospitalizations in patients with COPD. Erythromycin has no significant activity against *H influenzae*, the most important pathogen in AECB, yet therapy with 200 mg/day to 400 mg/day of erythromycin for one year led to a 4.71 decrease in the relative risk of developing AECB (11% versus 56% in the placebo group) and a significant decrease in hospitalizations due to AECB (370).

Overall, there is evidence to support antibiotic prophylaxis in patients with frequent exacerbations (Level II evidence). However, decisions regarding prophylactic antibiotic treatment should be made on an individual basis.

### THE FUTURE

The past decade has brought with it renewed interest into the pathogenesis of chronic bronchitis and a greater understanding of some of the basic mechanisms of the disease. Paradoxically, these discoveries have brought with them more questions. To improve our therapy of AECB, we need better evidence on which to base future guidelines. The following

are the issues most urgently in need of answers in order to make future AECB guidelines more evidence based:

1. We need a better definition of AECB to help guide the design of clinical trials, to allow the results to be generalizable and to better determine the health and economic impact of exacerbations.
2. Antibiotic trials that compare different classes of drugs powered to show superiority of one class over another are desperately needed to make evidence-based recommendations regarding drugs of first choice for AECB.
3. The importance of bacterial eradication in terms of both symptom resolution and determination of remission-free period requires further study.
4. The importance of reducing airway inflammation either with antibiotics with anti-inflammatory effects or with novel anti-inflammatory agents must be studied prospectively in a controlled trial. Ideally, a study looking at the effects of oral steroids alone without concomitant antibiotics should be carried out. This may be ethically difficult to do in patients with Anthonisen type I exacerbations stratified to our

groups II or III but would be reasonable for patients with an Anthonisen type II or III exacerbations or for patients in our stratification group I.

5. A study examining the potential role for prophylactic antibiotics for patients in our stratification group III would be welcome.
6. We need better surrogate markers for bacterial infections. A better understanding of the antigenic structures of many of the common bacteria involved in AECB might lead to the development of monoclonal antibodies targeted against these antigens, which may help define acute bacterial infections.

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## APPENDIX

### Chronic Bronchitis Working Group

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