

# Canadian guidelines for the management of acute exacerbations of chronic bronchitis: Executive summary

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**A**cute 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). The present document is an update of our original guidelines, and is a joint effort by the Canadian Thoracic Society and the Canadian Infectious Disease Society.

## METHODS

Early in 1999, a needs assessment survey was sent, along with the 1994 guidelines, to representative family physicians from across Canada. The purpose behind this was to obtain insight into the major challenges these physicians faced in diagnosing and managing AECB. A committee was established comprised of members from both the Canadian Thoracic Society and the Canadian Infectious Disease Society, as well as two family physicians with strong interests in continuing medical education. Relevant articles published between 1966 and July 1, 2002 were retrieved from MEDLINE using the index terms 'chronic obstructive pulmonary disease' (COPD), '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 more recently published papers. The Cochrane Controlled Trials Register was also searched until the end of the year 2001. 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 the grading 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 constitute level III or weak evidence. In the present guidelines, these ratings appear as Roman numerals in parentheses after each recommendation.

## DEFINITION

COPD is now the fifth leading cause of death in Canada, and its prevalence is increasing (3). Most definitions consider COPD to be a disease state characterized by air flow limitation that is not fully reversible (4,5). The air flow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to inhaled particles or gases. COPD 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 is defined as expectoration of sputum on most days during at least three consecutive months for more than two successive years, with other causes of cough and sputum having been excluded (6). Chronic bronchitis occurs in approximately 85% of COPD patients. It is essential to recognize that chronic bronchitis commonly occurs without airway obstruction; a minority of patients with chronic bronchitis have evidence of COPD (7).

## AECB

Defining AECB is not simple. Because there are no characteristic laboratory, radiographic or physiological tests for AECB, clinical definitions have traditionally been used. Anthonisen and colleagues (8) proposed three clinical criteria to define AECB: increased sputum volume, increased sputum purulence and increased dyspnea over baseline. The most severe, or type I, exacerbation includes the presence of all three of these symptoms. A type II exacerbation exhibits two symptoms. A type III exacerbation has one symptom plus at least one of the following: an upper respiratory tract infection in the previous five days, increased wheezing, increased cough, fever without an obvious source, or a 20% increase in respiratory rate or heart rate above baseline. Seemungal and colleagues (9) have proposed the use of major and minor criteria to define an exacerbation. The major criteria are the three proposed by Anthonisen et al (8). Minor criteria include wheeze, sore throat, or symptoms of a common cold such as nasal discharge or congestion. An exacerbation was defined as the presence of at least two major symptoms or one major and one minor

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symptom for at least two consecutive days. The incidence of AECB varies depending on which definition is used. By applying the Anthonisen et al (8) criteria, the typical patient with COPD averages two to three AECB episodes annually.

### 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* (10-12). 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 loss of ciliated epithelium and more viscous airway secretions. The delay in mucociliary clearance allows inhaled bacteria to colonize airways (13). Once bacteria adhere to mucin or epithelial cells in the lower airway, they may further impair mucociliary clearance and may contribute to progressive airway obstruction (Figure 1) (14,15).

Approximately 50% of exacerbations, particularly those meeting the Anthonisen et al criteria (8), are believed to result from infection, with a minority of these due to viral infection and the remainder due to bacterial infection. Exposure to allergens, pollutants or irritants (cigarette smoke, dust) may also precipitate exacerbations.

Exacerbation rates are an important determinant of disease-specific health status as measured by a standard quality of life questionnaire (16). Exacerbations may lead to hospitalization, which carries with it a short term mortality rate of 4% for patients with mild to moderate disease (17), but this rate may be as high as 24% if patients are admitted to an intensive care unit (ICU) with respiratory failure (18-21). After intensive care, COPD patients have one-year mortality rates of up to 46% (18-20). Many patients requiring hospitalization for AECB require subsequent readmissions because of persistent symptoms (18,21,22). In addition, they experience at least a temporary decrease in their functional abilities (23).

### DIAGNOSTIC EVALUATION

Congestive heart failure, pneumonia, pulmonary emboli, pneumothorax, inappropriate oxygen administration and drugs such as tranquilizers may cause worsening of COPD, which must be differentiated from exacerbations. There are no characteristic physical findings in AECB. Fever is uncommon (18) despite statements to the contrary (24), and its presence should suggest a viral infection (25) or underlying pneumonia.

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. An exception 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 (26-28).

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. Sputum analysis should be reserved for patients with frequent exacerbations or chronic

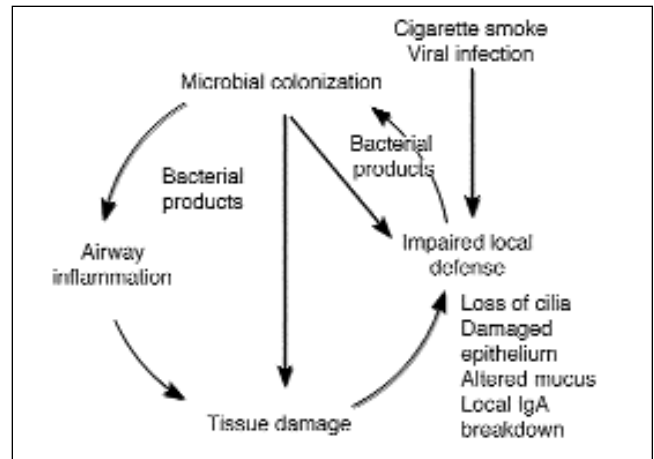


Figure 1) The role of cigarette smoke and viral infection in initializing and perpetuating the 'vicious circle' of impaired local defenses. IgA Immunoglobulin A. Reprinted with permission from reference 134

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. Further, in COPD the forced expiratory volume in 1 s (FEV<sub>1</sub>) is the best predictor of mortality (29) and is important in predicting the need for admission to an ICU (30). Exacerbation frequency is related to the severity of underlying obstruction (31,32), and FEV<sub>1</sub> is predictive of clinical outcomes during AECB (33), including benefit from antibiotic therapy (34). There is continued evidence that spirometry is underused in patients at risk for COPD (35-37). However, unless previous lung function values are available, there is little evidence to suggest that spirometry is important in evaluating AECB. Measurement of FEV<sub>1</sub> may not be possible in patients with severe AECB. Therefore, it is not necessary for spirometry to be performed during the actual exacerbation (level III evidence). However, an AECB episode is an indication to obtain measurements of pulmonary function after recovery in patients who have not previously had these measurements taken (level III evidence).

### MANAGEMENT OF AECB

Most studies of exacerbation treatment that do not concern antibiotics are focused on exacerbations of COPD, and results may be extrapolated, perhaps inappropriately, to the management of AECB.

Treatment of AECB should provide symptomatic relief, prevent transient loss of pulmonary function and lead to a re-evaluation of the disease to reduce the risk of future exacerbations. Patients should be removed from sources of irritants that may worsen lower airway inflammation, including dust, pollutants, and first- and secondhand 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 used for the treatment of dyspnea. The majority of the studies examining the role of

inhaled bronchodilators in patients with exacerbations of COPD have been completed with patients in the emergency room or hospital. It is not clear whether these results are applicable to the much larger population of AECB patients treated at home. Some of the studies comparing anticholinergics with short-acting beta-agonists have combined asthmatic patients with COPD patients. Nonetheless, certain general statements can be made based on the available literature (38).

Most studies comparing short-acting beta-agonists with inhaled anticholinergic agents show no appreciable difference between the two in terms of their effects on pulmonary function (39-42). Some patients clearly benefit from combination bronchodilator therapy, and there does not appear to be a significant increase in side effects with such combinations (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 meta-analysis of studies in patients with either asthma or COPD that compared the use of metered dose inhalers (MDIs) with nebulized bronchodilators reported no differences in pulmonary function outcomes between delivery systems (43). Therefore, the choice of delivery system should be based on cost and on 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 side effects (44,45). 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. Low flow oxygen should be administered if hypoxemia is present (46-49). Excess use of oxygen should be avoided, because this may lead to progressive hypercapnia (50,51). The goal of therapy with supplemental oxygen should be to maintain a partial pressure of arterial oxygen at or just above 60 mmHg. Decisions regarding the long term need for supplemental oxygen should not be made during an AECB, because up to 50% of patients requiring oxygen during an exacerbation no longer meet the criteria for home use if reassessed one to three months later (52-54).

### MUCUS CLEARING STRATEGIES

Expectorants or cough suppressants are not effective during AECB. Pharmacological therapy to enhance mucus clearance has not been shown to improve lung function or hasten clinical recovery (55-57), although it may lead to subjective improvement (57). There is no beneficial effect of chest physiotherapy on recovery time from AECB (58,59), and there is some suggestion of worsening pulmonary function and gas exchange with this therapy (60,61). 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 mucus 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 in acute exacerbations of COPD has been demonstrated to reduce mortality and decrease the need for intubation and mechanical ventilation (62,63) (level I evidence). Overall, noninvasive ventilation also reduces morbidity and hospital or ICU length of stay (64).

### 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 (Table 1). These studies demonstrate that systemic steroids lead to a faster improvement in pre- and post-bronchodilator FEV<sub>1</sub>, more rapid recovery of the partial pressure of oxygen, decreased treatment failures and shorter hospitalization rates. The one negative study used only a single dose of methylprednisolone 100 mg in the emergency room, and measured FEV<sub>1</sub> outcomes 3 h and 5 h after this bolus (65). The follow-up interval was probably not sufficient to detect a significant improvement.

These trials have limitations. All but one (66) were performed in emergency rooms or hospitals, so these results may not be applicable to outpatient populations. Most of the patients 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 and more prolonged corticosteroid doses in this elderly group of individuals. In the studies quoted, the major side effect in the steroid treatment group was hyperglycemia (67,68).

Systemic steroid therapy may have benefits aside from speeding up recovery from AECB. There is evidence favouring reduced likelihood of relapse (69) and prolongation of the time to the next exacerbation (9).

There is good evidence to support the use of oral or parenteral steroids for most moderately to severely ill patients with AECB (level I evidence). However, further evidence is required before recommending an exact dose and duration for these steroids. It appears that 10 days of therapy is more effective than three days, but no other comparisons have been made (70). 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% or greater than predicted) also benefit from a course of oral steroids during AECB is unknown at the present time. There are significant negative health consequences with the use of continuous oral corticosteroids in COPD, and similar effects may occur in patients treated with frequent short courses (71).

The role for inhaled steroids in AECB has not yet been defined. Although some studies have failed to demonstrate that inhaled steroids speed up symptom resolution in AECB, these trials were not designed to answer this question (72). A

**TABLE 1**  
**Randomized trials of corticosteroids in chronic obstructive pulmonary disease exacerbations**

Study (reference)	Year	Sample size	Intervention	Outcomes	P (steroids versus placebo)
Emerman et al (65)	1989	96	Methylprednisolone 100 mg × 1 dose	• FEV <sub>1</sub> at 3 and 5 h postdose • Hospitalization	NS NS
Albert et al (135)	1980	44	Methylprednisolone 0.5 mg/kg every 6 h × 72 h	• Pre- and postbronchodilator FEV <sub>1</sub> three times daily × 72 h	<0.001
Thompson et al (66)	1996	27	Prednisone 30 mg × 3 days, 40 mg × 3 days, 20 mg × 3 days	• Improvement in partial pressure of oxygen • Improvement FEV <sub>1</sub> • Decreased treatment failures	0.002 0.006 0.002
Davies et al (67)	1999	56	Prednisolone 30 mg once daily × 2 weeks	• Postbronchodilator FEV <sub>1</sub> • Length of hospitalization	<0.0001 0.027
Niewoehner et al (68)	1999	271	Methylprednisolone 125 mg every 6 h × 72 h followed by prednisone 60 mg once daily × 4 days tapered over 2 versus 6 weeks	• Treatment failure • Length of hospitalization • Increased FEV <sub>1</sub> days 1 to 3	0.04 0.03 <0.05
Maltais et al (73)	2002	199	Prednisolone 30 mg every 12 h × 6 doses? budesonide 2 mg every 6 h × 3 days	• Postbronchodilator FEV <sub>1</sub>	<0.05 versus placebo NS budesonide versus prednisone

FEV<sub>1</sub> Forced expiratory volume in 1 s; NS Not significant

**TABLE 2**  
**Randomized trials of antibiotics in acute exacerbations of chronic bronchitis**

Comparators	Patients (n)	Outcome of therapy	Reference
Placebo versus oxytetracycline	37 37	Treated patients lost one-half as much time from work, and exacerbations were shorter	Elmes et al, 1957 (74)
Placebo versus oxytetracycline	27 26	Treated patients recovered sooner and deteriorated less often	Berry et al, 1960 (75)
Placebo versus ampicillin	28 28	No significant difference in clinical response	Elmes et al, 1965 (76)
Placebo versus physiotherapy versus chloramphenicol	10 10 9	No significant differences	Peterson et al, 1967 (77)
Placebo versus chloramphenicol versus tetracycline	86 84 89	Antibiotic therapy was superior to placebo but there were no differences between antibiotics	Pines et al, 1972 (78)
Placebo versus tetracycline	20 20	100% versus 100% clinical response	Nicotra et al, 1982 (79)
Placebo versus one of cotrimoxazole, amoxicillin or doxycycline	180 182	55% versus 68% success (P<0.01)	Anthonisen et al, 1987 (8)
Placebo versus coamoxiclav	179 190	50.3% versus 86.4% success (P<0.01)	Allegre et al, 1991 (80)
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 (81)

recently published, prospective, randomized trial comparing high dose nebulized budesonide (2 mg every 6 h for 72 h) with 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> (73).

### ANTIBIOTIC THERAPY

Early, randomized, placebo-controlled antimicrobial trials were inconclusive (Table 2) (74-79), but more recent, well-designed studies have concluded that antibiotics are effective. Anthonisen and coworkers (8), in a landmark study, developed a classification

that identified patients that benefited from antimicrobial therapy. Patients who had increased dyspnea, plus increased sputum volume and sputum purulence (type I exacerbation) improved with antibiotics compared with patients receiving placebo. Individuals with only one of the cardinal symptoms (type III exacerbation) did not differ from patients receiving placebo. In another well-designed trial, Allegre and coworkers (80) demonstrated the superiority of amoxicillin/clavulanate to placebo. A more recent study in 93 mechanically ventilated patients demonstrated that the use of fluoroquinolones compared with placebo was associated with a reduction in mortality, duration of hospital stay and time



**TABLE 3**  
**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 longer than 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> species, <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> species and other Gram-negative bacteria • 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 • Multiple risk factors (eg, frequent exacerbations and FEV <sub>1</sub> <50%)	As in group II, plus <i>Pseudomonas aeruginosa</i> and multiresistant <i>Enterobacteriaceae</i> family	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

on mechanical ventilation, and a decrease in the need for additional antibiotics (81).

Although the Anthonisen et al (8) classification is helpful in predicting an antimicrobial response, it has only a sensitivity of 59% and a specificity of 60% in predicting a bacterial exacerbation (82). While an advance, 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 is 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 (83). In a meta-analysis examining placebo-controlled trials in AECB, antibiotic therapy improved clinical outcomes, and hastened clinical and physiological recovery (84).

Antibiotic resistance and widespread clinical failure in lower respiratory tract infections have not been linked at this time. However, more highly resistant strains have been associated with clinical treatment failures (85) in nosocomial outbreaks. If levels of resistance continue to increase, the value of many classes of antibiotics combinations may diminish. Antibiotic overprescription for nonbacterial infections is a major factor in the emergence of bacterial resistance. We need a risk stratification system that identifies patients not requiring antimicrobial therapy, as well as those requiring more aggressive therapy.

### RISK STRATIFICATION

Failure and relapse rates for AECB in the literature vary from 17% to 32% depending on the definition used. Treatment failure can be associated with substantial additional expenditures

among patients with significant compromise of lung function who require hospitalization and are at risk for respiratory failure (86). Identification of patients at risk of failing standard antimicrobial therapy with the usual first-line agents may lead to improved outcomes. Patients associated with significant cardiac disease, frequent purulent exacerbations of COPD, generalized debility, malnutrition, chronic corticosteroid administration, use of supplemental oxygen, lengthy duration of COPD, chronic mucous hypersecretion and severe underlying lung function abnormalities tend to fail therapy with usual antimicrobial therapy and have early relapse or hospitalization (16,87-97). Frequent exacerbations, chronic use of oral steroids and poor underlying lung function increase the risk for *Klebsiella pneumoniae* or *Pseudomonas aeruginosa* infection (98-100). Frequent courses of antibiotics increase the risk of infection with beta-lactamase-producing bacteria (101). Treatment directed toward resistant pathogens with potent antimicrobial drugs may lead to improved clinical outcomes and overall lower costs if hospital admissions and respiratory failure can be prevented (102,103). Stratification of patients into risk categories may allow the physician to select targeted antimicrobial therapy to prevent some of these consequences.

Our proposed classification system divides patients into four groups (Table 3). 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 have no underlying lung disease and do not have chronic bronchitis, although they may smoke. They present with the acute onset of cough associated with sputum production, often in association with a preceding coryzal illness and

fever. 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. Because there is no underlying lung disease in this group, the illness is usually self limited and runs a benign course. The routine use of antibiotics in patients with uncomplicated acute tracheobronchitis is not justified (104). Giving patients a written leaflet explaining why they do not require an antibiotic has been shown to reduce the use of antibiotics (105). Patients in group 0 may benefit from one to two weeks of inhaled beta-agonist bronchodilator therapy to reduce the severity and duration of cough, particularly if wheezing is also present (104).

A small number of these patients have a more protracted course. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are known etiological agents for acute tracheobronchitis and may be responsible for lack of rapid clinical improvement. Treatment with a macrolide or doxycycline might be considered for patients in whom the cough has not improved after 10 to 14 days (level III evidence). However, there is no good evidence supporting this course.

Group I patients have chronic bronchitis, defined as chronic cough and sputum production for at least three months for two consecutive years, and exacerbations are associated with worsening cough and increased production of purulent sputum. However, they have only mild to moderate impairment of lung function ( $FEV_1$  greater than 50% predicted), have less than four exacerbations per year and have no significant cardiac disease. In this group of patients, usual pathogens, including *H influenzae*, *S pneumoniae* and *M catarrhalis*, are present, although viral infection often precedes bacterial superinfection. Treatment with virtually any antibiotic is usually successful and the prognosis is excellent. Until a prospective pharmacoeconomic or clinical study demonstrates some advantage for more potent agents among this group of patients, the recommendation for simple therapy – using agents such as an aminopenicillin, doxycycline or trimethoprim/sulfamethoxazole – is justified. However, most studies showing beneficial results from the use of these agents were performed more than 10 years ago. Given 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 treatment failure, alternative therapies such as a beta-lactam/beta-lactamase inhibitor or fluoroquinolones can be used. However, there are no data demonstrating that these failures are due to resistant organisms.

Group II patients have risk factors for treatment failure such as poor underlying lung function ( $FEV_1$  less than 50% predicted). Alternatively, they may demonstrate only moderate impairment of lung function ( $FEV_1$  between 50% and 65% predicted) but have significant comorbidity (ischemic heart disease or 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, and 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.

A number of studies have demonstrated significantly superior bacterial eradication rates with fluoroquinolones compared with cefuroxime or clarithromycin (106-108). There is some evidence suggesting that the enhanced bacterial eradication associated with fluoroquinolones leads to faster symptom resolution and results in more prolonged exacerbation-free intervals compared with cephalosporins and extended spectrum macrolides (level II evidence) (109-112). This preliminary evidence does not warrant fluoroquinolone use in all cases of AECB. There is evidence showing that frequent use of fluoroquinolones leads to the emergence of resistant strains and that COPD patients are a major reservoir for these resistant organisms (113).

It is unclear how group II patients who fail to respond to antimicrobial therapy or who quickly relapse should be treated. 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  $FEV_1$  less than 50% are infected with *Pseudomonas* species (98-100). Whether this occurs only 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 to 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 will have evidence for bronchiectasis on high resolution computed tomography scans. Besides 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 patient in group III.

An algorithmic approach to choosing antimicrobial therapy for AECB is summarized in Figure 2.

#### SUMMARY OF EVIDENCE REGARDING ANTIBIOTIC THERAPY FOR AECB

1. Antimicrobial therapy is warranted for patients with AECB if they fall into the Anthonisen et al (8) type I or type II categories (level I evidence – two randomized, large scale, double-blind trials and 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 less than predicted), frequent exacerbations (four or more per year), lengthy duration of disease, significant comorbidity, use of supplemental oxygen and chronic oral corticosteroid use (level II evidence).

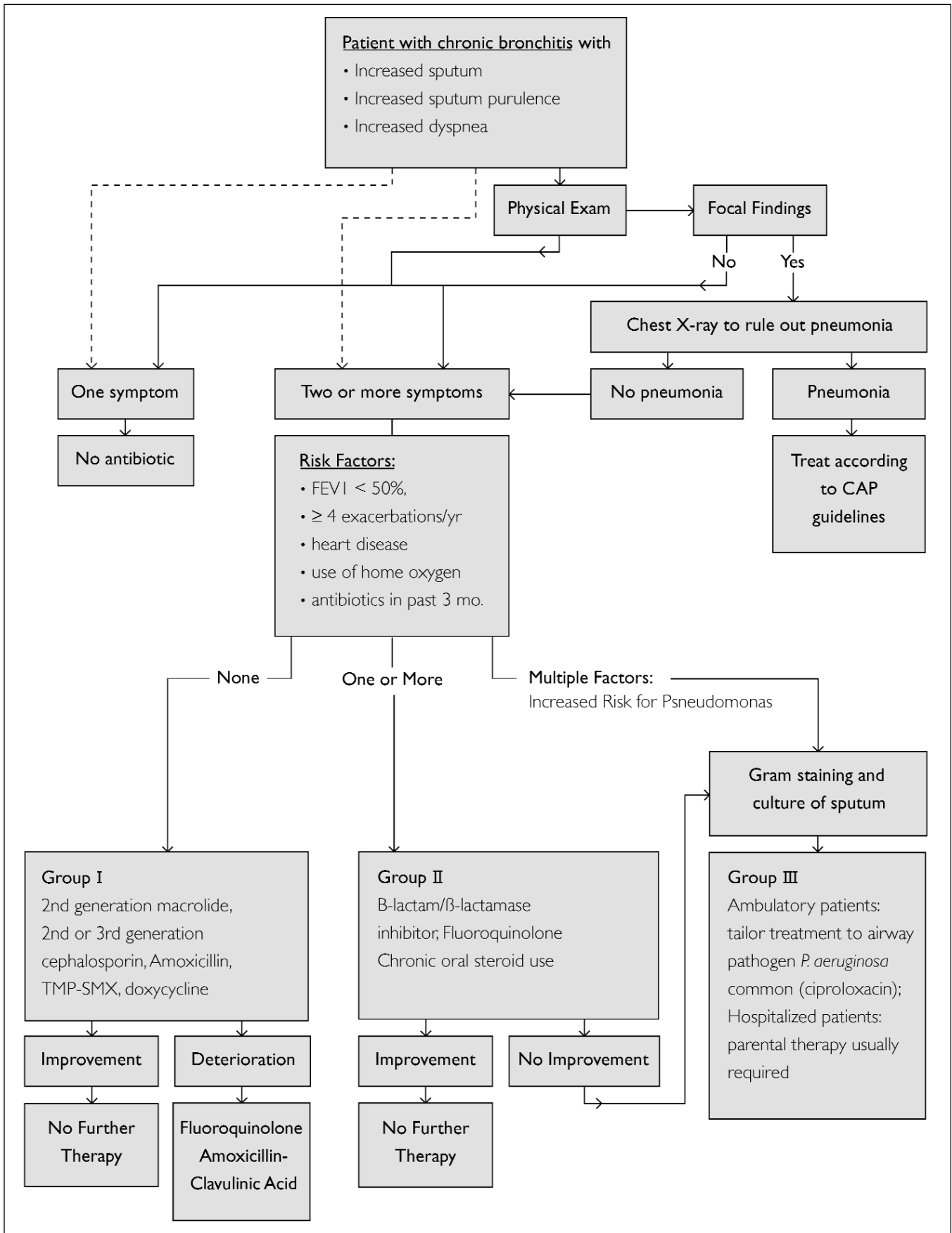


Figure 2) Algorithm for choosing antimicrobial therapy in acute exacerbations of chronic bronchitis. CAP Community-acquired pneumonia; FEV<sub>1</sub> Forced expiratory volume in 1 s; mo. Months; TMP SMX Trimethoprim/sulfamethoxazole

5. Risk group 0 patients (acute tracheobronchitis) should not be treated with antibiotics unless symptoms persist longer than 10 to 14 days (level I evidence).
6. For risk group 0 patients with persistent symptoms, a macrolide or tetracycline is recommended, because *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, trimethoprim/sulfamethoxazole) 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 in group II patients (level II evidence).
11. Group III patients at risk for *P aeruginosa* infection (with 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 because of a higher risk of harbouring resistant organisms (level III evidence).

### PREVENTION OF AECB

Cigarette smoking remains the primary risk factor for the development of chronic bronchitis. Smoking cessation has been shown to reduce the rate of decline of FEV<sub>1</sub> (114), even in those older than 60 years (115), and also confers a survival advantage (level II evidence) (116). Coughing stops in as many as 77% of patients who quit smoking and improves in another 17% of patients. Since patients with chronic cough and sputum production have increased numbers of AECB episodes, it is probable that smoking cessation leads to fewer exacerbations. A recent analysis of patients in the Lung Health Study revealed that recurrent lower respiratory infections hastened the decline in FEV<sub>1</sub> in current smokers but not exsmokers (117). A discussion of smoking behavior 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. Annual influenza vaccination reduces morbidity and mortality from influenza in elderly patients by 50% and reduces hospitalization for acute and chronic respiratory conditions by as much as 39% (118,119). Annual influenza vaccination for all patients with chronic bronchitis is strongly recommended (level II evidence). Oral and inhaled neuraminidase inhibitors, which are effective

against strains of influenza A and B, are currently under study for preventing AECB during influenza outbreaks in high risk patients. High risk patients who have not been vaccinated should probably receive prophylaxis during an outbreak (level III evidence).

The value of pneumococcal vaccination in patients with chronic bronchitis is less well established. It is not clear whether vaccination prevents AECB in COPD (120). However, pneumococcal vaccination is safe and can reduce invasive pneumococcal infection, and current recommendations favour vaccinations in all patients with COPD at least once in their lives. In addition, consideration should be given to repeating the vaccine after five to 10 years in high risk patients (level III evidence) (121).

There is no benefit in terms of the rate of decline in lung function in COPD patients treated chronically with inhaled steroids versus those receiving placebo (31,122-124). In addition, patients receiving inhaled steroids had a higher percentage of skin bruising (122), a decrease in bone density of the lumbar spine and femur (124), and a small decrease in mean cortisol concentrations, although this was not associated with any clinical effects (31).

The Inhaled Steroids in Obstructive Lung Disease in Europe study (31) revealed a 25% reduction in the median exacerbation rate 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 (32). Patients with severe impairment in FEV<sub>1</sub> and those with frequent exacerbations requiring the use of oral corticosteroids should be considered for therapy with inhaled corticosteroids (level III evidence).

There is little to suggest that there is benefit in regular therapy with oral corticosteroids in patients with COPD. This, combined with the recognition of the significant complications of chronic oral corticosteroid therapy (125,126), including a dose-dependent increase in mortality (127), 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 of this medication without any adverse effects on pulmonary function, quality of life or frequency of AECB (128).

There is some preliminary evidence to suggest that COPD patients treated with long-acting beta-agonists or tiotropium, a long-acting anticholinergic agent, have a delayed time to their next exacerbation compared with patients receiving placebo or ipratropium (129-131). Further investigations are necessary before long-acting beta-agonists or long-acting anticholinergics can be recommended for this purpose.

Numerous trials dating back to the mid-1950s have been carried out to determine whether antibiotic prophylaxis reduces the frequency of AECB (15,132,133). 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.

*Please refer to the Canadian Respiratory Journal, Volume 10, Supplement B, for the complete document of Canadian guidelines for the management of acute exacerbations of chronic bronchitis.*



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