Guideline for

The Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

This clinical practice guideline was developed by an Alberta Clinical Practice Guideline working group. This guideline applies to patients with an exacerbation of their AECOPD.

This guideline might not apply to patients who:
- Are immunocompromised
- Have severe underlying systemic disease
- Have bronchiectasis
- Have respiratory failure

DEFINITIONS
- In a patient with COPD, an acute exacerbation (AECOPD) is the onset of:
  - Increased sputum production
  - Increased sputum purulence
  - Increased dyspnea

ISSUES
- Smoking cessation is the key to the prevention and amelioration of COPD
- The etiology of AECOPD is often multifactorial including both infectious and non-infectious causes:
  - The most common infections are viral in etiology
- The treatment approach to AECOPD is multifaceted. Over-reliance on antibiotics at the expense of other therapies may lead to treatment failure
- The overuse of antibiotics in AECOPD has led to increasing antimicrobial resistance.

GOALS
- To optimize the prevention and management of AECOPD
- To optimize the use of antibiotics in the treatment of bacterial AECOPD
- To optimize the use of laboratory and diagnostic imaging services

PREVENTION
- Smoking cessation and avoidance of environmental tobacco smoke
- Limit the spread of viral infections (e.g., hand washing)
- Influenza vaccine is recommended annually
- Pneumococcal vaccine is recommended
- Rehabilitation and nutritional programs

DIAGNOSIS
- History of COPD with acute onset of symptoms which include:
  - Increased sputum production
  - Increased sputum purulence
  - Increased dyspnea
- Physical findings of:
  - Increased respiratory rate
  - Increased wheezing
  - Might have diffuse crackles without localization

Note: Evidence of consolidation (localized crackles, bronchial breath sounds, dullness on percussion) should alert to possibility of pneumonia

The above recommendations are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.
Investigations

- Measurement of expiratory airflow (peak flow and/or FEV₁) is generally recommended
- Measurement of O₂ saturation (+/- blood gases) is recommended in moderate to severe cases

PRACTICE POINT

- Sputum cultures are not routinely recommended as these patients are often colonized with respiratory pathogens.
  - Sputum cultures might be helpful in patients with end-stage COPD, frequent exacerbations or bronchiectasis to determine colonization with gram-negative organisms such as Pseudomonas spp.

Corticosteroids

- Systemic corticosteroids are indicated in most cases
  - Prednisone 0.5 to 1 mg/kg per day for 5 to 14 days, sometimes longer
- Inhaled corticosteroids do not offer a significant benefit in AECOPD

Antibiotics

- Antibiotics only have proven value if the patient has at least 2 of the 3 following symptoms:
  - Increased sputum production
  - Increased sputum purulence
  - Increased dyspnea
- If treating with antibiotics, treatment must include coverage for:
  - Haemophilus influenzae
  - Streptococcus pneumoniae
  - Moraxella catarrhalis
- For specific antibiotic recommendations, see Algorithm

Agents NOT Recommended in AECB

- Cephalexin - poor activity against penicillin intermediate/resistant Streptococcus pneumoniae
  - no activity against Haemophilus/Moraxella
- Cefaclor - no activity against penicillin intermediate/resistant Streptococcus pneumoniae
  - marginal activity against Haemophilus
- Cefixime - no activity against penicillin intermediate/resistant Streptococcus pneumoniae
  - excellent activity against Haemophilus
- Ceftriaxone - routine use of this agent is not recommended in AECOPD due to potential for increased resistance to third generation cephalosporins
- Erythromycin - poor activity against Haemophilus and Moraxella
- Clindamycin - no activity against Haemophilus and Moraxella

MANAGEMENT

- The mainstays of therapy for AECOPD are:
  - Smoking cessation
  - Adequate bronchodilation
  - Optimal oxygenation
  - Systemic corticosteroids are often indicated
  - Antibiotics when appropriate
  - Rehabilitation and nutritional programs where appropriate

Bronchodilators

- Bronchodilators are the mainstay of therapy:
  - Ipratropium and short-acting β-agonists (fenoterol, salbutamol, terbutaline) are an effective combination
  - Long-acting β-agonists (formoterol, salmeterol) and anticholinergics (tiotropium) are not currently indicated in the management of AECOPD but may be useful in chronic COPD.

Oxygen

- Assessment for oxygen supplementation is recommended
Prophylaxis

- Given the high risk of developing antimicrobial resistance associated with prolonged use of antibiotics, antimicrobial prophylaxis is not recommended in the management of AECOPD.

Follow-up

- Routine follow-up is recommended to evaluate maintenance therapy.
- Spirometry/peak flows are a useful way to measure response to treatment.

BACKGROUND

Introduction

Chronic obstructive pulmonary disease (COPD) is largely caused by cigarette smoking and characterized by progressive partially reversible airway obstruction, systemic, and increasing frequency and severity of exacerbations. An acute exacerbation is the abrupt onset of increased sputum production, sputum purulence and dyspnea in a patient with COPD.

Epidemiology

COPD may affect 4-8% of the adult population. It is more common in men, in persons older than 40 years of age, and those who smoke. COPD is the fourth leading cause of death in North America. Acute exacerbations of COPD are often seasonal with the highest incidence in winter months.

Pathogenesis

In patients with severe COPD (FEV\textsubscript{1} <1L), respiratory failure following an acute exacerbation is the most frequent terminal event. Acute exacerbations are most often precipitated by viral upper respiratory infections but other precipitants include seasonal weather changes, medications, exposure to environmental irritants or allergens, and intercurrent illness.

Airflow obstruction is exacerbated by excessive tracheobronchial mucus production, bronchial wall thickening and smooth muscle spasm.

Cigarette smoking is the most important risk factor for the development of COPD. Over 90% of patients with the disease have a smoking history.

Other possible causes include inhalation of environmental pollutants and allergens, and infections. Although bacterial infections do not appear to initiate COPD, they might play a role in perpetuating increased mucus production in chronic bronchitis. A non-specific inflammatory response appears to be the prominent feature of acute exacerbations in patients with COPD.

Etiology

Viruses are the most common pathogens causing AECOPD. They include influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, adenovirus and the common cold (rhinovirus).

The role of bacterial infections in AECOPD is not clear. Although potential bacterial pathogens such as Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis are recovered in 30 to 50% of patients experiencing an acute exacerbation, the presence of these organisms may represent colonization. These organisms may be recovered during quiescent intervals and may not be greatly increased during AECOPD. In exacerbations marked by increased quantity and purulence of sputum, a quantitative increase in Streptococcus pneumoniae might be present.

Both Mycoplasma pneumoniae and Chlamydia pneumoniae are thought to be associated with a mild form of bronchitis, which is usually self-limiting, but may produce a prolonged cough. The role of these organisms in AECOPD is not clear. The need for empiric antibiotic therapy to cover these organisms has not been established.
Corynebacterium pseudodiphtheriticum, Staphylococcus aureus and β-haemolytic Streptococci have occasionally been implicated in chronic bronchitis, but it is not clear what role these organisms play in AECOPD. Gram-negative bacilli, including Pseudomonas aeruginosa, might colonize the airways of patients with end-stage COPD, and are thought to play a role in acute exacerbations in these patients.

Overall, it appears that bacterial pathogens probably do not initiate AECOPD but may have a role in prolonging and complicating the course of illness.

**Diagnosis**

Documentation of airflow obstruction by pulmonary function testing is critical for the diagnosis of AECOPD and provides valuable therapeutic information on severity of disease and response to therapy.\(^1\) A measured forced expiratory volume in one second of less than 70% predicted suggests obstructive airway disease. An FEV\(_1\) of less than 50% of predicted indicates severe obstructive airway disease.\(^1\)

Evidence of obstructive airflow changes on pulmonary function testing without sputum production is often accompanied by radiographic findings consistent with emphysema. Younger patients with emphysematous obstructive pulmonary findings, especially those without a smoking history, should be evaluated for alpha-I-antitrypsin deficiency.\(^4\)

**Sputum Cultures in AECOPD**

Microbiologic studies have failed to identify a definite pathogen in 50% of cases of AECOPD. Sputum cultures during quiescent intervals in patients with COPD indicate that 30 to 50% are colonized with non-encapsulated Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. Therefore, sputum cultures are not routinely recommended but may be helpful in patients with end-stage COPD, frequent exacerbations or bronchiectasis.

**Management**

**Lifestyle Modification**

Smoking cessation is the single most effective way to reduce the risk of future morbidity from COPD.\(^1,4,11\) Once a patient makes a commitment to stop smoking, use of various smoking cessation tools can be helpful. Primary care physicians, community health nurses, and pharmacists should enlist and educate available family members to aid in the patient’s smoking cessation efforts.\(^1\)

The documentation of an accelerated decline in FEV\(_1\) (greater than the normal decline of 30 mL per year) may provide motivation for smokers who continue to deny that their persistent smoking will cause future symptoms.

Reduction or elimination of exposure to inhaled irritants including environmental pollutants and occupational irritants is also a prudent management suggestion.\(^7,11\)

Educating the patient about the progressive nature of COPD and its potential impact on future lifestyle and function is another important aspect for the family physician. A multidisciplinary approach to teach the patient about the disease should be encouraged.\(^1\)

**Bronchodilators**

Inhaled anticholinergics and sympathomimetic agents are the mainstays of therapy to treat airway obstruction.\(^12,13\) For treatment of acute exacerbations, the anticholinergic agent ipratropium is an effective bronchodilator but has a slightly slower onset of action than sympathomimetic drugs although a slightly longer duration of action. Conversely, β\(_2\)-agonists such as salbutamol provide more rapid bronchodilation. Both ipratropium and β-agonists are available in metered dose inhalers (MDI) and solutions for nebulized aerosol administration.\(^1\) Optimal use of an MDI for administration of these agents, as well as corticosteroid preparations, requires patient education and training.\(^1\) Spacers are strongly encouraged for MDI delivery.
A spectrum of delivery devices are available for delivery of inhaled medication to the respiratory tract. These range from MDI which can be used with or without spacers, to a variety of dry powdered inhalers, to nebulizers. The current MDI is being phased out in favour of CFC free MDI. Each delivery device has its own particular attributes and the choice for each patient should be individualized based on a number of factors including the patient’s ability to use the device, compliance, patient and physician choice, and the medication which is selected (as some are available only in certain devices). When using the MDI, the addition of a spacer enhances the delivery of the medication to the lower respiratory tract with reduction in associated side effects. Long acting beta-agonists and tiotropium are recommended for maintenance bronchodilator therapy.

Theophyllines are third-line bronchodilator agents used in the therapy of COPD. A narrow therapeutic range and potential medication interactions may limit their use. An increased dosage may be necessary for patients who continue to smoke and in patients taking hepatically cleared medications.

**Oxygen**

Evidence suggests that patients with severely hypoxaemic chronic obstructive pulmonary disease survive longer if given domiciliary oxygen for at least 15 hours per day, however, patients whose PaO$_2$ exceeds 7.9 kilopascals (60 mm Hg) gain only small benefits (as measured by physiological function, exercise tests, and quality of life).

**Systemic Corticosteroids**

For patients with advanced lung disease or patients with less severe lung disease having a severe exacerbation, systemic corticosteroids are indicated. The dosage and duration of therapy is variable depending on clinical judgement although evolving data suggest that most of the improvement in lung function occurs during the first 3 to 5 days of corticosteroid treatment. Oral prednisone is usually used beginning at a dosage of 0.5 to 1.0 mg/kg/day and then tapered at a rate and duration based on response. For those severely ill or unable to take oral medications, intravenous methylprednisolone (40 to 125 mg every 8 to 12 hours) or hydrocortisone (100 mg every 6 to 8 hours) may be used initially.

**Antibiotics**

Antibiotics have no role in stable COPD and their role in AECOPD is limited. Antibiotics may be of some benefit when used empirically for patients who demonstrate at least 2 of the 3 major symptoms of acute exacerbations: (i) increased sputum production (ii) increased sputum purulence, and (iii) increased dyspnea.

Antibiotic selection should be directed against Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae/parainfluenzae. Local resistance patterns dictate optimal therapy.

In Alberta, approximately 20% of Streptococcus pneumoniae isolates exhibit decreased susceptibility to penicillin. In-vitro resistance of Streptococcus pneumoniae to macrolides exceeds 10%. Broader antibiotic coverage may be required in a recently hospitalized patient or in patients with end-stage disease.

Amoxicillin is a good antibiotic choice for mild to moderate AECOPD for the following reasons:

- Adequate coverage for organisms involved in AECOPD
- Best activity of all oral β-lactam agents against penicillin intermediate Streptococcus pneumoniae
- Relatively few adverse effects
- Low potential to induce resistance
- No other antibiotic agent has been proven superior to amoxicillin in clinical trials

For patients who are allergic to penicillin, doxycycline or TMP/SMX are acceptable alternatives. Ce-furoxime-axetil and amoxicillin-clavulanate should be reserved as second-line agents. In β-lactam allergic patients, azithromycin and clarithromycin are reasonable options. However, because resistance to macrolides continues to increase, the routine use of these agents in AECOPD is not recommended.
Quinolones may play a role in the management of this disease. Levofloxacin, moxifloxacin, and gatifloxacin provide excellent coverage for the pathogens involved, but because of their broad spectrum and potential for increasing resistance in Streptococcus pneumoniae, levofloxacin, moxifloxacin and gatifloxacin should be reserved for patients who have failed recent antibiotic therapy.

Ciprofloxacin does not have adequate coverage for Streptococcus pneumoniae and should not be used routinely in the management of AECOPD. It may have a role in end-stage disease, with or without bronchiectasis, where there has been documentation of previous Pseudomonas aeruginosa colonization/infection.

**Prophylaxis**

Although antibiotic prophylaxis in patients having 4 or more acute exacerbations per year has been suggested, the effectiveness of this approach has not been documented. Given the increasing resistance in respiratory tract pathogens this practice not recommended.

**Prevention**

A clear role exists for yearly influenza immunizations to decrease acute exacerbations due to influenza and potential secondary bacterial infections in these patients. All patients with COPD should receive the polyvalent pneumococcal vaccine at least once with more current recommendations suggesting every 5 to 10 years.

**REFERENCES**


TOWARD OPTIMIZED PRACTICE (TOP) PROGRAM

The successor to the Alberta Clinical Practice Guideline (CPG) program, TOP is an initiative directed jointly by the Alberta Medical Association, Alberta Health and Wellness, the College of Physicians and Surgeons, and Alberta’s Health Regions. The TOP Program promotes appropriate, effective and quality medical care in Alberta by supporting the use of evidence-based medicine.

TOP Leadership Committee

Alberta Health and Wellness
Alberta Medical Association
Regional Health Authorities
College of Physicians and Surgeons of Alberta

TO PROVIDE FEEDBACK

The Alberta CPG Working Group for Antibiotics is a multi-disciplinary team composed of family physicians, infectious diseases specialists, internal medicine, pediatricians, microbiologist, hospital and community pharmacists, epidemiologist, consumers, and Alberta Health and Wellness representative. The team encourages your feedback.

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Algorithm: Antibiotic Therapy in AECOPD
(Secondary to oxygen, bronchodilator, and steroid therapy)

Pre-existing COPD

Patient has at least 2 of: increased sputum production, increased sputum purulence, increased dyspnea?

NO

Antibiotic therapy NOT indicated unless patient develops at least 2 of the above symptoms.

YES

No antibiotics in last 6 weeks AND < 4 episodes in past year

Amoxicillin
500mg PO tid for 7 to 10 days
OR
Doxycycline
200mg PO day 1 then 100 mg PO daily for 7 to 10 days
OR
TMP/SMX
1 DS tab PO bid for 7 to 10 days

Treatment failure?

Cefuroxime axetil
250-500mg PO bid for 7 to 10 days
OR
Amoxicillin-clavulanate
500mg PO tid for 7 to 10 days
Beta-lactam allergy
Clarithromycin
250-500mg PO bid for 7 to 10 days
OR
Azithromycin
500mg PO day 1 then 250mg PO daily for 4 days

Treatment failure or advanced lung disease with severe exacerbation?

Levofloxacin
500mg PO daily for 5 to 10 days
OR
Moxifloxacin
400mg PO daily for 5 to 10 days
OR
Gatifloxacin
400mg PO daily for 5 to 10 days

Notes:
1. COPD: a clinical diagnosis characterized by a productive cough of more than 3 months duration in each of 2 consecutive years
2. Treatment failure = clinical deterioration after 72 hours of antibiotic therapy or no improvement after 7 to 10 days of antibiotic therapy
3. Patients with advanced lung disease and severe bacterial exacerbation recommend use levofloxacin, gatifloxacin, or moxifloxacin for 10 days.
4. Role of quinolones: Levofloxacin, moxifloxacin and gatifloxacin have excellent coverage of pathogens involved, however to minimize the development of resistance, these agents should be reserved for patients who have failed therapy. Ciprofloxacin has sub-optimal coverage of S. pneumoniae and should not be used routinely in AECOPD. For documented Pseudomonas aeruginosa, use ciprofloxacin 750mg BID for 10 days
5. Duration: The efficacy of 5 days of therapy has been shown with moxifloxacin. Note: These studies did not specifically address failure of initial antibiotic therapy. The efficacy of a 5 day course of antibiotics requires further study in this patient population.