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Review

Acute exacerbation of chronic bronchitis: Need for an evidence-based approach

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Abstract

Acute exacerbations of chronic bronchitis (AECB) can be classified into three levels according to severity: (1) home treatment sufficient; (2) hospitalisation required; (3) hospitalisation in the presence of respiratory failure. This evidence-based classification is useful in ranking the clinical relevance of the episode and its outcome, and makes it possible to define the clinical history, clinical evaluation and diagnostic procedures of an exacerbation. Treatment guidelines vary according to severity, but they are essentially based on appropriate bronchodilator therapy (β_2 agonists and/or anticholinergics, corticosteroids and antibiotics selected according to the local bacterial resistance pattern). It is important that cases requiring management in an intermediate/special respiratory care unit or intensive care unit (ICU) be identified. This is the stage where oxygen therapy and ventilatory support become particularly important. As first choice, they should be non-invasive, saving intubation and invasive ventilatory support for most severe cases characterised by severe acidemia and hypercapnia. We identify the optimal criteria for hospital discharge and follow-up of patients with AECB. In view of the chronic nature of the underlying disease, a correct follow-up is essential to avoid frequent and repeated relapses.

Keywords: Acute exacerbation of chronic bronchitis; Definition; Evaluation; Treatment

Contents

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1. Introduction

Acute exacerbations of chronic bronchitis (AECB) are a common cause of morbidity [1–3] and mortality in patients with chronic obstructive pulmonary disease (COPD) [4–6]. COPD affects 15 million people and is the fourth leading cause of death in the USA, annually accounting for 16,000,367 outpatient visits, 500,000 hospitalisations and US $18 billion in direct healthcare costs [6–9]. In the EU, the annual number of consultations per 100,000 inhabitants averages 17,300 and accounts for €10.3 billion in healthcare costs.

According to these data, COPD places a considerable burden on healthcare systems, and exacerbations constitute a significant proportion of this burden. Despite aggressive medical treatment, approximately one-third of the patients discharged from hospital emergency departments with acute exacerbations of chronic bronchitis develop recurrent symptoms within 14 days (10), and 17% relapse and require hospitalisation [11]. The identification of patients at risk for relapse improves decisions about hospital admission and follow-up [12–14].

Patients with recurrent exacerbation, who experience more than two exacerbations per year, are especially difficult to manage. Several potential host, pathogen and treatment factors can be identified that contribute to recurrent exacerbation. Patients with recurrent exacerbations are often exposed to frequent courses of antimicrobials. Therefore, antimicrobial resistance among common bacterial pathogens is likely to be prevalent in this group of patients, and further complicates the treatment of "difficult-to-treat" patient populations. The decreased frequency of exacerbations should be a goal in the management of patients with recurrent exacerbation, and several strategies have been suggested to achieve this objective [15]. Conventional end-points for assessing efficacy of pharmacological treatments in chronic bronchitis exacerbations are the resolution of symptoms and the bacteriological eradication observed at the test of cure (TOC) visit, generally scheduled between 72 h and 10 days after completion of treatment, as suggested by the most recent European guidelines on the matter (CPMP/EWP/558/95 rev 1—London, 22 April 2004). These end-points have been used to evaluate new drugs but may be lacking of clinical relevance. Other end-points, such as the exacerbation-free interval, resource utilisation (hospitalisation, outpatient visits, use of medication, lost work days, etc.) and improved quality of life may be more suitable end-points in this particular patient population [16–19].

In the natural course of the disease, the AECB is an event characterised by changes in the patient's baseline dyspnoea, cough and/or sputum, which are beyond the level of the day-to-day variability and warrant a change in management.

There is no agreed classification of AECB. The following evidence-based classification according to severity, can help in ranking the clinical relevance of an episode and the relevant outcome [20]:

Level I: the patient can be treated at home.

Level II: hospitalisation is required.

Level III: respiratory failure is a likely consequence and management in an intermediate/special respiratory care unit or intensive care unit (ICU), if available, should be considered.

1.1. Risk factors

Major risk factors for exacerbation are infectious processes [7,8] of viral (*Rhinovirus* spp., *influenza*) or bacterial origin (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Enterobacteriaceae* spp., *Pseudomonas* spp.), environmental conditions, air pollution exposure, lack of compliance with long-term oxygen therapy and failure to participate in pulmonary rehabilitation programs.

The incidence of relapse ranges from 21% to 40% [11,14,21–23] and risk factors for relapse include [11–14,21–23]: increased need for bronchodilators or corticosteroids; previous exacerbations (more than 3 in the past 2 years); prior antibiotic treatment (mainly ampicillin); presence of comorbid conditions (congestive heart failure, coronary artery disease, chronic renal or liver failure).

1.2. Assessment

Several clinical findings should be considered in evaluating patients with exacerbations. These include severity of the underlying disease, presence of comorbidity and history of previous exacerbations. The physical examination should evaluate how the episode affected the haemodynamic and respiratory systems. The selection of diagnostic procedures depends on the evaluation setting [24,25].

Table 1 shows the clinical evaluation elements and the diagnostic procedures that are usually informative in patients with exacerbations according to the severity of the episode.

2. Outpatient setting

2.1. Treatment

The outpatient treatment for exacerbation should be based on the clinical presentation of the patient (Level I) and consistent with the following guidelines [20]:

- *patient education*: check the inhalation technique and consider use of spacing devices;
- administer bronchodilators (short-acting β_2-agonist and/or anticholinergic by metered-dose inhaler (MDI) with spacer or hand-held nebuliser as needed [26–28] and consider adding a long-acting bronchodilator if the patient is not using it;

Table 1
Clinical history, physical findings and diagnostic procedures (from Celli et al. [20], modified)

	Level I	Level II	Level III
Clinical history			
Co-morbid conditions[a]	+	+ + +	+ + +
Frequent exacerbations	+	+ + +	+ + +
Severity of COPD	Mild/moderate	Moderate/severe	Severe
Physical findings			
Haemodynamic evaluation	Stable	Stable	Stable/unstable
Use of accessory respiratory muscles, tachypnoea	Not present	+ +	+ + +
Persistent symptoms after initial therapy	No	+ +	+ + +
Diagnostic procedures			
Oxygen saturation	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Chest roentgenogram	No	Yes	Yes
Blood tests[b]	No	Yes	Yes
Serum drug concentrations[c]	If applicable	If applicable	If applicable
Sputum gram stain and culture	No[d]	Yes	Yes
Electrocardiogram	No	Yes	Yes

+, Unlikely to be present; + +, likely to be present; + + +, very likely to be present.
[a]The more common comorbid conditions are congestive heart failure, coronary artery disease, diabetes mellitus, renal and liver failure.
[b]Include cell blood count, serum electrolytes, renal and liver function.
[c]Consider if patients are using theophyllin, warfarin, carbamezepine, digoxin.
[d]Consider if patient has recently been on antibiotics.

- administer corticosteroids (prednisone 30–40 mg *per os*/day for 5–7 days [29–31] and consider using an inhaled corticosteroid [32];
- administer antibiotics [7,11,19,33–36] in patients with altered sputum characteristics (purulence and/or volume) basing the choice on the local bacteria resistance patterns (amoxicillin/ampicillin, cephalosporins, doxycycline, macrolides (azithromycin, clarithromycin, dirithromycin, roxithromycin, [37–39]. If the patient has failed prior antibiotic therapy consider amoxicillin/clavulanate [39] and respiratory fluoroquinolones (gatifloxacin, prulifloxacin, levofloxacin and moxifloxacin, [19,40–43].

3. Inpatient setting

3.1. Hospitalisation

Traditionally, the decision to admit a patient is based on the physician's subjective interpretation of clinical features such as severity of dyspnoea, determination of respiratory failure, short-term response to emergency room therapy, severity of cor pulmonale and presence of complicating features (severe bronchitis, pneumonia or other comorbid conditions).

Few clinical studies investigated the objective, patient-specific clinical and laboratory features that may identify patients with COPD requiring hospitalisation. General consensus supports the need for hospitalisation in cases where severe acute hypoxaemia or acute hypercarbia are present, but less extreme arterial blood gas abnormalities do not assist the decision analysis. Other factors that identify "high-risk" patients include a prior emergency room visit within the previous 7 days, the number of nebulised bronchodilator doses, use of home oxygen, previous relapse rate, administration of aminophylline, and use of corticosteroids and antibiotics at the time of the previous discharge from emergency room [10,44–46].

In acute settings, nurses play a vital role in caring for individuals during acute exacerbation of COPD. It is imperative that clinical nursing practice be based upon research-supported interventions: use of appropriate medications, monitoring of acid–base status, administration of controlled oxygen therapy, assessment of need for mechanical ventilation, close monitoring of comorbid conditions. Nurses also play an important role in health promotion, through patient and family education on early recognition of symptoms, on smoking quitting strategies, and on the need to participate in pulmonary rehabilitation, which can reduce long-term morbidity from this chronic disease [47].

3.2. Indications

Rational criteria, based on expert consensus, for hospitalising patients with COPD exacerbation are [20]:

- the presence of high-risk comorbid conditions (pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal or liver failure);
- inadequate response of symptoms to outpatient management;
- marked increase in dyspnoea;
- inability to eat or sleep due to symptoms;

- worsening hypoxaemia;
- worsening hypercapnia;
- changes in mental status;
- lack of home support or inadequate home care;
- uncertain diagnosis.

3.3. Treatment

The inpatient treatment of exacerbation, based on the clinical presentation of the patient (Level II), should be based on the following guidelines:

- administer bronchodilators (short acting β_2 agonist and/or anticholinergic MDI with spacer or hand-held nebuliser as needed) [26–28];
- if saturation is <90%, give supplemental oxygen;
- administer corticosteroids: if patient tolerates oral intake, prednisone 30–40 mg *per os*/day for 5–7 days [30–32]; if patient does not tolerate oral intake, equivalent dose i.v. for up to 14 days [45,46]; consider the use of inhaled corticosteroids by MDI or hand-held nebuliser [32];
- in patients who show changes in their sputum characteristics (purulence and/or volume), administer antibiotics [7–11,19,30–38], basing the choice on the local bacteria resistance patterns: amoxicillin/clavulanate [38] and respiratory fluoroquinolones (gatifloxacin, prulifloxacin, levofloxacin, moxifloxacin) [19,40–43]. If *Pseudomonas* spp. and/or other *Enterobactereaces* spp. are suspected, consider a combined therapy.

4. Criteria for admission to special care and/or intensive care unit

4.1. Indications

The severity of the respiratory dysfunction dictates the need for admission to an ICU. Depending on the resources available within an institution, admission of patients with severe exacerbations of COPD to an intermediate or special respiratory care unit may be appropriate if personnel, skills and equipment are available and can successfully identify and manage acute respiratory failures.

Indications for admission to ICU or intermediate/special respiratory care units include impending or actual respiratory failure, presence of other end-organ dysfunction/failure (i.e. shock, renal, liver or neurological disturbances), and haemodynamic instability.

4.2. Treatment

The treatment for exacerbation should be based on the clinical presentation of the patient (Level III) and should conform to the following guidelines [20]:

- supplemental oxygen;
- ventilatory support;
- administration of bronchodilators (short acting β_2 agonist and anticholinergic by MDI with spacer, two puffs every 2–4 h (26–28). If the patient is on the ventilator, consider MDI administration [48,49]. Consider a long-acting β_2 agonist;
- *administration of corticosteroids*: if patient tolerates oral medications, prednisone 30–40 mg *per os*/day for 5–7 days (30–32). If oral medications are not tolerated, give the equivalent dose i.v. for up to 14 days [50,51]. Consider use of inhaled corticosteroids by MDI or hand-held nebuliser [31];
- administration of antibiotics (choice to be based on the local bacteria resistance patterns) [7–11,19,30–38]: amoxicillin/clavulanate, respiratory fluoroquinolones (gatifloxacin, prulifloxacin, levofloxacin, moxifloxacin). If *Pseudomonas* spp. and/or other *Enterobacteriaaces* spp. are suspected, consider a combined therapy [7].

4.3. Inpatient oxygen therapy

The goal of inpatient oxygen therapy is to maintain $PaO_2 > 8$ kPa (60 mmHg) or $SpO_2 > 90\%$ in order to prevent tissue hypoxia and preserve cellular oxygenation. Due to the shape of the oxyhaemoglobin dissociation curve, increasing PaO_2 to values higher than 8 kPa (60 mmHg) confers little added benefit (1–2 vol%) and may increase the risk of CO_2 retention, which may lead to respiratory acidosis.

Main delivery devices include nasal cannula and Venturi mask, while alternative delivery devices include nonrebreather mask, reservoir cannula, nasal cannula or transtracheal catheter [52,53].

Arterial blood gases should be monitored for arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$) and pH, and arterial oxygen saturation as measured by pulse oximetry (SpO_2) should be monitored for trending and adjusting oxygen settings.

Prevention of tissue hypoxia supercedes CO_2 retention concerns; if CO_2 retention occurs, acidemia should be monitored [54,55].

For details about oxygen flow setting and adjusting, further information can be found in [20].

If acidemia occurs, consider mechanical ventilation.

4.4. Ventilatory support

Several controlled trials have evaluated the effect of non-invasive ventilation on different outcomes, including rate of intubation, length of ICU and hospital stay, dyspnoea and mortality [56–60]. Although with dissimilar results in the most important outcomes, such as mortality, all uniformly agreed on the fact that non-invasive positive-pressure ventilation (NPPV) is effective in reversing acute respiratory failure. Patients most likely to benefit from NPPV are those with elevated arterial CO_2, who are able to cooperate with their caregivers and have no other

important comorbid problems (sepsis, severe pneumonia, cardiovascular collapse, arrhythmias) [61,62].

NPPV should be offered to patients with exacerbations when, after optimal medical therapy and oxygenation, respiratory acidosis (pH < 7.36) or excessive breathlessness or respiratory frequency > 24 breaths min^{-1} persist. If pH is < 7.30, NPPV should be delivered in controlled environments such as an intermediate ICU or high-dependency unit [63]. If pH < 7.25, NPPV should be administered in the ICU and intubation should be readily available.

The combination of some continuous positive airway pressure (CPAP) (e.g. 4–8 cmH_2O) and pressure support ventilation (PSV) (e.g. 10–15 cmH_2O) provides the most effective NPPV [64]. In the first hours, NPPV requires the same level of assistance as conventional mechanical ventilation.

Patients meeting exclusion criteria for NPPV should be considered for immediate intubation and ICU admission. Intubation should be considered in cases of NPPV failure (worsening of arterial blood gases and or pH in 1–2 h, lack of improvement in arterial blood gases and or pH after 4 h), severe acidosis (pH < 7.25) and hypercapnia ($PaCO_2$ > 8 kPa (60 mmHg)), life-threatening hypoxaemia (arterial oxygen tension/inspiratory oxygen fraction < 26.6 kPa (200 mmHg)), tachypnoea > 35 breaths min^{-1} and other complications such as metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion) [60].

5. Criteria for hospital discharge

As a general rule, patients hospitalised for acute exacerbations can be considered for discharge once the reasons for admission are controlled and/or reversed. Based on consensus, the following guidelines have proven useful in practice. These conditions need to be met when considering patients for discharge [20]: the symptoms are returning to baseline, including eating, sleeping etc., there is haemodynamic stability, the oxygenation is returning to baseline, the inhaled β-agonist therapy is required less frequently, the patient is able to resume ambulation.

6. Follow-up evaluation

Once discharged, the patient should be followed up. There are no studies that have addressed the specific schedules most likely to result in positive outcome, but patients with frequent exacerbations are more likely to relapse. Likewise, patients who have developed respiratory failure requiring admission to an ICU carry a very high mortality risk. The following guidelines about conditions that need to be met when considering patients for discharge seem reasonable [20]:

- the patient needs to be re-evaluated within 4 weeks for the assessment of improvement in symptoms, physical examination and need for supplemental oxygen;
- repeated complementary examinations are mandatory, if previous abnormalities were present;
- the patient's ability to cope with the environment needs to be assessed;
- the treatment regimen needs to be understood and re-adjusted.

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