ACUTE EXACERBATION OF ASTHMA AND COPD: WHAT TO DO AS THE FRONTLINERS

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ABSTRACT

Exacerbations characterized by an increase in patients' symptoms above baseline, represent an important feature of the clinical manifestation and natural history of asthma and chronic obstructive pulmonary disease (COPD). Acute asthma and COPD exacerbations are the most common respiratory diseases requiring emergent medical evaluation and treatment. Asthma and COPD exacerbations impose an enormous economic burden on health care budget. In daily clinical practice, a distinction between bronchial asthma and exacerbated COPD is difficult because symptoms are similar. Exacerbations represent a change in symptoms and lung function from the patient usual status. The decrease in expiratory airflow can be quantified by lung function measurements such as peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV1), compared with the patient's previous lung function or predicted values. Medications most commonly used for exacerbations are oxygen supplementation, bronchodilators inhalation, corticosteroids, and antibiotics. For severe asthma attacks the administration of magnesium is a possible additional option. Invasive ventilation remains a last resort to ensure respiratory function and indications for this are given in patients with clinical signs of impending exhaustion of breathing.
Keyword : exacerbation, asthma, COPD, lung function, medications

Abstrak :
Eksaserbasi yang ditandai oleh adanya perburukan gejala pasien, merupakan salah satu bagian penting dari manifestasi klinis dan perjalanan penyakit pasien dengan asma dan penyakit paru obstuktif kronis (PPOK). Eksaserbasi asma akut dan PPOK merupakan penyakit respirasi yang paling umum ditemukan yang membutuhkan evaluasi dan pengobatan medis segera. Eksaserbasi asma dan PPOK memiliki dampak ekonomi yang besar pada pembiayaan kesehatan. Dalam praktik klinis sehari-hari, perbedaan antara eksaserbasi asma dan PPOK kadang disulitkan oleh gejalanya yang serupa. Eksaserbasi menunjukkan adanya perubahan pada gejala dan fungsi paru dari status pasien biasanya, Penurunan pada aliran eksiprasi dapat dinilai oleh pengukuran fungsi paru seperti alur puncak ekspirasi (APE) atau volume paksa eksiprasi 1 detik (VEP1), dibandingkan dengan nilai fungsi paru sebelumnya atau nilai prediksi. Medikasi yang biasanya digunakan untuk eksaserbasi adalah suplementasi oksigen, inhalasi bronkodilator, kortikosteroid dan antibiotik. Pada pasien serangan asma berat, pemberian magnesium dapat menjadi opsi tambahan. Ventilasi invasif merupakan pilihan terakhir bantuan fungsi respirasi pada pasien dengan tanda ancaman gagal nafas.
Kata kunci : eksaserbasi, asma, PPOK, fungsi paru, medikasi

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ACUTE EXACERBATION OF ASTHMA AND COPD: WHAT TO DO AS THE FRONTLINERS

Exacerbation, a key clinical feature of both asthma and chronic obstructive pulmonary disease (COPD), is characterized by an acute (days to a few weeks) increase in patient symptoms above that experienced during the course of their normally stable disease. Because "stable" disease, in both asthma and COPD, is characterized by some variability in symptoms, however, the intensity and duration of increased symptoms required to qualify as an "exacerbation" are difficult to define. The definition of exacerbation is further complicated in that the symptoms that may be present in exacerbations of asthma or COPD are variable and may reflect heterogeneity of the trigger(s) of exacerbation and individual patient differences. Nevertheless, exacerbations are important clinical events, and they are appropriately the subject of considerable research.

Acute asthma and chronic obstructive pulmonary disease (COPD) exacerbations are the most common respiratory diseases requiring emergent medical evaluation and treatment. Asthma and COPD are chronic, debilitating disease processes that have been differentiated traditionally by the presence or absence of reversible airflow obstruction. In daily clinical practice, it is difficult to differentiate these 2 obstructive processes based on their symptoms, and on their nearly identical acute treatment strategies. Their major differences are important only when discussing anatomic sites involved, long-term prognosis, and the nature of inflammatory markers. These aspects affect disease response to certain pharmacologic treatment options.

The mechanisms by which exacerbations may lead to progressive compromise of lung function are unknown. However, the acute inflammation that characterizes an exacerbation likely leads to lung tissue damage and as a result to initiation of repair mechanisms that restore pulmonary structure and function. In the airway, the initiation of repair processes occurs very rapidly after injury. This then leads to an orderly sequence of events with recruitment and proliferation of epithelial cells followed by their redifferentiation into mature epithelium. This is associated with a slightly delayed recruitment and proliferation of mesenchymal cells in the subepithelial tissues. Resorption of these cells and the connective tissue matrix they produce can lead to restoration of tissue structure and function. Persistence of the excess connective tissue, in contrast, could lead to peribronchial fibrosis, a characteristic feature of tissue remodeling associated with fixed airflow obstruction. The mediators that regulate these processes remain to be defined, but transforming growth factor beta and fibronectin, important mediators of tissue repair in many settings, have also been suggested to play a role in COPD as well as asthma.

There is not strong evidence suggesting histopathologic overlap between these obstructive entities, known as the asthma–COPD overlap syndrome. The most important pathologic difference between asthma and COPD is the inflammatory cells that mediate each respective disease process. Eosinophils and CD4 cells mainly mediate asthma, whereas neutrophils and CD8 cells mediate COPD. This basic difference allows inhaled corticosteroids (CS) to be more efficacious against eosinophilic mediated asthma, and largely ineffective against the primarily neutrophilic inflammation seen in COPD. Regardless of their pathologic differences or their similar inciting agents, it is paramount that emergent risk stratification and treatment modalities be initiated expeditiously to decrease clinical deterioration, morbidity, and mortality.

Exacerbation on Asthma Bronchiale

The Global Initiative for Asthma (GINA) described asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive

decrease in lung function, i.e. they represent a change from the patient's usual status that is sufficient to require a change in treatment. Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally, as the first presentation of asthma. Exacerbations usually occur in response to exposure to an external agent (e.g. viral upper respiratory tract infection, pollen or pollution) and/or poor adherence with controller medication; however, a subset of patients present more acutely and without exposure to known risk factors. Severe exacerbations can occur in patients with mild or well-controlled asthma.

In addition to factors known to increase the risk of asthma exacerbations, some features are specifically associated with an increase in the risk of asthma-related death. The presence of one or more of these risk factors should be quickly identifiable in the clinical notes, and these patients should be encouraged to seek urgent medical care early in the course of an exacerbation. Factors that increase the risk of asthma-related death:

- A history of near-fatal asthma requiring intubation and mechanical ventilation, Hospitalization or emergency care visit for asthma in the past year
  Currently using or having recently stopped using oral corticosteroids (a marker of event severity)
- Not currently using inhaled corticosteroids
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly
- A history of psychiatric disease or psychosocial problems, Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan
- Food allergy in a patient with asthma

Diagnosis of Exacerbation on Asthma

Exacerbations represent a change in symptoms and lung function from the patient usual status. The decrease in expiratory airflow can be quantified by lung function measurements such as peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV1), compared with the patient's previous lung function or predicted values. In the acute setting, these measurements are more reliable indicators of the severity of the exacerbation than symptoms. The frequency of symptoms may, however, be a more sensitive measure of the onset of an exacerbation than PEF.

A minority of patients may perceive symptoms poorly and experience a significant decline in lung function without a perceptible change in symptoms. This situation especially affects patients with a history of near-fatal asthma and also appears to be more common in males. Severe exacerbations are potentially life threatening and their treatment requires careful assessment and close monitoring. Patients with severe exacerbations should be advised to see their health care provider promptly or depending on the organization of local health services, to proceed to the nearest facility that provides emergency access for patients with acute asthma.

Management of Asthma Exacerbation in Primary Care

1. Assessing exacerbation severity

A brief focused history and relevant physical examination should be conducted concurrently with the prompt initiation of therapy, and findings documented in the notes. If the patient shows signs of a severe or life-threatening exacerbation, treatment with SABA, controlled oxygen and systemic corticosteroids should be initiated while arranging for the patient's urgent transfer to an acute care facility where monitoring and expertise are more readily available. Milder exacerbations can usually be treated in a primary care setting, depending on resources and expertise.

2. History

The history should including:

- Timing of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Any risk factors for asthma-related death.

- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy

3. Physical examination

The physical examination should assess:

- Signs of exacerbation severity and vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles, wheeze).
- Complicating factors (e.g. anaphylaxis, pneumonia, pneumothorax)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, upper airway dysfunction, inhaled foreign body or pulmonary embolism).

4. Objective measurements

- Pulse oximetry. Saturation levels <90% in children or adults signal the need for aggressive therapy.
- PEF in patients older than 5 years

Treating exacerbations in primary care

The main initial therapies include repetitive administration of short-acting inhaled bronchodilators, early introduction of systemic corticosteroids, and controlled flow oxygen supplementation. The aim is to rapidly relieve airflow obstruction and hypoxemia, address the underlying inflammatory pathophysiology, and prevent relapse.

Inhaled short-acting beta2-agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 minutes for the first hour) is usually the most effective and efficient way to achieve rapid reversal of airflow limitation. After the first hour, the dose of SABA required varies from 4–10 puffs every 3–4 hours up to 6–10 puffs every 1–2 hours, or more often. No additional SABA is needed if there is a good response to initial treatment (e.g. PEF >60–80% of predicted or personal best for 3–4 hours).

Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer. However, patients with acute severe asthma were not included in these studies. The most cost-effective route of delivery is pMDI and spacer provided the patient can use this device. Because of the static charge on plastic spacers, they should be pre-washed with detergent and air-dried to be ready for immediate use; if a pre-treated spacer is not available, a new spacer should be primed with at least 20 puffs of salbutamol before use can usually be treated in a primary care setting, depending on resources and expertise.

Controlled oxygen therapy (if available)

Oxygen therapy should be titrated against pulse oximetry (if available) to maintain oxygen saturation at 93–95% (94–98% for children 6–11 years). Controlled or titrated oxygen therapy gives better clinical outcomes than high-flow 100% therapy oxygen. Oxygen should not be withheld if oximetry is not available, but the patient should be monitored for deterioration, somnolence or fatigue.

Systemic corticosteroids

OCS should be given promptly, especially if the patient is deteriorating, or had already increased their reliever and controller medications before presenting. The recommended dose for adults is 1 mg prednisolone/kg/day or equivalent up to a maximum of 50 mg/day. OCS should usually be continued for patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux and mood changes.

Controller medication

Patients already prescribed controller medication should be provided with advice about increasing the dose for the next 2–4 weeks. Patients not currently taking controller medication should usually be commenced on regular ICS-containing therapy, as an exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations.

Antibiotics (not recommended)
Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong evidence of lung infection (e.g. fever and purulent sputum or radiographic evidence of pneumonia). Aggressive treatment with corticosteroids should be implemented before antibiotics are considered.

Reviewing response
During treatment, patients should be closely monitored, and treatment titrated according to their response. Patients who present with signs of a severe or life-threatening exacerbation, who fail to respond to treatment, or who continue to deteriorate should be transferred immediately to an acute care facility. Patients with little or slow response to SABA treatment should be closely monitored.

For many patients, lung function can be monitored after SABA therapy is initiated. Additional treatment should continue until PEF or FEV1 reaches a plateau or (ideally) returns to the patient's previous best. A decision can then be made whether to send the patient home or transfer them to an acute care facility.

Follow up
Discharge medications should include as-needed reliever medication, a short course of OCS and, for most patients, regular controller treatment. Inhaler technique and adherence should be reviewed before discharge. Patients should be advised to use their reliever inhaler only as-needed, rather than routinely. A follow-up appointment should be arranged for about 2–7 days later, depending on the clinical and social context. At the review visit the health care provider should assess whether the flare-up has resolved, and whether OCS can be ceased. They should assess the patient's level of symptom control and risk factors; explore the potential cause of the exacerbation; and review the written asthma action plan (or provide one if the patient does not already have one). Maintenance controller treatment can generally be stepped back to pre-exacerbation levels 2–4 weeks after the exacerbation, unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. this situation, provided inhaler technique and adherence have been checked, a step up in treatment is indicated.

Management of Asthma Exacerbation in The Emergency Department
Severe exacerbations of asthma are life-threatening medical emergencies, which are most safely managed in an acute care setting e.g. emergency department. Management of asthma in the intensive care unit is beyond the scope of this report and readers are referred to a recent comprehensive review.

Assessment
History
A brief history and physical examination should be conducted concurrently with the prompt initiation of therapy.

- Time of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Risk factors for asthma-related death
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination
The physical examination should assess:

- Signs of exacerbation severity, including vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles)
- Complicating factors (e.g. anaphylaxis, pneumonia, atelectasis, pneumothorax or pneumomediastinum)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, upper airway dysfunction, inhaled foreign body or pulmonary embolism).

Objective assessments
Objective assessments are also needed as the physical examination alone may not indicate

the severity of the exacerbation. However, patients, and not their laboratory values, should be the focus of treatment.

- Measurement of lung function: this is strongly recommended. If possible, and without unduly delaying treatment, PEF or FEV1 should be recorded before treatment is initiated, although spirometry may not be possible in children with acute asthma. Lung function should be monitored at one hour and at intervals until a clear response to treatment has occurred or a plateau is reached.
- Oxygen saturation: this should be closely monitored, preferably by pulse oximetry. This is especially useful in children if they are unable to perform PEF. In children, oxygen saturation is normally >95%, and saturation <92% is a predictor of the need for hospitalization. Saturation levels <90% in children or adults signal the need for aggressive therapy. Subject to clinical urgency, saturation should be assessed before oxygen is commenced, or 5 minutes after oxygen is removed or when saturation stabilizes.
- Arterial blood gas measurements are not routinely required. They should be considered for patients with a PEF or FEV1 <50% predicted, or for those who do not respond to initial treatment or are deteriorating. Supplemental controlled oxygen should be continued while blood gases are obtained. A PaO2<60 mmHg (8 kPa) and normal or increased PaCO2 (especially >45 mmHg, 6 kPa) indicate respiratory failure. Fatigue and somnolence suggest that pCO2 may be increasing and airway intervention may be needed.
- Chest X-ray (CXR) is not routinely recommended: In adults, CXR should be considered if a complicating or alternative cardiopulmonary process is suspected (especially in older patients), or for patients who are not responding to treatment where a pneumothorax may be difficult to diagnose clinically.

Treatment in acute care settings such as the emergency department

The following treatments are usually administered concurrently to achieve rapid improvement

Oxygen

To achieve arterial oxygen saturation of 93–95% (94–98% for children 6–11 years), oxygen should be administered by nasal cannulae or mask. In severe exacerbations, controlled low flow oxygen therapy using pulse oximetry to maintain therapy saturation at 93–95% is associated with better physiological outcomes than with high flow 100% oxygen. However, oxygen therapy should not be withheld if pulse oximetry is not available. Once the patient has stabilized, consider weaning them off oxygen using oximetry to guide the need for ongoing oxygen therapy.

Inhaled short-acting beta 2-agonists

Inhaled SABA therapy should be administered frequently for patients presenting with acute asthma. The most cost effective and efficient delivery is by pMDI with a spacer. Evidence is less robust in severe and near-fatal asthma. Systematic reviews of intermittent versus continuous nebulized SABA in acute asthma provide conflicting admissions but a later review with additional studies found reduced hospitalizations and better lung function with continuous compared with intermittent nebulization, particularly in patients with worse lung function. An earlier study in hospitalized patients found that intermittent on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations and fewer palpitations when compared with 4-hourly intermittent therapy. A reasonable approach to inhaled SABA in exacerbations, therefore would be to initially use continuous therapy, followed by intermittent on-demand therapy for hospitalized patients. There is no evidence to support the routine use of intravenous beta2-agonists in patients with severe asthma exacerbations.

Epinephrine (for anaphylaxis)

Intramuscular epinephrine (adrenaline) is indicated in addition to standard therapy for acute asthma associated with anaphylaxis and angioedema. It is not routinely indicated for

other asthma exacerbations.

Systemic corticosteroids

Systemic corticosteroids speed resolution of exacerbations and prevent relapse, and should be utilized in all but the mildest exacerbations in adults, adolescents and children 6–11 years. Where possible, systemic corticosteroids should be administered to the patient within 1 hour of presentation. Use of systemic corticosteroids is particularly important in the emergency department if :

- Initial SABA treatment fails to achieve lasting improvement in symptoms
- The exacerbation developed while the patient was taking OCS
- The patient has a history of previous exacerbations requiring OCS.

Route of delivery: oral administration is as effective as intravenous. The oral route is preferred because it is quicker, less invasive and less expensive. OCS require at least 4 hours to produce a clinical improvement. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation. In patients discharged from the emergency department, an intramuscular corticosteroid may be helpful, especially if there are concerns about adherence with oral therapy. Dosage: daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients. Duration: 5- and 7-day courses in adults have been found to be as effective as 10- and 14-day courses respectively. Oral dexamethasone for 1-2 days can also be used but there are concerns about metabolic side-effects if it is continued beyond 2 days. Evidence from studies in which all patients were taking maintenance ICS after discharge suggests that there is no benefit in tapering the dose of OCS, either in the short or over several.

Inhaled corticosteroids

Within the emergency department: high-dose ICS given within the first hour after presentation reduces the need for hospitalization in patients not receiving corticosteroids systemic. When given in addition to systemic corticosteroids, conflicting. Overall, ICS are well tolerated; however, cost is a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the emergency department remain unclear.

On discharge home: the majority of patients should be prescribed regular ongoing ICS treatment since the occurrence of a severe exacerbation is a risk factor for future exacerbations and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization. For short-term outcomes such as relapse requiring admission, symptoms, and quality of life, a systematic review found no significant differences when ICS were added to systemic corticosteroids after discharge. There was some evidence, however, that post-discharge ICS were as effective as systemic corticosteroids for milder exacerbations, but the confidence limits were wide. Cost may be a significant factor for patients in the use of high-dose ICS, and further studies are required to establish their role

Other treatments

Ipratropium bromide

For adults and children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations and greater improvement in PEF and FEV1 compared with SABA alone.

Aminophylline and theophylline

Intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations, in view of their poor efficacy and safety profile, and the greater effectiveness and relative safety of SABA. The use of intravenous aminophylline is associated with severe and potentially fatal side-effects, particularly in patients already treated with

sustained-release theophylline. In adults with severe asthma exacerbations, add-on treatment with aminophylline does not improve outcomes compared with SABA alone.

Magnesium

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, when administered as a single 2 g infusion over 20 minutes, it reduces hospital admissions in some patients, including adults with FEV1 <25–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV1 fails to reach 60% predicted after 1 hour of care. Randomized, controlled trials that excluded patients with more severe asthma showed no benefit with the addition of intravenous or nebulized magnesium compared with placebo in the routine care of asthma exacerbations in adults and adolescents. Nebulized salbutamol is most often administered in normal saline; however, it can also be administered in isotonic magnesium sulfate. While the overall efficacy of this practice is unclear, pooled data from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV1 <50% predicted).

Helium oxygen therapy

A systematic review of studies comparing helium-oxygen with air–oxygen suggests there is no role for this intervention in routine care, but it may be considered for patients who do not respond to standard therapy availability, cost and technical issues should be considered.

Leukotriene receptor antagonists

There is limited evidence to support a role for oral or intravenous LTRAs in acute asthma. Small studies have function demonstrated improvement in lung but the clinical role of these agents requires more study.

ICS/LABA combinations

The role of these medications in the emergency department or hospital is unclear. One study showed that high-dose budesonide/formoterol in patients in the emergency department, all of whom received prednisolone, had similar efficacy and safety profile to SABA. Another study examined addition of salmeterol to OCS for hospitalized patients, but was not adequately powered to support a recommendation.

Antibiotics (not recommended)

Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong evidence of lung infection (e.g. fever or purulent sputum or radiographic evidence of pneumonia). Aggressive treatment with corticosteroids should be implemented before antibiotics are considered.

Sedatives

Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths has been reported.

Non-invasive ventilation (NIV)

The evidence regarding the role of NIV in asthma is weak. A systematic review identified five studies involving participants with acute severe asthma treated with NIV or placebo. Two studies found no difference in need for endotracheal intubation but one study identified fewer admissions in the NIV group. No deaths were reported in either study. Given the small size of the studies, no recommendation is offered. If NIV is tried, the patient should be monitored closely. It should not be attempted in agitated patients, and patients should not be sedated in order to receive NIV.

Reviewing response

Clinical status and oxygen saturation should be re-assessed frequently, with further treatment titrated according to the patient's response. Lung function should be measured after one hour, i.e. after the first three bronchodilator treatments, and patients who deteriorate despite

intensive bronchodilator and corticosteroid treatment should be re-evaluated for transfer to the intensive care unit.

Follow up after emergency department presentation or hospitalization for asthma

Following discharge, the patient should be reviewed by their health care provider regularly over subsequent weeks until good symptom control is achieved and personal best lung function is reached or surpassed. Incentives such as free transport and telephone reminders improve primary care follow up but have shown no effect on long-term outcomes.

Patients discharged following an emergency department presentation or hospitalization for asthma should be especially targeted for an asthma education program, if one is available. Patients who were hospitalized may be particularly receptive to information and advice about their illness. Health care providers should take the opportunity to review:

- The patient's understanding of the cause of their asthma exacerbation
- Modifiable risk factors for exacerbations (including, where relevant, smoking)
- The patient's understanding of the purposes and correct uses of medications
- The actions the patient needs to take to respond to worsening symptoms or peak flows.

After emergency department presentation, comprehensive intervention programs that include optimal controller management, inhaler technique, and elements of self-management education are cost effective and have shown significant improvement in asthma. Referral for expert advice should be considered for patients who have been hospitalized for asthma, or who repeatedly present to an acute care setting despite having a primary care provider. No recent studies are available, but earlier studies suggest that follow-up by a specialist is associated with fewer subsequent emergency department visits or hospitalizations and better asthma control.

Exacerbations of chronic obstructive pulmonary disease (COPD)

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression COPD exacerbations are complex events usually associated with increased airway inflammation, increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze. As comorbidities are common in COPD patients, exacerbations must be differentiated clinically from other events such as acute coronary syndrome, worsening congestive heart failure, pulmonary embolism and pneumonia.

They are classified as:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

It is now recognized that many exacerbations are not reported to healthcare professionals for therapy and yet these events, although often shorter in duration, also have a significant impact on health status. Thus COPD patients need to receive education about the importance of understanding exacerbation symptoms and when to seek professional healthcare.

Exacerbations are mainly triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. Short-term exposure to fine particulate matter (PM2.5) is associated with increased hospitalizations for acute exacerbations of COPD and increased mortality. The most common virus isolated is human rhinovirus (the cause of the common cold) and can be detected for up to a week after an exacerbation onset. When associated with viral infections, exacerbations are often more

severe, last longer and precipitate more hospitalizations, as seen during winter.

Exacerbations can be associated with increased sputum production and, if purulent, there are studies that demonstrated increased bacteria in the sputum. There is reasonable evidence to support the concept that eosinophils are increased in the airways, lung, and blood in a significant proportion of patients with COPD. Furthermore, eosinophil numbers increase together with neutrophils and other inflammatory cells during exacerbations in a proportion of subjects with COPD exacerbations. The presence of sputum eosinophilia has been related to susceptibility to viral infection. It has been suggested that exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids although more prospective trials are needed to test this hypothesis.

During a COPD exacerbation, symptoms usually last between 7 to 10 days, but some events may last longer. At 8 weeks, 20% of patients have not recovered to their pre-exacerbation state. It is well established that COPD exacerbations contribute to disease progression. Disease progression is even more likely if recovery from exacerbations is slow. Exacerbations can also cluster in time and once a COPD patient experiences an exacerbation, they will show increased susceptibility to another event. Some COPD patients are particularly susceptible to frequent exacerbations (defined as two or more exacerbations per year), and these patients have been shown to have worse health status and morbidity than patients with less frequent exacerbations. Patients at high risk of frequent exacerbations can be recognized across all disease severity groups. However, the perception of breathlessness is greater in frequent exacerbators than infrequent exacerbators, suggesting that a perception of breathing difficulty may contribute to precipitating the respiratory symptoms of an exacerbation rather than solely physiological, or causative factors. The strongest predictor of a patient's future exacerbation frequency remains the number of exacerbations they have had in the prior year. It is recognized that these patients form a moderately stable phenotype, although some studies have shown that a significant proportion of patients change their exacerbation frequency especially with worsening FEV1.

Other factors that have been associated with an increased risk of acute exacerbations and/or severity of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross sectional dimension (i.e., ratio > 1) a greater percentage of emphysema or airway wall thickness measured by chest CT imaging and the presence of chronic bronchitis.

Treatment Setting

The goals of treatment for COPD exacerbations are to minimize the negative impact of the current exacerbation and prevent the development of subsequent events. Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in either the outpatient or inpatient setting. More than 80% of exacerbations are managed on an outpatient basis with pharmacologic therapies including bronchodilators, corticosteroids, and antibiotics.

The indications for assessing the need for hospitalization during a COPD exacerbation. When patients with a COPD exacerbation come to the emergency department, they should be provided with supplemental oxygen and undergo assessment to determine whether the exacerbation is life-threatening and if increased work of breathing or impaired gas exchange requires consideration for non-invasive ventilation. If so, healthcare providers should consider admission to the respiratory or intensive care unit of the hospital. Otherwise, the patient may be managed in the emergency department or hospital ward unit. In addition to pharmacologic therapy, hospital management of exacerbations includes respiratory support (oxygen therapy, ventilation).

The clinical presentation of COPD exacerbation is heterogeneous, thus we recommend that in the severity of the exacerbation should be based on the patient's hospitalized patients. Clinical signs and recommend the following classification :

No respiratory failure: Respiratory rate: 20-30 breaths per minute; no use of accessory. respiratory muscles; no changes in mental status; hypoxemia improved with supplemental oxygen given via venturi mask 28-35% inspired oxygen (FiO2); no increase in PaCO2.

Acute respiratory failure — non-life-threatening: Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; no change in mental status.; hypoxemia improved with supplemental oxygen via venturi mask 25-30% FiO2; hypercarbia i.e., PaCO2 increased compared with baseline or elevated 50-60 mmHg. Respiratory rate: > 30 breaths per minute;

Acute respiratory failure — life-threatening: using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via venturi mask or requiring FiO2 > 40%; hypercarbia i.e., PaCO2 increased compared with baseline or elevated > 60 mmHg or the presence of acidosis (pH < 7.25).

Long-term prognosis following hospitalization for COPD exacerbation is poor, with a five-year mortality rate of about 50%. Factors independently associated with poor outcome include older age, lower body mass index, comorbidities (e.g., cardiovascular disease or lung cancer), previous hospitalizations for COPD exacerbations, clinical severity of the index exacerbation and need for long-term oxygen therapy at discharge. Patients characterized by a higher prevalence and severity of respiratory symptoms, poorer quality of life, worse lung function, lower exercise capacity, lower lung density and thickened bronchial walls on CT-scan are also at increased risk for a higher mortality following an acute COPD exacerbation.

A recent updated Cochrane review concluded that the use of COPD exacerbation action plans with a single short educational component, in conjunction with ongoing support, reduced in-hospital healthcare utilization. Such educational interventions were also found to increase the treatment of COPD exacerbations with corticosteroids and antibiotics.

Pharmacologic Treatment

The three classes of medications most commonly used for COPD exacerbations are bronchodilators, corticosteroids, and antibiotics.

Bronchodilators

Although there is no high-quality evidence from RCTs, it is recommended that short-acting inhaled beta 2-agonists, with or without short-acting anticholinergics, are the initial bronchodilators for acute treatment of a COPD exacerbation. A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in FEV1 between using metered dose inhalers (MDI) (with or without a spacer device) or nebulizers to deliver the agent, although the latter may be an easier delivery method for sicker patients. It is recommended that patients do not received continuous nebulization, but use the MDI inhaler one puff every one hour for two or three doses and then every 2-4 hours based on the patient's response. Although, there are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either beta 2-agonists or anticholinergics or combinations) with or without inhaled corticosteroids during an exacerbation, we recommend continuing these treatments during the exacerbation or to start these medications as soon as possible before hospital discharge. Intravenous methylxanthines (theophylline or aminophylline) are not recommended to use in these patients due to significant side effects.

Glucocorticoids

Data from studies indicate that systemic glucocorticoids in COPD exacerbations shorten

recovery time and improve lung function (FEV1). They also improve oxygenation, the risk of early relapse, treatment failure and the length of hospitalization. A dose of 40 mg prednisone per day for 5 days is recommended. Therapy with oral prednisolone is equally effective to intravenous administration. Nebulized budesonide alone, although more expensive, may be an alternative to oral corticosteroids in some patients for treatment of exacerbations. Recent studies suggest that glucocorticoids may be less efficacious to treat acute COPD exacerbations in patients with lower levels of blood eosinophils. Although the infectious agents in COPD exacerbations can be viral or bacterial,

Antibiotics

The use of antibiotics in exacerbations remains controversial**.** The uncertainties originate from studies that did not differentiate between bronchitis (acute or chronic) and COPD exacerbations, studies without placebo-control, and/or studies without chest X-rays that do not exclude that patients may have had underlying pneumonia. There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a bacterial infection e.g., increased sputum purulence.

A systematic review of placebo-controlled studies has shown that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44%. The review provides evidence to treat moderately or severely ill patients with COPD exacerbations and increased cough and sputum purulence with antibiotics. These data are supported by more recent RCTs in patients with diagnoses of moderate COPD. In the outpatient setting, sputum cultures are not feasible as they take at least two days and frequently do not give reliable results for technical reasons. Several biomarkers of airway infection are being studied in exacerbations of COPD that have a better diagnostic profile.

Studies of C-reactive protein (CRP) have reported contradictory findings; CRP has been reported to be elevated in both bacterial and viral infections, therefore its use in this condition is not recommended. Another biomarker that has been investigated is procalcitonin, a marker that is more specific for bacterial infections and that may be of value in the decision to use antibiotics, but this test is expensive and not readily available. Several studies have suggested that procalcitonin-guided antibiotic treatment reduces antibiotic exposure and side effects with the same clinical efficacy

A recent meta-analysis of available clinical studies suggests that procalcitonin-based protocols to trigger antibiotic use are associated with significantly decreased antibiotic prescription and total antibiotic exposure, without affecting clinical outcomes (e.g., rate of treatment failure, length of hospital stay, mortality). However, the quality of this evidence is low to moderate, because of methodological limitations and smaller overall study populations. Procalcitonin-based protocols may be clinically effective; however, confirmatory trials with rigorous methodology are required.

A study in COPD patients with exacerbations requiring mechanical ventilation (invasive or noninvasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary nosocomial pneumonia. In summary, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive).

The recommended length of antibiotic therapy is 5-7 days. The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation cultures from sputum or

other materials from the lung should be performed, as gram-negative bacteria (e.g.species). Pseudomonas or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally. Improvements in dyspnea and sputum purulence suggest clinical success.

Adjunct Therapies

Depending on the clinical condition of the patient, an appropriate fluid balance, use of diuretics when clinically indicated, anticoagulants, treatment of comorbidities and nutritional aspects should be considered. At all times, healthcare providers should strongly enforce the need for smoking cessation. Given that patients hospitalized with COPD exacerbations are at increased risk of deep vein thrombosis and pulmonary embolism, prophylactic measures for thromboembolism should be instituted.

Respiratory Support

This is a key component of hospital treatment of an exacerbation.

Oxygen therapy

Supplemental oxygen should be titrated to improve the patient's hypoxemia with a target saturation of 88-92%. Once oxygen is started, blood gases should be checked frequently to ensure satisfactory oxygenation without carbon dioxide retention and/or worsening acidosis. A recent study demonstrated that venous blood gas to assess bicarbonate levels and pH is accurate when compared with arterial blood gas assessment. Additional data are needed to clarify the utility of venous blood gas sampling to make clinical decisions in scenarios of acute respiratory failure; most patients included had a pH > 7.30 on presentation, PCO2 levels were dissimilar when measured by venous compared to arterial blood samples and the severity of airflow limitation was not reported. Venturi masks (high-flow devices) offer more accurate and controlled delivery of oxygen than do nasal prongs.

High-flow oxygen therapy by nasal cannula

In patients with acute hypoxemic respiratory failure, high-flow oxygen therapy by nasal cannula (HFNC) may be an alternative to standard oxygen therapy or noninvasive positive pressure ventilation; some studies have shown that HFNC can reduce the need for intubation or mortality in patients with acute hypoxemic respiratory failure (ARF). Studies to date were performed in COPD patients with very severe underlying disease that required supplemental oxygen; a randomized cross-over trial demonstrated that HFNC improved oxygenation and ventilation, and decreased hypercarbia. A systematic review of RCTs in patients with acute hypoxemic respiratory failure suggests that HFNC tends to reduce intubation rate, but did not meet statistical significance compared with conventional oxygen therapy or NIV, and had no effect on mortality

However, the meta-analysis included no studies of patients with acute respiratory failure due to a COPD exacerbation. There is a need for well-designed, randomized, multicenter trials to study the effects of HFNC in acute hypoxemic/hypercarbic respiratory failure in COPD patients.

Ventilatory Support

Some patients need immediate admission to the respiratory care or intensive care unit (ICU). Admission of patients with severe exacerbations to intermediate or special respiratory care units may be appropriate if adequate personnel skills and equipment exist to identify and manage acute respiratory failure. Ventilatory support in an exacerbation can be provided by either noninvasive (nasal or facial mask) or invasive (oro-tracheal tube or tracheostomy) ventilation. Respiratory stimulants are not recommended for acute respiratory failure.

Noninvasive mechanical ventilation.

The use of noninvasive mechanical ventilation (NIV) is preferred over invasive ventilation (intubation and positive pressure ventilation) as the initial mode of ventilation to treat acute respiratory failure in patients hospitalized for acute exacerbations of COPD. NIV has been studied in RCTs showing a success rate of 80-85%. NIV has been shown to improve oxygenation and acute respiratory acidosis i.e., NIV increases pH and decreases PaCO2. NIV also decreases respiratory rate, work of breathing and the severity of breathlessness but also decreases complications such as ventilator associated pneumonia, and length of hospital stay. More importantly, mortality and intubation rates are reduced by this intervention.

Invasive mechanical ventilation

The indications for initiating invasive mechanical ventilation during an exacerbation are shown in and include failure of an initial trial of NIV. As experience is gained with the generalized clinical use of NIV in COPD, a number of indications for invasive mechanical ventilation are being successfully treated with NIV, thus eliminating invasive mechanical ventilation as first line treatment of acute respiratory failure during hospitalization for COPD exacerbation

In patients who fail non-invasive ventilation as initial therapy and receive invasive ventilation as subsequent rescue therapy, morbidity, hospital length of stay and mortality are greater. The use of invasive ventilation in patients with very severe COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities.

When possible, a clear statement of the patient's own treatment wishes, such as an advance directive or "living will", makes these difficult decisions easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma and volutrauma, and the risk of tracheostomy and consequential prolonged ventilation

Acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes. Despite this, there is evidence that patients who might otherwise survive are frequently denied admission to intensive care for intubation because of unwarranted prognostic pessimism.

A large study of COPD patients with acute respiratory failure reported in-hospital mortality of 17-49%. Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before invasive ventilation (FEV1 < 30% predicted), had a non-respiratory comorbidity, or were housebound. Patients who did not have a previously diagnosed comorbidity, had respiratory failure due to a potentially reversible cause (such as an infection), or were relatively mobile and not using long-term oxygen, did well after ventilator support.

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Hospital discharge and follow-up

The cause, severity, impact, treatment and time course of exacerbations varies from patient to patient and facilities in the community, and healthcare systems, differ from country to country. Accordingly, there are no standards that can be applied to the timing and nature of discharge. However, it is recognized that recurrent exacerbations leading to short-term readmission and increased all-cause mortality are associated with the initial hospitalization for an acute episode of deterioration. Consequently, the clinical practice and management of the acute hospitalization have been studied extensively and the introduction of factors thought to be beneficial has been investigated increasingly in recent years. When

features related to re-hospitalization and mortality have been studied, defects in perceived optimal management have been identified including spirometry assessment and arterial blood gas analysis. Mortality relates to patient age, the presence of acidotic respiratory failure, the need for ventilatory support and comorbidities including anxiety and depression.

The introduction of care bundles at hospital discharge to include education, optimization of medication, supervision and correction of inhaler technique, assessment and optimal management of comorbidities, early rehabilitation, telemonitoring and continued patient contact have all been investigated to address these issues. Whereas these measures all seem sensible there is insufficient data that they influence either readmission mortality rates or short-term and there is little evidence of cost-effectiveness. Nevertheless, it remains good clinical practice to cover these issues before discharge and their effectiveness on health status and readmission rates may be increased if they are delivered with an approach that includes motivational interview-based health coaching. The only possible exception is early rehabilitation as there is some evidence that this factor is associated with increased mortality, although the reasons remain unknown. However, other data suggest that early rehabilitation post hospital discharge (i.e., <4 weeks) may be associated with improved survival.

Early follow-up (within one month) following discharge should be undertaken when possible and has been related to less exacerbation-related readmissions. There are many patient issues that prevent early follow-up; those not attending early follow-up have increased 90-day mortality. This may reflect both patient compliance, limited access to medical care, poor social support, and/or the presence of more severe disease. Nevertheless, early follow-up permits a careful review of discharge therapy (and especially any remaining need for long-term oxygen treatment by assessment of both oxygen saturation and arterial blood gases) and an opportunity to make any needed changes in therapy (antibiotic and steroid therapy review). Additional follow-up at three months is recommended to ensure return to a stable clinical state and permit a review of the patient's symptoms, lung function (by spirometry), and where possible the assessment of prognosis using multiple scoring systems such as BODE. In addition, arterial oxygen saturation and blood gas assessment will determine the need for long-term oxygen therapy more accurately at prolonged follow-up compared to shortly after discharge. CT assessment to determine the presence of bronchiectasis and emphysema should be done in patients with recurrent exacerbations/and or hospitalizations. A further detailed assessment of the presence and management of comorbidities should also be undertaken.

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