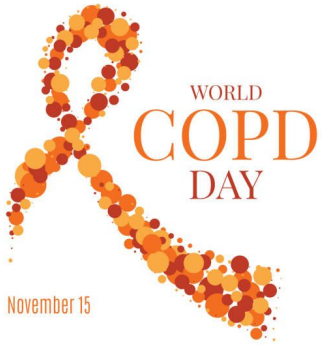

COPD exacerbations: Management

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Global Initiative for Chronic Obstructive Lung Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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DEFINITION
COPD exacerbation

- acute worsening of respiratory symptoms that results in additional therapy.

- associated with increased airway inflammation, increased mucus production and marked gas trapping.

DIFFERENTIAL DIAGNOSIS OF COPD EXACERBATION

WHEN THERE IS CLINICAL SUSPICION OF THE FOLLOWING ACUTE CONDITIONS, CONSIDER THE FOLLOWING INVESTIGATIONS:

PNEUMONIA

- Chest radiograph
- Assessment of C-reactive protein (CRP) and/or procalcitonin

PNEUMOTHORAX

- Chest radiograph or ultrasound

PLEURAL EFFUSION

- Chest radiograph or ultrasound

PULMONARY EMBOLISM

- D-dimer and/or Doppler sonogram of lower extremities
- Chest tomography – pulmonary embolism protocol

PULMONARY EDEMA DUE TO CARDIAC RELATED CONDITIONS

- Electrocardiogram and cardiac ultrasound
- Cardiac enzymes

CARDIAC ARRHYTHMIAS – ATRIAL FIBRILLATION/FLUTTER

- Electrocardiogram

Exacerbationsare classified as

- ►**Mild:**
  (treated with short acting bronchodilators only, SABDs)

- ►**Moderate:**
  (treated with SABDs plus antibiotics and/or oral corticosteroids)

- ►**Severe :**
  (patient requires hospitalization or visits the emergency room).
  Severe exacerbations may also be associated with acute respiratory failure.

Classification of COPD exacerbation

- **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 24-35% 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 >35% FiO2; hypercarbia i.e., PaCO2increased compared with baseline or elevated 50-60 mmHg.

- **Acute respiratory failure–life-threatening:**
  Respiratory rate > 30 breaths per minute; 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., PaCO2increased compared with baseline or elevated > 60 mmHg or the presence of acidosis (pH ≤7.25).

Exacerbations are mainly triggered by

- **respiratory viral infections**
  (human rhinovirus (the cause of the common cold))

{exacerbations are often more severe, last longer and precipitate more hospitalizations}

- **bacterial infections**
- but **PE, MI, CHF** must be considered

- **environmental factors** such as pollution
- **30% of patients** with COPD, **no cause** for exacerbations can be identified.

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**

factors that have been associated with an increased risk of acute exacerbations and/or severity of exacerbations

- 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**.

- **Vitamin D deficiency**

TREATMENT OPTIONS

- minimize the negative impact of the current exacerbation and **prevent the development of subsequent events.**

- can be managed in either the outpatient or inpatient setting.

- **More than 80%** of exacerbations are managed on **an outpatient basis** with pharmacological therapies including bronchodilators, corticosteroids, and antibiotics.

POTENTIAL INDICATIONS FOR HOSPITALIZATION ASSESSMENT*

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness.
- Acute respiratory failure.
- Onset of new physical signs (e.g., cyanosis, peripheral edema).
- Failure of an exacerbation to respond to initial medical management.
- Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias, etc.).
- Insufficient home support.

*Local resources need to be considered.

In all people presenting to hospital with an acute exacerbation:

- obtain a **chest X-ray**
- measure **arterial blood gas** tensions and record the inspired oxygen concentration
- record an **ECG** (to exclude comorbidities)
- perform a **full blood count** and measure **urea** and **electrolyte** concentrations
- measure a **theophylline level** on admission in people who are taking theophylline therapy
- send a **sputum** sample for **microscopy and culture** if the sputum is **purulent**
- take **blood cultures** if the person has **pyrexia**.

TRIAGE TO HOME OR HOSPITAL

- More than 80 percentof exacerbations of COPD can be managed on an outpatient basis

- Home management of COPD exacerbations generally includes:
  - intensification of bronchodilator therapy
  - initiation of a course of oral glucocorticoids
  - oral antibiotics

INDICATIONS FOR RESPIRATORY OR MEDICAL INTENSIVE CARE UNIT ADMISSION*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia ($PaO_2 < 5.3$ kPa or 40mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability - need for vasopressors.

*Local resources need to be considered.

KEY POINTS FOR THE MANAGEMENT OF EXACERBATIONS

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**.
- Systemic corticosteroids can improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days **(Evidence A)**.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days **(Evidence B)**.
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**.
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**.

COPD exacerbation come to the emergency department

- should be provided with **supplemental oxygen**
- undergo **assessment** to determine whether the exacerbation is life-threatening
- if increased work of breathing or impaired gas exchange requires **consideration for non-invasive** ventilation.
- consider **admission** to the respiratory or **intensive care unit** of the hospital.

MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS*

- Assess severity of symptoms, blood gases, chest radiograph.
- Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements.
- Bronchodilators:
  - » Increase doses and/or frequency of short-acting bronchodilators.
  - » Combine short-acting beta 2-agonists and anticholinergics.
  - » Consider use of long-active bronchodilators when patient becomes stable.
  - » Use spacers or air-driven nebulizers when appropriate.
- Consider oral corticosteroids.
- Consider antibiotics (oral) when signs of bacterial infection are present.
- Consider noninvasive mechanical ventilation (NIV).
- At all times:
  - » Monitor fluid balance.
  - » Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis.
  - » Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.).

*Local resources need to be considered.

Pharmacological treatment

most commonly used for COPD exacerbations :

- bronchodilators
- Corticosteroids
- antibiotics.

Bronchodilators

- short-acting inhaled beta2-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

- **no significant differences** in FEV1between using metered dose inhalers **(MDI)** (with or without a spacer device) **or nebulizers** to deliver the agent

- recommended that patients do not receive continuous nebulization, but use the MDI inhaler one or two puffs every one hour for two or three doses and then every 2-4 hours based on the patient's response.

Bronchodilators

- **no clinical studies** that have evaluated the use of **inhaled long-acting bronchodilators** (either beta2-agonists or anticholinergics or combinations) with or without ICS during an exacerbation

- we recommend **continuing these treatments** during the exacerbation or to start these medications as soon as possible before hospital discharge.

Bronchodilators

- Intravenous methylxanthines (theophylline or aminophylline) are **not recommended** to use in these patients due to significant side effects.

Systemic corticosteroids
BTS

- use **oral corticosteroids**, in conjunction with other therapies, in **all people admitted to hospital** with a COPD exacerbation.

- consider oral corticosteroids for people in the community who have an exacerbation with a **significant increase in breathlessness** that interferes with **daily activities**.

- **Offer 30 mg oral prednisolone daily for 5 days.**

Glucocorticoids

- systemic glucocorticoids in COPD exacerbations:
  -shorten **recovery** time
  - improve **lung function** (FEV1).

- **Improve :**
  - oxygenation
  -the risk of early relapse
  - treatment failure
  -the length of hospitalization.

Glucocorticoids

- 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 may be a suitable **alternative** for treatment of exacerbations in **some patients**, and provides similar benefits to intravenous methylprednisolone

Glucocorticoids

- Intensified combination therapy with **LABA/ICS for 10 days** at **URTI onset** could be associated with a reduction of exacerbations, particularly in patients with severe disease.

Glucocorticoids

- short bursts of corticosteroids are associated with subsequent **increased risk of pneumonia**, sepsis and death and **use** should be confined to **patients with significant exacerbations**.

- Recent studies suggest that glucocorticoids may be **less efficacious** to treat acute COPD exacerbations in patients with **lower levels of blood eosinophils**

Glucocorticoids
ATS & ERS

- For patients requiring emergency department or hospital-based treatment for a COPD exacerbation, we recommend a course of systemic glucocorticoids.

Antibiotics

- use of antibiotics in exacerbations remains **controversial.**

- There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a **bacterial infection** e.g., increased **sputum purulence.**

- observed sputum purulence has **94.4% sensitivity and 52% specificity** for high bacterial load, indicative of a causative relationship.

Antibiotics
systematic review of placebo-controlled studies

- antibiotics **reduce :**
  - the risk of short-term **mortality by 77%**
  -treatment failure by 53%
  - sputum purulence by 44%.

- evidence to treat moderately or severely ill patients with COPD exacerbations and increased cough and sputum purulence with **antibiotics**.

Antibiotics

- data has indicated that antibiotic usage can **be safely reduced** from **77.4% to 47.7%** when CRP is low.

- The efficacy of **Procalcitonin** is controversial.

- studies, mainly done in **the outpatient setting** :
  suggested that **procalcitonin-**guided antibiotic treatment reduces antibiotic exposure and side effects with the same clinical efficacy.

- **Asystematic review** and meta-analysis on the use of procalcitonin in hospitalized patients with a COPD exacerbation **found no significant reduction** in overall antibiotic exposure.

Antibiotics

- patients with COPD exacerbations treated in **an ICU** setting, the **use of a procalcitonin**-based algorithm for initiating or stopping antibiotics was associated with a **higher mortality rate** when compared to those receiving standard antibiotic regimens.

- Based on these conflicting results we **cannot recommend** at this time the use of procalcitonin-based protocols to make the decision on using antibiotics in patient with COPD exacerbations

Antibiotics

- antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms:
  - increase in dyspnea
  - increase sputum volume
  -sputum purulence;
  * or 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.**

Antibiotics

- initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline.

- **cultures from sputum** or other materials from the lung should be performed, as gram-negative bacteria (e.g., Pseudomonas species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present :
  - patients with frequent exacerbations
  -severe airflow limitation
  - exacerbations requiring mechanical ventilation

Adjunct therapies

- Suspected exacerbation : up to 5.9% were found to have pulmonary embolism

- prophylactic measures for thromboembolism should be instituted

Respiratory support
Oxygen therapy

- Supplemental oxygen should be titrated to improve the patient's hypoxemia with a **target saturation of 88-92%.**

- blood gases should be checked frequently to ensure satisfactory oxygenation without carbon dioxide retention

- **venous blood gas** to assess **bicarbonate levels and pH** is **accurate** when compared with arterial blood gas assessment

Oxygen therapy

- **Venturi masks** offer more accurate and controlled delivery of oxygen than do nasal prongs

High-flow nasaltherapy (HFNT)

- Delivers heated and humidified air-oxygen blends via special devices) at rates up to 8 L/min in infants and up to 60 L/min in adults
- - decreased respiratory rate and effort
  - decreased work of breathing
  -improved gas exchange
  -improved lung volume and dynamic compliance, transpulmonary pressures and homogeneity.

- **improve oxygenation** and **clinical outcomes** in patients with acute hypoxemic respiratory failure.

High-flow nasaltherapy (HFNT)

- - Improve oxygenation and ventilation
  -decrease hypercarbia
  - improve health-related quality of life in patients with acute hypercapnia during an acute exacerbation

- A **meta-analysis,** based on poor quality studies, showed **no clear benefit**.

Ventilatory support
Noninvasive mechanical ventilation.

- (NIV) is preferred over invasive ventilation
- NIV has been studied in RCTs showing a **success rate of 80-85%**
- improve **oxygenation** and acute respiratory acidosis
- **NIV also decreases :**
  - respiratory rate
  - work of breathing and the severity of breathlessness
  -complications such as ventilator associated pneumonia
  - length of hospital stay.
- **mortality and intubation rates are reduced**

INDICATIONS FOR NONINVASIVE MECHANICAL VENTILATION (NIV)

At least one of the following:

- Respiratory acidosis ($PaCO_2 \geq 6.0$ kPa or 45 mmHg and arterial pH ≤ 7.35).
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.
- Persistent hypoxemia despite supplemental oxygen therapy.

Invasive mechanical ventilation

- number of indications for invasive mechanical ventilation are being successfully treated with NIV

- 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

Invasive mechanical ventilation

- 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

Invasive mechanical ventilation

- large study of COPD patients with acute respiratory failure reported **in-hospital mortality of 17-49%.**

- **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
  -housebound

INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

- Unable to tolerate NIV or NIV failure.
- Status post - respiratory or cardiac arrest.
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation.
- Massive aspiration or persistent vomiting.
- Persistent inability to remove respiratory secretions.
- Severe hemodynamic instability without response to fluids and vasoactive drugs.
- Severe ventricular or supraventricular arrhythmias.
- Life-threatening hypoxemia in patients unable to tolerate NIV.

DISCHARGE CRITERIA AND RECOMMENDATIONS FOR FOLLOW-UP

- Full review of all clinical and laboratory data.
- Check maintenance therapy and understanding.
- Reassess inhaler technique.
- Ensure understanding of withdrawal of acute medications (steroids and/or antibiotics).
- Assess need for continuing any oxygen therapy.
- Provide management plan for comorbidities and follow-up.
- Ensure follow-up arrangements: early follow-up < 4weeks, and late follow-up < 12weeks as indicated.
- All clinical or investigational abnormalities have been identified.

1 – 4 WEEKS FOLLOW-UP

- Evaluate ability to cope in his/her usual environment.
- Review and understanding treatment regimen.
- Reassessment of inhaler techniques.
- Reassess need for long-term oxygen.
- Document the capacity to do physical activity and consider patient eligibility to be enrolled in pulmonary rehabilitation.
- Document symptoms: CAT or mMRC.
- Determine status of comorbidities.

12 – 16 WEEKS FOLLOW-UP

- Evaluate ability to cope in his/her usual environment.
- Review understanding treatment regimen.
- Reassessment of inhaler techniques.
- Reassess need for long-term oxygen.
- Document the capacity to do physical activity and activities of daily living.
- Measure spirometry: FEV_1.
- Document symptoms: CAT or mMRC.
- Determine status of comorbidities.

TABLE 5.8

Hospital discharge and follow-up

- **no standards** that can be applied to the timing and nature of discharge

- significant risk factors for 30-and 90-day all-cause readmission after an index hospitalization with an exacerbation of COPD :
  - comorbidities
  - previous exacerbations and hospitalization
  - increased length of stay

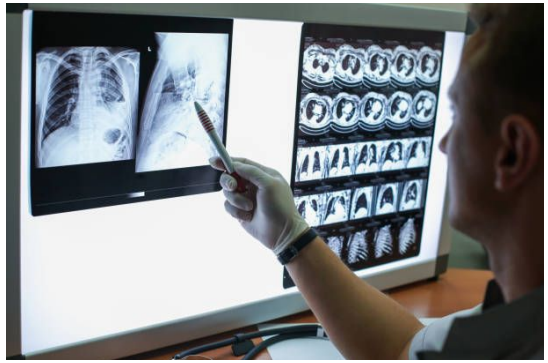
Hospital discharge and follow-up

- **Mortality relates to** :
  - patient age
  - the presence of acidotic respiratory failure
  - the need for ventilatory support
  - comorbidities including anxiety and depression

Hospital discharge and follow-up

- CT assessment to determine the presence of bronchiectasis and emphysema should be done in patients with **recurrent exacerbations/ and or hospitalizations**

- assessment of the presence and management of comorbidities should also be undertaken



INTERVENTIONS THAT REDUCE THE FREQUENCY OF COPD EXACERBATIONS

INTERVENTION CLASS	INTERVENTION
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast
Anti-infectives	Vaccines Long Term Macrolides
Mucoregulators	N-acetylcysteine Carbocysteine Erdosteine
Various others	Smoking Cessation Rehabilitation Lung Volume Reduction Vitamin D Shielding measures (e.g., mask wearing, minimizing social contact, frequent hand washing)

TABLE 5.9

Long-term prognosis

- following **hospitalization** for COPD exacerbation is poor, with a five-year mortality rate of about 50%.
- older age
- lower BMI
- 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.
- 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