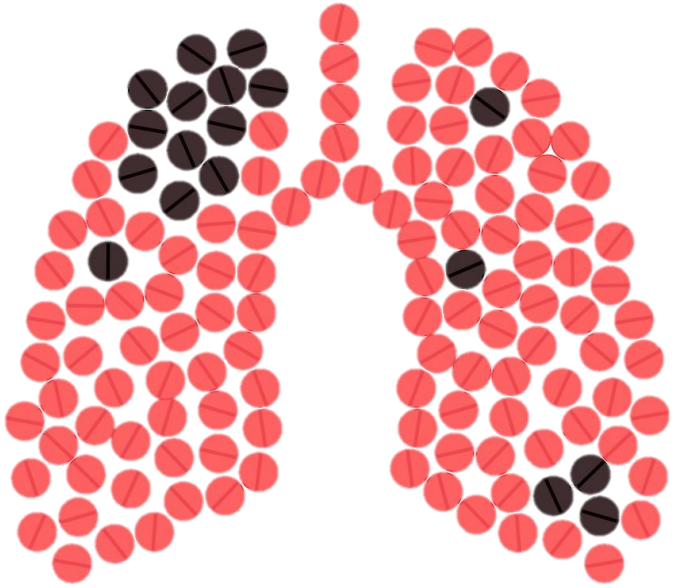
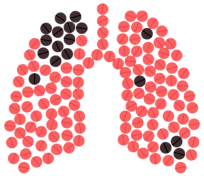
COPD in Critical Situation:

Triggers & Prevention of Acute Exacerbation



ERWIN ARIEF

Introduction

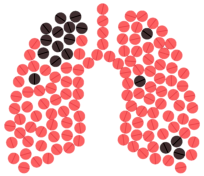


- COPD is a mainly chronic disease, a substantial number of patient suffer from exacerbation
- Exacerbation are an important medical and healthcare problem

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2019

COPD exacerbation is an event in the natural course of the disease that is characterized by a change in the patient's baseline dyspnea, cough and sputum that is beyond normal day-to-day variations, is acute in onset and warrants a change in regular medication

Introduction

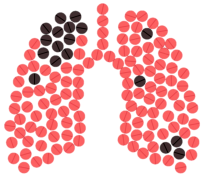


Critical situation

- Large scale natural disaster, such as earthquakes or tsunami, destroy buildings, vital infrastructure, communication technology, and transportation facilities

- These disasters may exacerbate chronic respiratory diseases, such as COPD. In the aftermath of the disaster, COPD patients often endure limited access to medication, medical equipment, and/or medical supplies

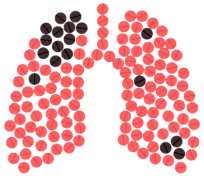
Introduction



Critical situation

- Extreme changes in the weather are notorious for interrupting breathing patterns, especially in COPD patients .
- Heat, humidity, dry air, wind, rain, cold — every climate characteristic has the potential to trigger symptoms, and in the worst cases, dangerous exacerbations.

Introduction



- Exacerbation of COPD have short long term clinical implication

Seemungal, et al. 2000

The time course of recovery of symptoms during an acute exacerbation

- 50% of community-treated exacerbation patient recovered to baseline symptoms within 7 days
- 14% of these patients symptoms did not return to baseline 35 days following the onset
- Some patient symptoms never returned to baseline level

- Recurrent exacerbation are associated with accelerated decline in lung function → hallmark of COPD

Donaldson, et al. 2002

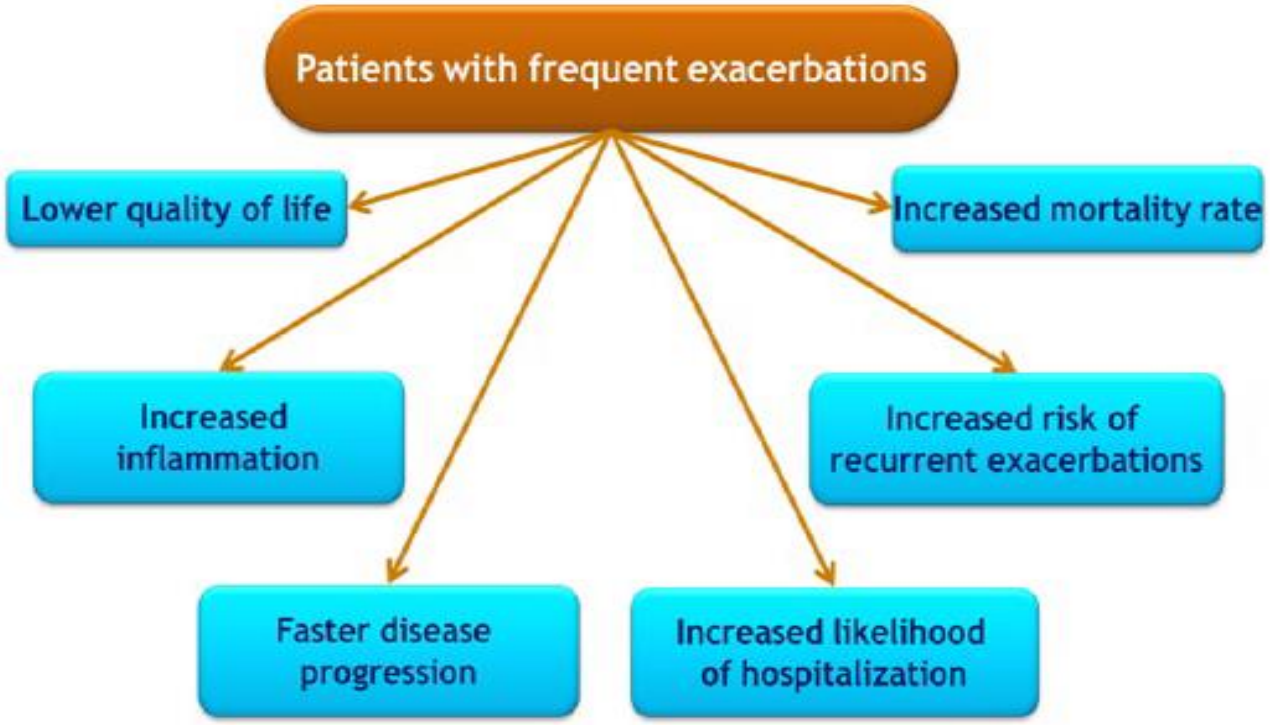
Frequent exacerbators had a decline in forced expiratory volume in 1s (FEV1) of 40.1 ml/year **versus** 32.1 ml/year in those with no exacerbation

Vestbo, et al. 2011

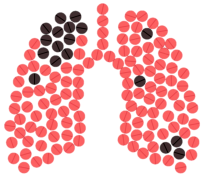
Exacerbation experienced during the study associated with an excess decline in lung function (FEV1) with a mean loss of 2 ml per year per exacerbation

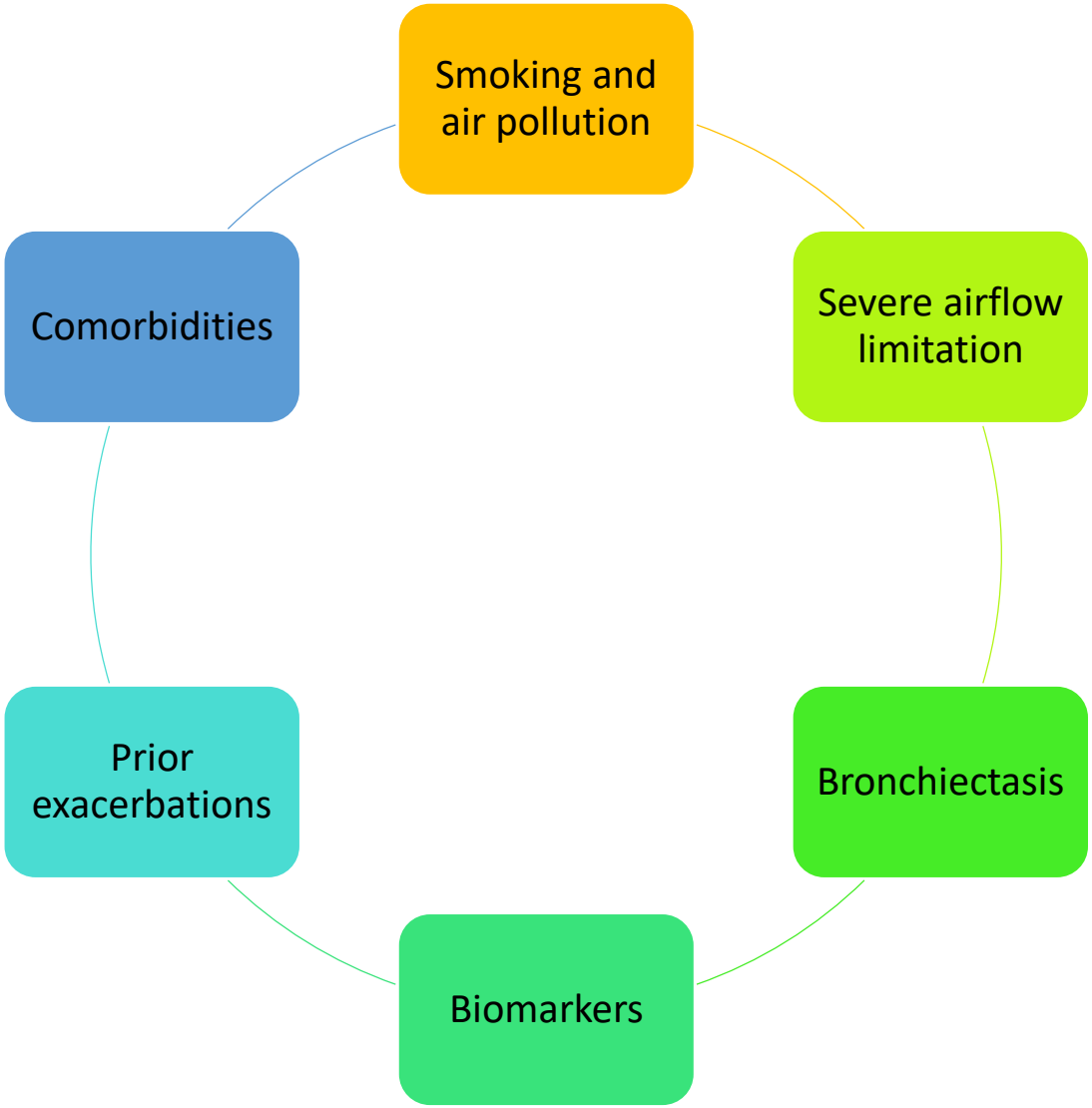
Introduction

- Frequent exacerbations are associated with reduced physical activity, poorer quality of life and even an increased risk of death

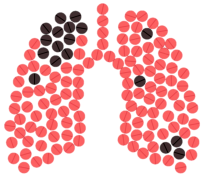


Risk Factors and Triggers





Smoking and Air Pollution



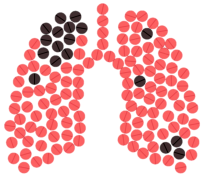
- Tobacco smoke is the major risk factor
- The effect of air pollution on COPD exacerbations is still under debate

De Vries, 2016 & Neuberger, 2013 → Air pollution significantly increase the risk of exacerbation

There is a trend towards an association of air pollution with exacerbation

Li J, 2016 (a systematic review and meta-analysis) → Short-term exposure to major air pollutants could significantly increase the risk for exacerbation of COPD

Severe Airflow Limitation



ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort study [Rennard, 2015]

Longitudinal outcomes	*Cluster A* (n = 205)	*Cluster B* (n = 98)	*Cluster C* (n = 423)			
*Died within 3 years (%)	3%	6%	13%			
Median time to COPD exacerbation (days)	492	318	347			
*COPD hospitalization-within 3 years (%)	25%	29%	33%			
COPD exacerbation rate (PPPY)	0.76	1.08	1.12	1.77	1.17	<0.001
COPD hospitalization rate (PPPY)	0.12	0.21	0.27	0.48		
Rate of decline in FEV_1 (mL)	34 (39)	35 (41)	33 (45)	33 (37)		
SGRQ total score change at year 3	1.7 (13.3)	2.6 (12.8)	–0.2 (13.3)	2.8 (11.2)		
Change in 6-minute walk distance (m) at year 3	2 (95)	–5 (94)	–15 (92)	–31 (106)		
Change in emphysema % LAA at year 3	1.9 (4.5)	2.9 (5.7)	1.0 (4.3)	2.3 (5.3)		

PPPY = per person per year. *Kaplan-Meier estimates; *P* values from log-rank test.

The highest mortality was seen in the group with severe airflow limitation

The subgroup with most exacerbations of COPD had the 2nd highest mortality within 3 years

Bronchiectasis

A Meta-analysis (Ni Y, et al. 2015)

Study or subgroup	With bronchiectasis Mean	SD	Total	Without bronchiectasis Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Fujimoto et al[11]	1.36	0.35	44	0.7	0.22	39	21.8%	0.66 (0.54, 0.78)	2006
Bafadhel et al[1]	4.6	0.6	33	3.7	0.9	13	20.5%	0.90 (0.37, 1.43)	2011
Martínez-García et al[7]	4.87	3.82	53	2.36	2.28	39	16.1%	2.51 (1.26, 3.76)	2011
Martínez-García et al[13]	1.88	2.13	115	1	1.48	86	20.7%	0.88 (0.38, 1.38)	2013
Tulek et al[12]	3.3	1.03	27	0.3	0.5	26	20.9%	3.00 (2.57, 3.43)	2013
Gatheral et al[4]	0	0	0	0	0	0		Not estimable	2014
Total (95% CI)			**272**			**203**	**100%**	**1.54 (0.56, 2.53)**	

Heterogeneity: τ^2=1.15; χ^2=110.26, *df*=4 (*P*<0.00001); I^2=96%
Test for overall effect: *Z*=3.07 (*P*=0.002)

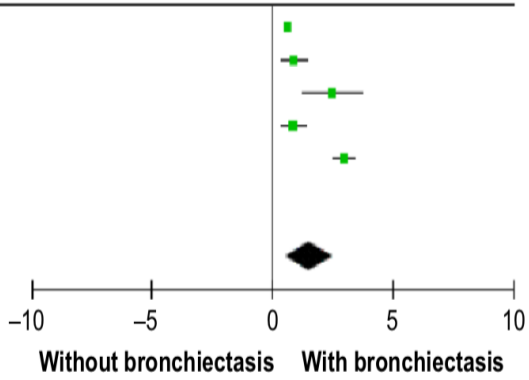
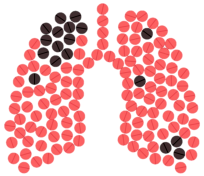


Figure 6 Forest plot of mean difference in exacerbations in COPD patients with and without bronchiectasis.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IV, inverse variance; SD, standard deviation.

There is correlation between the detection of bronchiectasis in patient with COPD and the frequency of exacerbation **(weighted mean difference 1.54 times in the previous year)**

Bronchiectasis



Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M–H, fixed, 95% CI	Year
Fujimoto et al[11]	0	0	0	0		Not estimable	2006
Bafadhel et al[1]	0	0	0	0		Not estimable	2011
Martínez-García et al[7]	18	53	2	39	9.1%	9.51 (2.06, 44.04)	2011
Martínez-García et al[13]	37	115	5	86	23.2%	7.68 (2.87, 20.56)	2013
Tulek et al[12]	0	0	0	0		Not estimable	2013
Gatheral et al[4]	143	278	17	128	67.7%	6.92 (3.94, 12.13)	2014
Total (95% CI)		**446**		**253**	**100%**	**7.33 (4.61, 11.67)**	
Total events	198		24				

Heterogeneity: χ^2=0.16, *df*=2 (*P*=0.92); I^2=0%
Test for overall effect: *Z*=8.40 (*P*<0.00001)

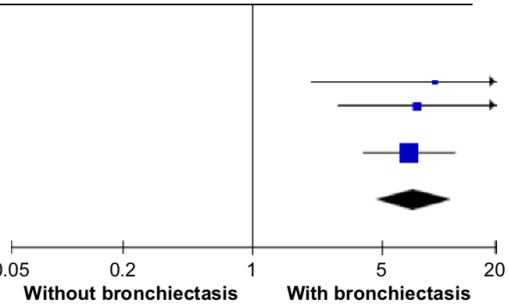


Figure 11 Forest plot of odds ratios of chronic PPM colonization in COPD patients with and without bronchiectasis.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; M–H, Mantel-Haenszel method; PPM, potentially pathogenic microorganisms.

Patient with bronchiectasis had more chronic colonization by pathogenic microorganism

Study or subgroup	With bronchiectasis Events	With bronchiectasis Total	Without bronchie Events	Without bronchie Total	Weight	Odds ratio M–H, fixed, 95% CI	Year
Fujimoto et al[11]	0	0	0	0		Not estimable	
Bafadhel et al[1]	0	0	0	0		Not estimable	2011
Martínez-García et al[7]	6	53	1	39	7.4%	4.85 (0.56, 42.05)	2011
Martínez-García et al[13]	15	115	4	86	28.7%	3.08 (0.98, 9.62)	2013
Tulek et al[12]	0	0	0	0		Not estimable	2013
Gatheral et al[4]	53	278	8	128	63.9%	3.53 (1.63, 7.67)	2014
Total (95% CI)		**446**		**253**	**100%**	**3.50 (1.89, 6.47)**	
Total events	74		13				

Heterogeneity: χ^2=0.14, *df*=2 (*P*=0.93); I^2=0%
Test for overall effect: *Z*=4.00 (*P*<0.0001)

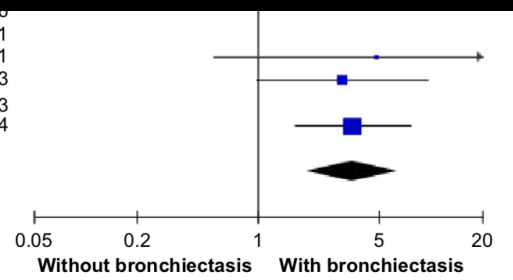
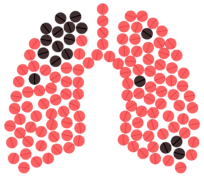


Figure 12 Forest plot of odds ratios of *Pseudomonas aeruginosa* isolation in COPD
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary d

Patient with bronchiectasis had a higher rate of Pseudomonas aeruginosa isolation

Biomarkers



FIBRINOGEN

patients with elevated levels of fibrinogen had a nearly two-fold increased risk of death from any cause over 3 years

(The COPD Foundation Biomarker Qualification Consortium)

Plasma fibrinogen as a prognostic biomarkers for all cause mortality and COPD exacerbation

(The U.S. Food & Drug Administration)

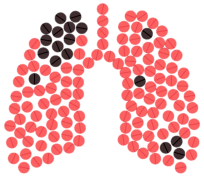
EOSINOPHYL COUNT

A high eosinophil count in blood is associated with an increased risk of COPD exacerbations

In patients with high eosinophil counts there were more exacerbations per year: the higher the eosinophil count, the more exacerbations

(Pascoe, et al. 2015)

Prior Exacerbations



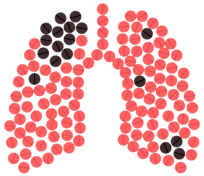
Suissa, et al. 2012

- The risk of subsequent severe exacerbation was increase three-fold after the second severe exacerbation and 24-fold after the 10th
- The median time from one to the next hospitalized exacerbation decrease with the number of previous exacerbations.

POET-COPD Trial

- Frequent exacerbators had three-fold increase in mortality
- Important prognostic factor was exacerbation-related hospitalization
- Readmission within 30 days after COPD exacerbation was correlated with an increase risk of mortality
- The most important predictors of frequent exacerbations is a history of exacerbations

Comorbidities

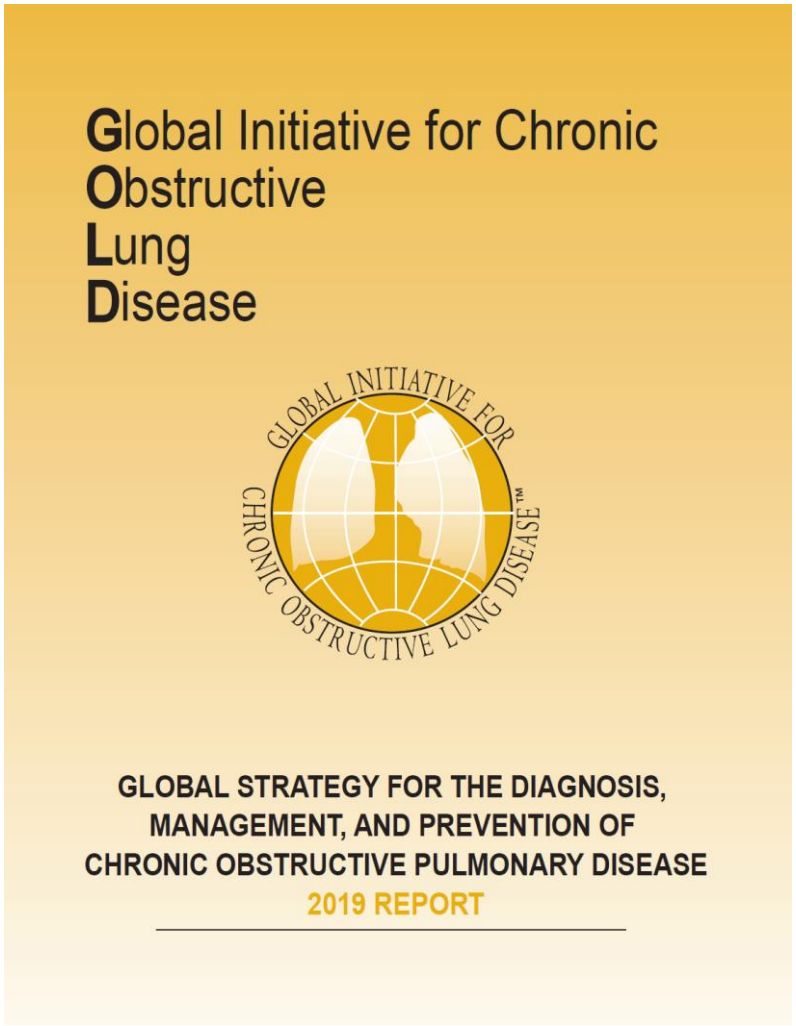


- Most patient COPD have comorbidities, the five most prevalent comorbidities :
  - **Hyperglicemia**
  - **Atherosclerosis**
  - **Hypertension**
  - **Dyslipidemia**
  - **Osteoporosis**

- Psychiatric comorbidities **(anxiety and depression)** may have negative impact on exacerbation frequency

- Some comorbidities may mimic an exacerbation of COPD **(decompensated heart failure or ischemic heart disease)**

GOLD 2019 Report: Chapters



1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations
6. COPD and Comorbidities

Management of Exacerbations

OVERALL KEY POINTS (1 of 3):

- An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.
- Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections.
- The goal for treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.

Management of Exacerbations

OVERALL KEY POINTS (2 of 3):

- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.
- 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.
- 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.
- Methylxanthines are not recommended due to increased side effect profiles.

Management of Exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

- 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.

Management of Exacerbations

Classification of hospitalized patients

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 (FiO_2); no increase in $PaCO_2$.

Management of Exacerbations

Classification of hospitalized patients

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% FiO_2; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg.

Management of Exacerbations

Classification of hospitalized patients

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 FiO_2 > 40%; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg or the presence of acidosis (pH ≤ 7.25).

Management of Exacerbations

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.

TABLE 5.2

Management of Exacerbations

Pharmacological treatment

The three classes of medications most commonly used for COPD exacerbations are:

- **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.
- **Corticosteroids**
  - Data from studies indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function (FEV_1). They also improve oxygenation, the risk of early relapse, treatment failure, and the length of hospitalization.
- **Antibiotics**

Management of Exacerbations

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.

TABLE 5.4

Management of Exacerbations

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.

TABLE 5.5

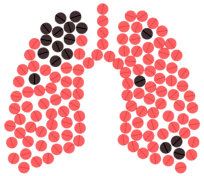
Management of Exacerbations

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.

TABLE 5.6

Prevention Strategies of COPD Exacerbations



- Prevention of exacerbation is a major goal in management
- Many modalities have been proposed to prevent exacerbation

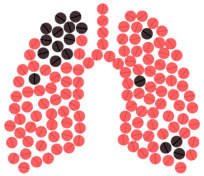
Non Pharmacological

- Smoking cessation
- Vaccines
- Pulmonary rehabilitation
- Disease management program and patient education

Pharmacological

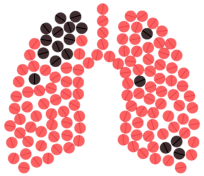
- LABA monotherapy
- LAMA monotherapy
- Inhaled corticosteroids
- Combination therapy
- Phospodiesterase-4 inhibitors
- Prophylactic antibiotics

Pharmacological



LABA monotherapy	• LABA salmeterol shown to reduce the annual rate of COPD exacerbation by 20% compared with placebo • A reduction in exacerbation rate was also seen with other LABAs • The effect of LABA on exacerbations is irrespective of previous exacerbation history
LAMA monotherapy	• Seem to be more effective in preventing exacerbation compared to LABA • Bronchodilation with LAMAs reduce exacerbation rates compared with placebo by ~35% overall • GOLD 2017 and ERS/ATS Guideline favour LAMA monotherapy over LABA monotherapy in patient with a history of exacerbation

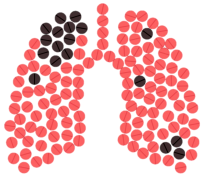
Pharmacological



Inhaled Corticosteroids	• Long-term treatment with inhaled corticosteroid (ICS) may be considered for patient with a history of exacerbation (**still controversial**) • Patient with overlap of Asthma and COPD and potentially high blood eosinophil count may benefit from addition of ICS to a bronchodilator therapy
Combination Therapy	• Significant reduction in terms of exacerbation can be achieved by combining a LABA and LAMA compared to both LAMA alone or LABA/ICS • **TRILOGY and TRINITY study** both showed a reduction of exacerbations with triple therapy compared to LABA/ICS

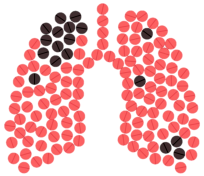
TRILOGY : Single inhaler triple therapy versus ICS/LABA therapy for COPD
TRINITY : Single inhaler Extrafine triple therapy versus LAMA therapy for COPD

Pharmacological



Phospodies-terase-4 Inhibitors	• GOLD 2019 and ERS/ATS guideline recommend a phosphodiesterase-4 inhibitor (roflumilast) as a treatment option for patients with COPD who have severe and very severe airflow limitation, chronic bronchitis and high risk of exacerbation • **Chong J, et al** → treatment with roflumilast compare with placebo was associated with reduced likelihood of COPD exacerbation
Prophylactic Antibiotic	• Long-term antibiotic treatment has been considered in COPD • **Herath, et al** → showed a clinically significant benefit with use of continuous prophylactic antibiotics compared with placebo. Number of patients experience exacerbation and frequency of exacerbation was reduced • GOLD 2017 report that macrolides can be considered in former smokers who have exacerbation • ERS/ATS suggest treatment with macrolides antibiotics for patient with moderate to very severe airflow limitation and exacerbations

Conclusions



- COPD has many triggers to exacerbated, and will remain a significant health burden
- The prevention of exacerbation is one of the most important treatment goals
- To achieve that goal, patient education and smoking cessation programs as well as patient-tailored pharmacological and non pharmacological treatments are mandatory

THANK YOU