INTRODUCTION

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Weaning from mechanical ventilation can be defined as the process of abruptly or gradually withdrawing ventilatory support. Two large multicenter studies.[1, 2] have demonstrated that mechanical ventilation can be discontinued abruptly in approximately 75% of mechanically ventilated patients whose underlying cause of respiratory failure has either improved or been resolved. The remaining patients will need progressive withdrawal from mechanical ventilation.[1,2]

Weaning from mechanical ventilation usually implies two separate but closely related aspects of care, discontinuation of mechanical ventilation and removal of any artificial airway. The first problem the clinician faces is how to determine when a patient is ready to resume ventilation on his or her own. Several studies[1-5]have shown that a direct method of assessing readiness to maintain spontaneous breathing is simply to initiate a trial of unassisted breathing. Once a patient is able to sustain spontaneous breathing, a second judgment must be made regarding whether the artificial airway can be removed. This decision is made on the basis of the patient's mental status, airway protective mechanisms, ability to cough and character of secretions. If the patient has an adequate sensorium with intact airway protection mechanisms, and is without excessive secretions, it is reasonable to extubate the trachea.[1-5]

A team approach and an organized problem-orientated plan are important to expedite successful discontinuation of mechanical ventilation. Ely et al [4] recently demonstrated that a protocol of weaning is superior to the physician's individual decision-making at the bedside. They enrolled 300 mechanically ventilated medical and nonsurgical cardiac patients into a randomized, controlled trial in which the treatment group was weaned using a two-step process of daily screening by respiratory care practitioners followed by spontaneous breathing trials when recovery was sufficient to pass the daily screen. Those investigators found that removal from mechanical ventilation was 2 days earlier in the protocol-directed group. The use of the protocol to manage just four patients (95% confidence interval 3-5) would result in one individual being off mechanical ventilation after 48 h who otherwise would not have been. [4]

Practice guidelines on weaning should be based on carefully performed clinical studies. Few areas in critical care have been evaluated as extensively by well-designed studies over the past decade as the discontinuation of mechanical ventilation. Therefore, every step in the process of weaning is supported by the results of at least one randomized clinical trial

Predictive weaning criteria: how useful are they?

Weaning procedures are usually started only after the underlying disease is resolved. The patient should also have an adequate gas exchange, appropriate neurological and muscular status, and stable cardiovascular function.

Weaning indices are objective criteria that are used to predict the readiness of patients to maintain spontaneous ventilation. Some parameters based on respiratory mechanics, gas exchange, and breathing pattern have been proposed as useful predictors of

weaning outcome that could guide clinicians in determining the optimal time to discontinue mechanical ventilation. [6-9]

According to the American college of chest physicians, society of critical care medicine and the American association of respiratory care the weaning indices that have some predictive capacity are: [10]

1) The integrative weaning index (IWI):

The IWI evaluates, in a single equation respiratory mechanics, oxygenation and respiratory pattern, through Cst, SaO_2 and RSBI respectively.

IWI = Cst,rs x SaO_2/ RSBI [11]

Cst,rs : static compliance of respiration.

IWI ≥ 25 ml/cmH_2O breaths/minute/liter is a good predictor for weaning from MV.

Several reasons concurred to the choice of the parameters above: RSBI is considered the best index to evaluate the weaning outcome. Cst is associated with a shorter time to weaning when more than 20 ml/cmH2O. [12] And SaO_2 has proven to be useful to indicate the weaning failure in several studies. so multiplying the respiratory compliance by SaO_2 can detect those patients who can or cannot maintain a good oxygenation, despite good or bad respiratory mechanics. Dividing this product by the f/Vt ratio can detect those patients who will or will not be able to maintain unassisted breathing.

2) Tidal volume:

Spontaneous tidal volumes greater than 5 ml/kg have been considered as good predictors of weaning outcome. [13]

3) Maximal inspiratory pressure(P_{Imax}):

It is commonly used to test respiratory muscle strength. The proximal end of the endotracheal tube is occluded for 20 to 25 seconds with a one-way valve that allows the patient to exhale but not to inhale. This procedure leads to increasing inspiratory effort and P_{Imax} is measured towards the end of the occlusion period. Several early studies have shown that $P_{Imax} \leq$ -30 cmH_2O has a high predictive value for weaning. [14]

4) Breathing frequency (f):

Tachypnea (f ≥ 30–35 breaths/minute) is a sensitive marker of respiratory distress but can prolong intubation when used as an exclusive criterion. [15]

5) $P_{0.1}/P_{Imax}$:

The airway occlusion pressure ($P_{0.1}$) is the pressure measured at the airway opening 0.1 second after inspiring against an occluded airway. The $P_{0.1}$ is effort independent and correlates well with central respiratory drive. When combined with the maximal inspiratory pressure P_{Imax}, the $P_{0.1}/P_{Imax}$ ratio at a value of <0.3 has been found to be a good early predictor of weaning success.[16]

6) Oxygenation:

Arterial oxygen saturation (SaO_2) ≥ 90% with a fraction of inspired oxygen FiO_2 ≤ 0.4 associated with successful weaning. [17]

7) Minute ventilation (V_E) :

V_E < 10 l/minute is associated with weaning success. Studies showed that V_E values > 15–20 l/minute are helpful in identifying patients who are unlikely to be liberated from mechanical ventilation. [18]

8) Rapid shallow breathing index:

It is the ratio of breathing frequency to tidal volume obtained during the first 1 minute of a T-piece trial. At a threshold value of ≤ 105 breaths/minute/liter, RSBI was a significantly better predictor of weaning outcomes than other 'classic' and commonly used parameters.[19, 20]

9) Static compliance (Cst):

Measured while patient on volume control ventilation, fully sedated and inspiratory pause for 0.5 to 1 S, Cst = VT / (inspiratory platue pressure – positive end expiratory pressure). [11, 12]

10) PaO2:

Measured using arterial blood gas analysis

11) PaCO2:

Measured using arterial blood gas analysis.

12) PEEP(positive end expiratory pressure): normal value is 5-8 cmH2O[1]

13) Hypoxic index:

Measured by dividing PaO2 by FiO2.

14) Haemoglobin level:

Should be more than 9 g/dl[201].

Is the patient able to sustain spontaneous breathing?

Once a patient has been considered ready to be weaned, the best method to assess whether the patient is able to breathe on his or her own is to perform a trial of spontaneous ventilation. Ely et al [4] showed that immediate extubation after successful trials of spontaneous breathing expedites weaning and reduces the duration of mechanical ventilation as compared with a more gradual discontinuation of ventilatory support. Several studies, [1-5, 21-23] have demonstrated that 60-80% of mechanically ventilated patients can be successfully extubated after passing a trial of spontaneous breathing. [1-5, 21-23]

Pressure-support, continuous positive airway pressure and T-piece trials are the most common methods used to test the readiness for liberation from mechanical ventilation. Few randomized studies[3, 24] have evaluated the best technique for performing spontaneous breathing trials before extubation. The first study that dealt with this issue[25] compared continuous positive airway pressure of 5 cmH_2O and T-piece in a group of 106 mechanically ventilated patients who underwent a 1 h trial of spontaneous breathing, and no difference in the percentage of patients failing extubation was found. Because the endotracheal tube imposes a resistive load on the respiratory muscles that is inversely related to its cross-sectional diameter, some clinicians advocate use of 5-8 cmH_2O pressure support to offset this imposed load. With this in mind, the study performed by the Spanish Lung Failure Collaborative Group[3] compared weaning outcome after trials of spontaneous breathing with either T-tube or pressure support of 7 cmH_2O, but no difference was observed in the percentage of patients who remained extubated for 48 h (63% in the group assigned to T-tube and 70% in the group assigned to pressure support; $P = 0.14$). [3]

The duration of a spontaneous breathing trial has been set at 2 h in most studies. [1, 2, 4, 22, 23] One prospective, multicenter, randomized trial of 526 patients[5] found that trials of spontaneous breathing for 30 or 120 min were equivalent in identifying patients who could tolerate extubation, and that patients had reintubation rates of approximately 13% at 48 h regardless of the duration of their T-tube trial. [5]

Precise criteria for terminating a weaning trial do not exist, and currently trials are terminated on the basis of the clinical judgment of the physician. There are two types of criteria used to determine whether a patient passes or fails a spontaneous breathing trial: objective criteria (abnormal arterial blood gas measurements) and subjective criteria (diaphoresis, evidence of increasing effort, tachycardia, agitation, anxiety). Patients have clearly failed a spontaneous breathing trial if they develop hypercapnia or hypoxaemia. The evaluation of clinical tolerance to spontaneous breathing by using exclusively subjective criteria has important drawbacks; on the one hand, strict criteria might increase the occurrence of unnecessarily prolonged mechanical ventilation but, on the other hand, permissive criteria might increase the occurrence of reintubation. Randomized studies are needed to compare outcome of weaning in patients whose clinical tolerance to spontaneous breathing trials is evaluated using either strict criteria or less strict criteria.[1-5]

Once a patient is able to sustain spontaneous breathing, a second judgment must be made regarding whether the artificial airway can be removed by assessing the patient's mental status, airway protective mechanisms, ability to cough and character of secretions.

It is our contention that there is little risk in performing a closely observed trial of spontaneous breathing in patients in whom any acute respiratory failure has resolved and who are awake and cardiovascularly stable, in order to assess their ability to sustain spontaneous breathing. When the patient remains clinically stable with no signs of poor tolerance until the end of the trial, the endotracheal tube should be immediately removed. If the patient develops signs of poor tolerance, weaning is considered to have failed and mechanical ventilation is reinstituted.[1-5]

What about patients failing the first attempt at weaning?

Weaning attempts that are unsuccessful usually indicate incomplete resolution of the illness that precipitated the need for mechanical ventilation, or the development of new problems. Failure to wean has been attributed to an imbalance between the load faced by the respiratory muscles and their neuromuscular competence. If a compensated balance of strength and load cannot be restored, attempts at spontaneous breathing will be futile. Therefore, once a patient fails a spontaneous breathing trial, the clinician must comprehensively evaluate the patient, looking for ways to improve his or her physiologic status.[26-29]

Failure to wean is usually multifactorial. A highly illustrative example of how different factors can lead to imbalance between ventilatory needs and respiratory capability is provided by acutely hyperinflated patients. In these patients, the load of the inspiratory muscles is increased for a variety of reasons. First, airway obstruction and/or decreased elastic recoil lead to prolongation of expiration that cannot be completed before the ensuing inspiration. It implies that at the end of an expiration there is still a positive pressure at the alveolar level. Consequently, during the next inspiration the inspiratory muscles have to develop an equal amount of pressure before airflow begins. Second, because of hyperinflation tidal breathing occurs at a steeper portion of the pressure-volume curve of the lung, further increasing the load. At the same time that the load is severely increased, the neuromuscular competence is decreased due to muscular weakness. Hyperinflation forces the inspiratory muscles to operate at an unfavourable position in their length-tension curve. In a state of hyperinflation the costal and crural fibres of the diaphragm are arranged in series, rather than in parallel, and this diminishes the force that can be generated. The resultant flattening of the diaphragm increases its radius of curvature and, according to Laplace's law ($P_{di} = 2T_{di}/R_{di}$; where P_{di} is the pressure-generating capacity, T_{di} is the tension and R_{di} is the radius of curvature), diminishes its pressure-generating capacity for a given tension developed.[26-29]

Hyperinflation is quite common in patients with chronic obstructive pulmonary disease (COPD), and could have a pivotal role in the failure of weaning, so the measurement of intrinsic positive end-expiratory pressure ($PEEP_i$) should be considered in every patient with COPD who fails a weaning attempt. Given the detrimental effects of $PEEP_i$ in increasing the load, every effort should be made to decrease it. Reducing the severity of airway obstruction by maximizing bronchodilator treatment, adjusting ventilator settings to provide as much time as possible for complete exhalation to occur, and improving tolerance to spontaneous breathing by decreasing the work of inspiration through the addition of external PEEP are proper therapeutic interventions.[26-29] The addition of external PEEP does not cause further hyperinflation or adversely affect

haemodynamics or gas exchange, provided that the added PEEP is less than approximately 85% of the level of $PEEP_i$.[29]

A number of studies performed in small and highly selected populations of patients with COPD have found a fatiguing pattern in the electromyogram power spectrum in mechanically ventilated patients during unsuccessful weaning trials.[30, 31] These changes have been interpreted as proof that failure to wean from mechanical ventilation may be due to diaphragm fatigue, and that is the final common pathway that leads to the development of hypercapnic respiratory failure. Because respiratory muscle fatigue probably develops during unsuccessful weaning and it is possible that it leads to persistent ventilator dependency, a major issue in the weaning approach is to provide rest for the respiratory muscles and allow them to recover from fatigue. One study that evaluated a group of healthy individuals in whom diaphragmatic fatigue was induced [32] found that diaphragmatic contractility remained significantly depressed for at least 24 h. Recovery from fatigue might be even slower in difficult-to-wean patients. Resting the respiratory muscles with mechanical ventilation is the only method of treating muscle fatigue. With this in mind, an expert panel recommended increasing ventilator support at night as a way to provide periods of rest in the management of difficult-to-wean patients.[33]

With most modes of assisted ventilation, the inspiratory muscles do not stop contracting once the ventilator has been triggered. Therefore, ventilator support should not be considered synonymous with respiratory rest. When the settings are not optimally set, the patient's active work may be even greater than that required for spontaneous chest inflation without mechanical ventilation.[34] A mode of ventilation that provides inadequate respiratory muscle rest is likely to delay rather than facilitate weaning, and therefore careful adjustment of the ventilator settings is necessary to minimize the respiratory work. Trigger sensitivity and inspiratory flow rate are the factors that primarily determine the patient's work of breathing during mechanical ventilation.[35] The importance of a high peak flow setting when pressure support is used has been demonstrated in a prospective study that involved patients with COPD,[23] in which the time to reach the set plateau pressure was manipulated with the aim of modulating the initial flow rate; the more rapidly the pressure plateau was achieved, the higher was the initial flow rate. Lengthening the pressure rise time almost invariably increased the patient's work of breathing, as well as several other indices of patient effort, whereas the breathing pattern was essentially not modified. The method of triggering, either by pressure or flow, may be also an important determinant of the patient effort during mechanical ventilation. Although a number of studies in patients with COPD have shown that a flow-triggered system decreases work of breathing in comparison with a pressure-triggered system during continuous positive airway pressure or synchronized intermittent mandatory ventilation (SIMV),[36, 37] other authors[38, 39]have reported that the triggering system of the mechanical ventilator does not have influence on work of breathing.

Optimal plumbing of the respiratory circuit is of major importance in minimizing respiratory work during a trial of spontaneous breathing. Important factors include the resistance of the endotracheal tube, equipment dead space, and resistance of the inspiratory circuit and humidifier. It has been demonstrated[40] that heat-moisture exchangers increase resistance to flow and add a substantial amount of dead space when compared with heated humidifiers. Although in many patients the amount of added dead space with heat-moisture exchangers is trivial and unlikely to adversely affect weaning trial outcome, this may not

be the case in patients who have limited ventilatory reserve, such as the majority of difficult-to-wean patients. [40]

In patients with repeatedly unsuccessful weaning trials, a gradual withdrawal from mechanical ventilation can be attempted while factors responsible for the ventilatory dependence are corrected. The most common methods of discontinuing mechanical ventilation are SIMV, pressure-support ventilation (PSV) and T-tube. Two well-designed, randomized, multicenter studies[1, 2] have compared the above methods of weaning. Brochard et al[2] studied 456 medical-surgical patients being considered for weaning. Three hundred and forty-seven patients (76%) were successfully extubated after a single 2 h T-piece trial. The remaining 109 patients (24%) who failed an initial trial of spontaneous breathing were randomized to be weaned by one of three strategies: T-piece trials of increasing duration until 2 h could be tolerated; SIMV with attempted reductions of two to four breaths/min, twice a day, until four breaths/min could be tolerated; and PSV with attempted reductions of 2-4 cmH_2O twice a day until 8 cmH_2O could be tolerated. Patients randomized to the three strategies were similar with regard to disease severity and duration of ventilation before weaning. There was no difference in the duration of weaning between the T-piece and SIMV groups, but PSV led to significantly shorter duration of weaning compared with the combined T-piece and SIMV cohorts (5.7 ± 3.7 days versus 9.3 ± 8.2 days). [2]

Esteban et al [1] performed a similar study of 546 medical-surgical patients. In that study, 416 (76%) patients were successfully extubated on their first day of weaning after a T-piece trial. The 130 patients who failed were randomized to undergo weaning by the following strategies: once a day T-piece trial; two or more T-piece or continuous positive airway pressure trials each day as tolerated; PSV with attempts at reduction of 2-4 cmH_2O at least twice a day; and SIMV with attempts at reduction by two to four breaths/min at least twice a day. Patients assigned to the four groups were similar with regard to demographic characteristics, acuity of illness and cardiopulmonary variables. The weaning success rate was significantly better with once daily and multiple T-trials than with PSV and SIMV. PSV was not superior to SIMV. The median duration of weaning was 5days for SIMV, 4 days for PSV and 3 days for the T-piece regimens. [1]

The studies by Brochard et al [2] and Esteban et al[1] yielded two important common conclusions: first, the pace of weaning depends on the manner in which the technique is applied; and second, that SIMV is the least efficient technique of weaning. With respect to PSV and intermittent trials of T-tube, a clear superiority of one technique over the other has not yet been established. The conflicting results in those studies concerning these two techniques may be explained, at least in part, by differences among the two studies in the criteria for weaning progress and the criteria for extubation.

Role of noninvasive mechanical ventilation in the weaning process:

Two randomized studies[41-43] [have evaluated the usefulness of noninvasive ventilation (NIV) as a weaning technique. In the study by Nava et al,[41] 50 patients with COPD who failed a T-tube trial after 36-48 h of mechanical ventilation were randomized to either immediate extubation with noninvasive pressure support via a face mask and a standard ventilator, or continued pressure support via an endotracheal tube. Both groups underwent trials of spontaneous breathing at least twice each day and reductions in the pressure support level of 2-4 cmH_2O/day as tolerated in an attempt to discontinue mechanical ventilation entirely. Compared with patients who were weaned while intubated, the group that was weaned with NIV had a lower rate of nosocomial pneumonia (0% versus 28%), a significantly higher weaning rate at 60 days (88% versus 68%), and a significantly lower 60-day mortality rate (8% versus 28%).[41]

In the study by Girault et al[42]33 patients with chronic respiratory failure who failed a 2-h T-piece weaning trial of spontaneous breathing were randomized to either extubation and NIV (n = 17) or conventional invasive PSV (n = 17). No differences were observed between the two groups with respect to clinical and functional characteristics, either at admission to the intensive care unit or at randomization. In the conventional invasive ventilation protocol, 75% of patients were successfully weaned and extubated versus 76.5% in the NIV group. As expected by the study design, the duration of endotracheal intubation was significantly shorter in the NIV group than in the control group (4.6 ± 1.5days versus 7.7 ± 3.8 days; P = 0.004). The total duration of ventilatory support related to weaning, however, was significantly higher in the NIV group (11.5 ± 5.2 days versus 3.5 ± 1.4 days; P <0.001). The durations of intensive care unit and hospital stay and the 3-month survival were similar in the two groups.[42]

The use of NIV to facilitate weaning has not been evaluated in postoperative patients or in those with altered neurologic status, haemodynamic instability, or any of a number of severe concomitant diseases. Nonetheless, NIV may become an important weaning mode in selected patients if its success is replicated in other trials.

Jiang et al [43] evaluated the role of NIV in preventing reintubation after elective or unplanned extubation. They conducted a prospective study in 93 extubated patients who were randomly assigned to receive either biphasic positive airway pressure via face mask or unassisted oxygen therapy. There was no significant difference in the percentage of patients who required reintubation (15% in the unassisted oxygen therapy group and 28% in the biphasic positive airway pressure group). [43]

After discussing methods of weaning from mechanical ventilator ,here is a discussion about COPD with more details than mentioned above. Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease and die prematurely from it or its complications.[44, 45] and the Global Burden of Disease Study projected that COPD will become the third leading cause of death worldwide by 2020. [44, 45]

Definition:

COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. [46]

Epidemiology and disease burden:

In the past, imprecise and variable definitions of COPD have made it difficult to quantify prevalence, morbidity and mortality. Furthermore, the under recognition and under diagnosis of COPD lead to significant underreporting. The extent of the underreporting varies across countries and depends on the level of awareness and understanding of COPD among health professionals, the organization of health care services to cope with chronic diseases, and the availability of medications for the treatment of COPD. [47]

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches. Survey methods can include: self report of a doctor diagnosis of COPD or equivalent condition, spirometry with or without a bronchodilator and questionnaires that ask about the presence of respiratory symptoms.[48, 49]

COPD is a costly disease with both direct costs (value of health care resources devoted to diagnosis and medical management) and indirect costs (monetary consequences of disability, missed work, premature mortality, and caregiver or family costs resulting from the illness).[50] In the United States in 2002, the direct costs of COPD were $ 18 billion and the indirect costs totaled $ 14.1 billion. [51] Costs per patient will vary across countries since these costs depend on how health care is provided and paid.[52]

There is a striking direct relationship between the severity of COPD and the cost of care, and the distribution of costs changes as the disease progresses. [53] For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases, as illustrated by data from Sweden shown in **(Figure 1)**. [53]

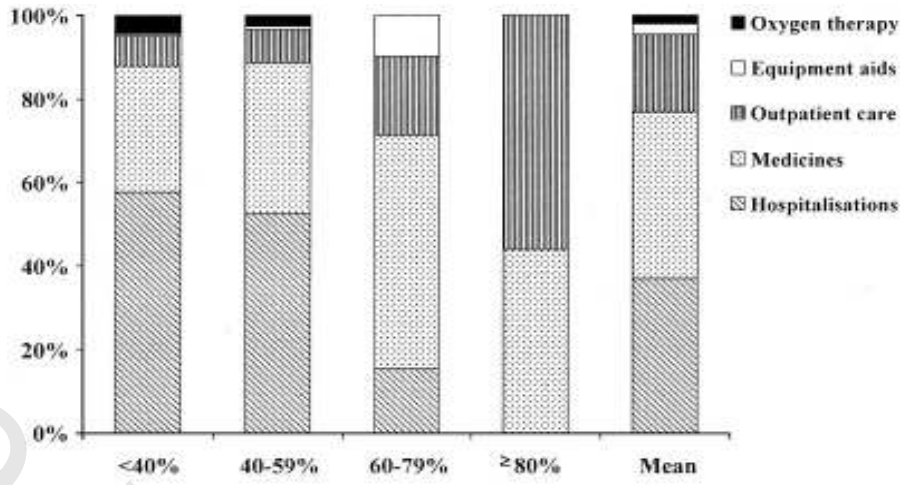

Figure (1) Distribution of direct costs of COPD by Severity [53]

The Global Burden of Disease Study has projected COPD mortality rates from 1990-2020 and estimates that COPD will account for over 6 million deaths per year in 2020, which will move COPD from the sixth to the third leading cause of death worldwide over this period. The overall mortality from COPD will probably increase in Europe due to the increased proportion of females who smoke, as well as the increased age of the population.[54] **Figure (2)** shows age adjusted death rates for COPD in 19 European countries. [54]

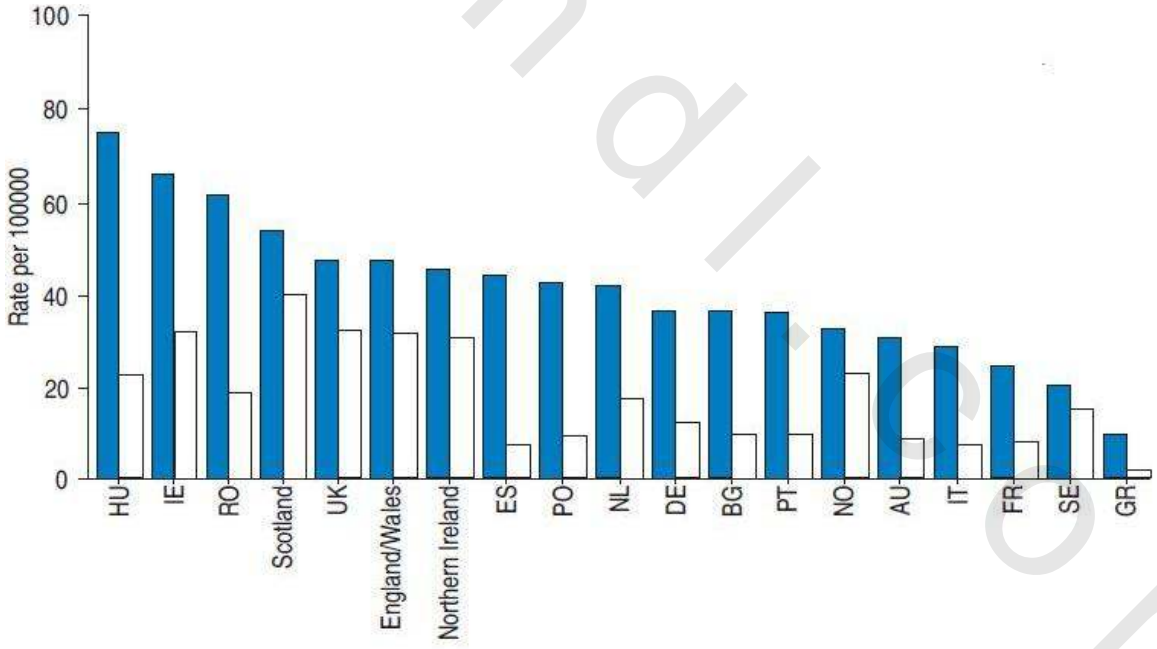

Figure (2): Age adjusted death rates for COPD for males and females in 19 European countries. [54]

The Global Burden of Disease Study designed a method to estimate the fraction of mortality and disability attributable to major diseases and injuries using a composite measure of the burden of each health problem, the Disability Adjusted Life Year (DALY).[45] The DALYs for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. According to the projections, COPD will be the fifth leading cause of DALYs lost worldwide in 2020, behind ischemic heart disease, major depression, traffic accidents, and cerebrovascular disease. [55]

Risk factors:

Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD, which led to the incorporation of smoking cessation programs as a key element of COPD prevention. However, although smoking is the best studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiological studies that nonsmokers may develop chronic airflow obstruction. [56, 57] Other risk factors for COPD are presented in table (1). [46]

Table (1): Risk Factors for COPD [46]

Genes
Exposure to particles
Tobacco smoke
Occupational dusts, organic and inorganic
Indoor air pollution from heating and cooking with biomass in poorly vented dwellings
Outdoor air pollution
Lung growth and development
Oxidative stress
Gender
Age
Respiratory infections
Previous tuberculosis
Socioeconomic status
Nutrition
Co-morbidities

Pathology:

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature **(Table 2)**. [58-61] The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation. [58-61]

Table (2): Pathological Changes in COPD [58-61]

Proximal airways (trachea, bronchi > 2 mm internal diameter)
Inflammatory cells: Macrophages, CD8+ (cytotoxic) T lymphocytes, few neutrophils or eosinophils
Structural changes: Goblet cells, enlarged submucosal glands (both leading to mucus hypersecretion), squamous metaplasia of epithelium
Peripheral airways (bronchioles < 2mm internal diameter)
Inflammatory cells: Macrophages, T lymphocytes (CD8+ > CD4+), B lymphocytes, lymphoid follicles, fibroblasts, few neutrophils or eosinophils
Structural changes: Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudate, airway narrowing (obstructive bronchiolitis)
Increased inflammatory response and exudate correlated with disease severity
Lung parenchyma (respiratory bronchioles and alveoli)
Inflammatory cells: Macrophages, CD8+ T lymphocytes
Structural changes: Alveolar wall destruction, apoptosis of epithelial and endothelial cells5
• Centrilobular emphysema: dilatation and destruction of respiratory
bronchioles; most commonly seen in smokers
• Panacinar emphysema: destruction of alveolar sacs as well as respiratory
bronchioles; most commonly seen in alpha-1 antitrypsin deficiency
Pulmonary vasculature
Inflammatory cells: Macrophages, T lymphocytes
Structural changes: Thickening of intima, endothelial cell dysfunction, smooth muscle pulmonary hypertension

Pathogenesis:

The inflammation in the respiratory tract of patients with COPD appears to be an amplification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplification are not yet understood but may be genetically determined. Some patients develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown.[62] Lung inflammation is further amplified by oxidative stress and an excess of proteinases in the lung. Together, these mechanisms lead to the characteristic pathological changes in COPD **(Figure 3)**. [62]

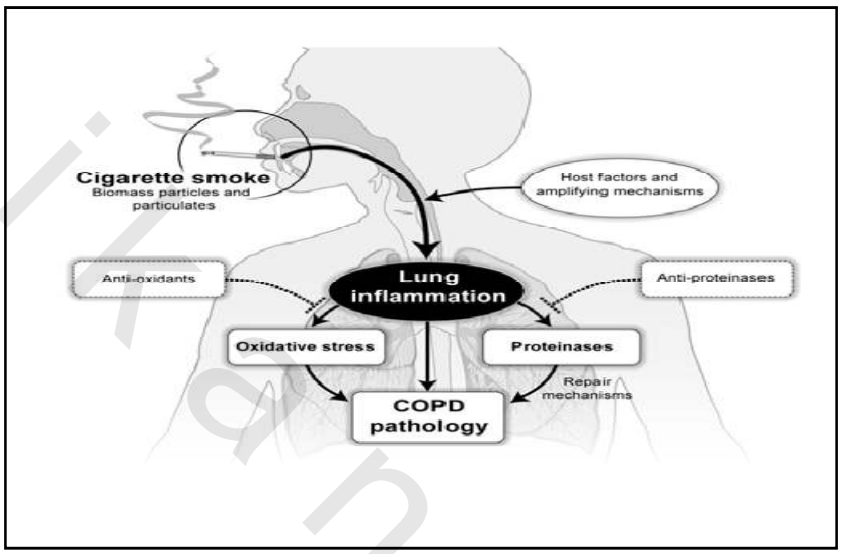

Figure (3): Pathogenesis of COPD [62]

COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes1 **(Table 3).**[63-65] These cells release inflammatory mediators and interact with structural cells in the airways and lung parenchyma. [63-65]

The wide variety of inflammatory mediators that have been shown to be increased in COPD patients attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors). Examples of each type of mediator are listed in **(Table 4)**. [66]

Table (3): Inflammatory cells in COPD [63-65]

Neutrophils: in sputum of normal smokers. Further in COPD and related to disease severity. Few neutrophils are seen in tissue. They may be important in mucus hypersecretion and through release of proteases.
Macrophages: Greatly numbers are seen in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid. Derived from blood monocytes that differentiate within lung tissue. Produce increased inflammatory mediators and proteases in COPD patients in response to cigarette smoke and may show defective phagocytosis.
T lymphocytes: Both CD4+ and CD8+ cells are increased in the airway wall and lung parenchyma, with CD8+:CD4+ ratio. CD8+ T cells (Tc1) and Th1 cells which secrete interferone and express the chemokine receptor CXCR39. CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction.
B lymphocytes: in peripheral airways and within lymphoid follicles, possibly as a response to chronic colonization and infection of the airways.
Eosinophils: eosinophil proteins in sputum and eosinophils in airway wall during exacerbations.
Epithelial cells: May be activated by cigarette smoke to produce inflammatory mediators.

Table (4): Inflammatory mediators involved in COPD [66]

Chemotactic factors:
Lipid mediators: e.g., leukotriene B4 (LTB4) attracts neutrophils and T lymphocytes.
Chemokines: e.g., interleukin-8 (IL-8) attracts neutrophils and monocytes.
Proinflammatory cytokines: e.g., tumor necrosis factor-α (TNF- α), IL-1β, and IL-6 amplify the inflammatory process and may contribute to some of the systemic effects of COPD.
Growth factors: e.g., transforming growth factor-ß (TGF-ß) may induce fibrosis in small airways.

Oxidative stress may be an important amplifying mechanism in COPD.[67] Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients. Oxidative stress is further increased in exacerbations. Oxidants are generated by cigarette smoke and other inhaled particulates, and released from activated inflammatory cells such as macrophages and neutrophils.[68]There may also be a reduction in endogenous antioxidants in COPD patients. Oxidative stress has several adverse consequences in the lungs, including activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion, and stimulation of increased plasma exudation. Many of these adverse effects are mediated by peroxynitrite, which is formed via an interaction between superoxide anions and nitric oxide. In turn, the nitric oxide is generated by inducible nitric oxide synthase, which is expressed in the peripheral airways and lung parenchyma of COPD patients. Oxidative stress may also account for a reduction in histone deacetylase activity in lung tissue from COPD patients, which may lead to enhanced expression of inflammatory genes and also a reduction in the anti-inflammatory action of glucocorticosteroids. [69]

There is compelling evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other **(Table 5)**. [64, 65] Protease mediated destruction of elastin, a major connective tissue component in lung parenchyma, is an important feature of emphysema and is likely to be irreversible. [64, 65]

Table (5): Proteases and Antiproteases Involved in COPD[64, 65]

Increased Proteases:	**Decreased Antiproteases:**
• Serine proteases • Neutrophil elastase • Cathepsin G • Proteinase 3 • Elafin • Cysteine proteinases • Cathepsins B, K, L, S • Matrix metalloproteinases (MMPs) • MMP-8, MMP-9, MMP-12 • (TIMP1-4)	• alpha-1 antitrypsin • alpha-1 antichemotrypsin • Secretory leukoprotease inhibitor • Cystatins • Tissue inhibitors of MMP 1-4

Pathophysiology:

As regarding the pathophysiology, there is now good understanding of how the underlying disease process in COPD leads to the characteristic physiologic abnormalities and symptoms.

The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD. [70] This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV_1, it does contribute to air trapping during expiration. This is especially so, as alveolar attachments to small airways are destroyed when the disease becomes more severe. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise (when this abnormality is known as dynamic hyperinflation), and this results in dyspnea and limitation of exercise capacity. It is now thought that hyperinflation develops early in the disease and is the main mechanism for exertional dyspnea. [71]

Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer worsens as the disease progresses. The severity of emphysema correlates with arterial PO_2 and other markers of ventilation-perfusion(V_A/Q)imbalance. Peripheral airway obstruction also results in V_A/Q imbalance, and combines with ventilatory muscle impaired function in severe disease to reduce ventilation, leading to carbon dioxide retention. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q abnormalities. [71]

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, it is due to mucous metaplasia with increased number of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR).[72]

Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that included intimal hyperplasia and later smooth muscle hypertrophy. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually cor-pulmonale. [73]

It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases. [74, 75] Cachexia is commonly seen in patients with severe COPD. There may be a loss of skeletal muscle mass and weakness as a result of increased apoptosis and/or muscle disuse. Patients with COPD also have increased likeliness of having osteoporosis, depression and chronic anemia.[76]Increased concentrations of inflammatory mediators, including TNF-α, IL-6 and oxygen derived free radicals, may mediate some of these systemic effects. There is an increase in the risk of cardiovascular diseases, which is correlated with an increase in C-reactive protein (CRP).[77]

Types of COPD:

Earlier definitions have distinguished different types of COPD (i.e. emphysema, chronic bronchitis, asthma), a distinction that is not included in the GOLD definition. [78-80] Chronic bronchitis is defined by a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded.[81] This definition has been used in many studies, despite the arbitrarily selected symptom duration and lack of biologic rationale. Emphysema is defined by abnormal and permanent enlargement of the airspaces that are distal to the terminal bronchioles. This is accompanied by destruction of the airspace walls, without obvious fibrosis (i.e. there is no fibrosis visible to the naked eye).[82] Exclusion of obvious fibrosis was intended to distinguish the alveolar destruction due to emphysema from that due to the interstitial pneumonias. However, many studies have found increased collagen in the lungs of patients with mild COPD, indicating that fibrosis exists.[83, 84] Emphysema can exist in individuals who do not have airflow obstruction; however, it is more common among patients who have moderate or severe airflow obstruction.[85]Asthma is "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variably, airflow obstruction within the lung that is often reversible either spontaneously or with treatment".[58]

The following observations are consistent with the notion that different types of COPD exist: The bronchial inflammation of asthma is different from that of chronic bronchitis or emphysema. [70, 86, 87] Asthma is associated with CD4+ T-lymphocytes, eosinophils, and increased interleukin (IL)-4 and IL-5. In contrast, chronic bronchitis and emphysema are associated with CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages.[88-91] Asthma affects patients of all ages and has a low mortality to prevalence ratio. In contrast, chronic bronchitis and emphysema typically manifest in the sixth decade of life and have a higher mortality to prevalence ratio. .[88-91]

Staging:

The FEV_1 (expressed as a percentage of predicted) is often used to stage disease severity. The FEV_1/FVC ratio is not used for this purpose because measurement of FVC becomes less reliable as the disease progresses (the long exhalations are difficult for the patients).

Different clinical practice guidelines use different cut-off values, but most are similar to the GOLD staging system **(Table 6)**. [85]

Table (6): Classification of severity of COPD [85]

Stage	Characteristics
I: Mild COPD	FEV1/FVC <70 percent
	FEV1 >80 percent predicted
II: Moderate COPD	FEV1/FVC <70 percent
	50 percent < FEV1 <80 percent predicted
III: Severe COPD	FEV1/FVC <70 percent
	30 percent < FEV1 <50 percent predicted
IV: Very Severe COPD	FEV1/FVC <70 percent
	FEV1 <30 percent predicted or FEV1 <50 percent predicted plus chronic respiratory failure

*FEV1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO2) less than 60 mm Hg (8.0 kPa) with or without arterial partial pressure of CO2 (PaCO2) greater than 50 mm Hg (6.7 kPa) while breathing air at sea level.

This staging system has been criticized for underestimating the importance of the extrapulmonary manifestations of COPD in predicting outcome. The BODE index addresses this criticism **(Table 7)**.[92] The four factors included in the BODE index are weight (BMI), airway obstruction (FEV_1), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walk distance). This index provides better prognostic information than the FEV_1 alone and can be used to assess therapeutic response.[92-95]

Table (7): (BODE) index [92]

Variable	Points on BODE index			
	0	1	2	3
FEV_1 (percent of predicted)*	>65	50-64	36-49	<35
Distance walked in 6 minutes (m)	>350	250-349	150-249	<149
MMRC dyspnea scale**	0-1	2	3	4
Body-mass index***	>21	<21		

*FEV_1 denotes forced expiratory volume in one second. The FEV_1 categories are based on stages identified by the American Thoracic Society.
** Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
***The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Definition of Acute Exacerbation of COPD (AECOPD):

AECOPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD. [96, 97]

Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting co-morbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests as shown in **(Table 8).** [97] In stage IV (Very Severe COPD), the most important sign of a severe exacerbation is a change in the mental status of the patient and this signals a need for immediate evaluation in the hospital. [97]

Table (8): Medical history and the signs of severity in the assessment of AECOPD [97]

Medical History	**Signs of Severity**
Severity of FEV_1	Use of accessory respiratory muscles
Duration of worsening or new symptoms	Paradoxical chest wall movements
Number of previous episodes (exacerbations/ hospitalizations)	Worsening or new onset central cyanosis
Comorbidities	Development of peripheral edema
Present treatment regimen	Hemodynamic instability
	Signs of right heart failure
	Reduced alertness

Classification of AECOPD:

The classification of Acute Exacerbation of COPD includes three types depending on the number of the cardinal symptoms present as shown in **(Table 9)**. [98]

Table (9): Classification of Acute Exacerbation of COPD[98]

Type III	All 3 cardinal symptoms*
Type II	2 of 3 cardinal symptoms
Type I	1 of 3 cardinal symptoms and 1 of the following: Upper respiratory tract infection in the past 5 days Fever without other apparent cause Increased wheezing Increased cough Increased in respiratory rate or heart rate by 20% above baseline

*Cardinal symptoms = (1) worsening dyspnea, (2) increase in sputum purulence, (3) increase in sputum volume.

Management of AECOPD:

A range of criteria to consider for hospital assessment/ admission for exacerbations of COPD are shown in **(Table 10)**.[99, 100] Some patients need immediate admission to an intensive care unit (ICU) **(Table 11)**. [99, 100]Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Table (10): Indications for Hospital Assessment or Admission for Exacerbations of COPD [99, 100]

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

Table (11): Indications for ICU Admission of Patients with Exacerbations of COPD[99, 100]

- 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, 40 mmHg), and/or severe/worsening hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mmHg), 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

The first actions when a patient reaches the emergency department are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening and should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital as shown in **(Figure 4)**.[78, 101-103]

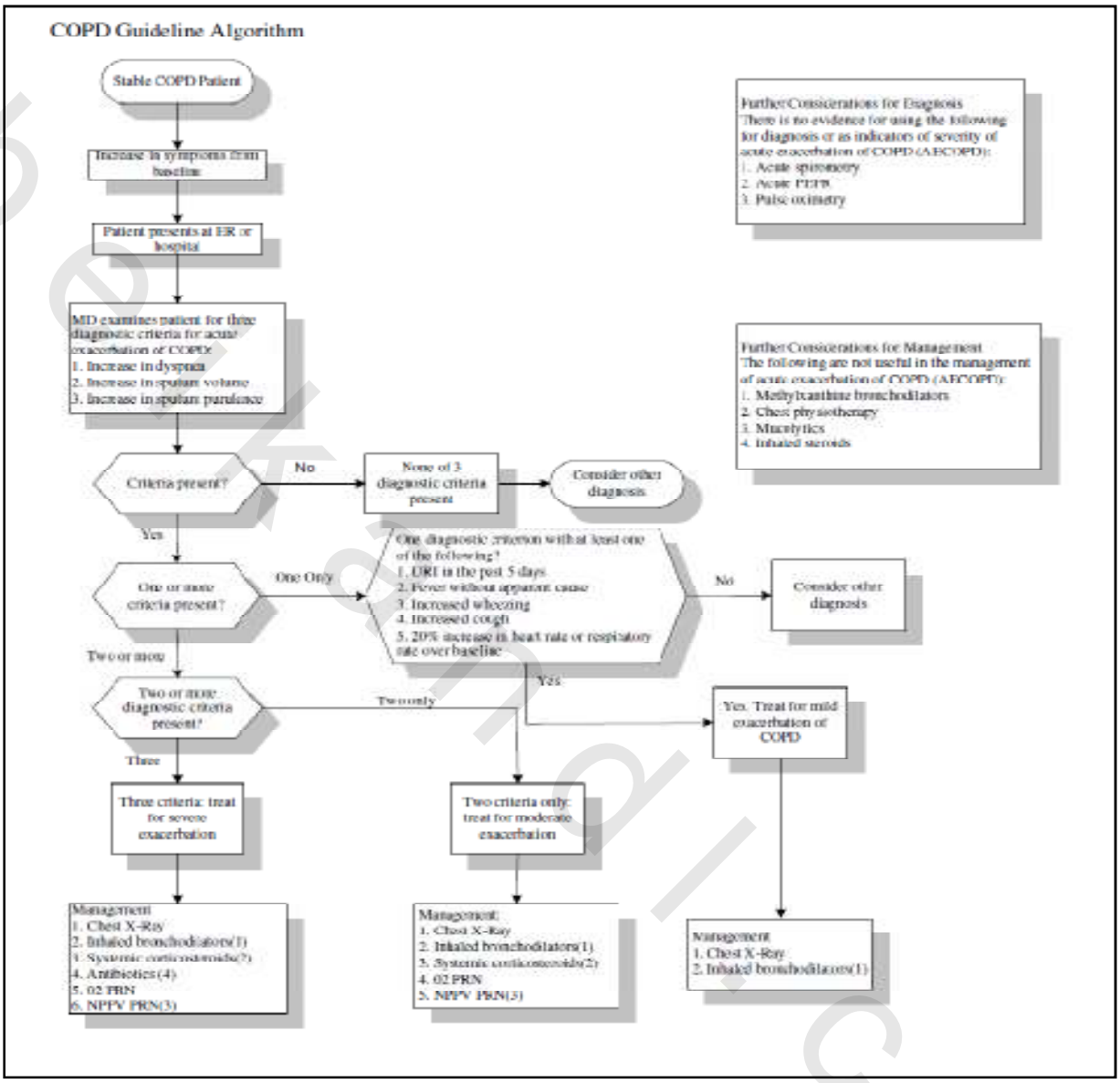

Figure (4): Algorithm for Management of Exacerbations of COPD [78, 101-103]

Treatment Goals:

Successful management of acute exacerbations of COPD in either the inpatient or outpatient setting requires attention to a number of key issues: [104, 105]

- Identifying and ameliorating the cause of the acute exacerbation, if possible.
- Optimizing lung function by administering bronchodilators and other pharmacologic agents.
- Assuring adequate oxygenation and secretion clearance averting the need for intubation, if possible.
- Preventing complications of immobility, such as thromboemboli and deconditioning.
- Addressing nutritional needs. [104, 105]

Treatment strategies include:

- Controlled oxygen therapy.
- Bronchodilator therapy.
- Glucocorticosteroids.
- Antibiotics.
- Other therapies: muco-active agents, methylxanthines, and respiratory stimulants.
- Chest physiotherapy.
- Ventilatory support.

1- Controlled oxygen therapy:

Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 > 8.0 kPa, 60 mm Hg, or SaO_2 > 90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. [106]

A high FiO_2 is not required to correct the hypoxemia associated with most acute exacerbations of COPD. Venturi masks (high flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient. Inability to correct hypoxemia with a relatively low FiO_2 should prompt consideration of pulmonary emboli, acute respiratory distress syndrome, pulmonary edema, or severe pneumonia as the cause of respiratory failure. [107]

Adequate oxygenation must be assured, even if it leads to acute hypercapnia. Hypercapnia is generally well tolerated in patients whose arterial carbon dioxide tension ($PaCO_2$) is chronically elevated. However, mechanical ventilation may be required if

hypercapnia is associated with depressed mental status, profound acidemia, or cardiac dysrhythmias. [108]

2- Bronchodilator therapy:

Short-acting inhaled β_2 agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD.[79, 100, 106] If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either β_2 agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.

These medications may be administered via a nebulizer or a metered dose inhaler (MDI) with a spacer device. [109] Despite evidence that the MDI may have equal efficacy during acute exacerbations of COPD, many clinicians prefer nebulized therapy on the presumption of more reliable delivery of drug to the airway as it is found that many patients have difficulty using proper MDI technique in this setting. [46]

Typical doses of albuterol for this indication are 2.5 mg (diluted to a total of 3 mL) by nebulizer every one to four hours as needed, or 4 to 8 puffs (90 mcg per puff) by MDI with a spacer every one to four hours as needed. Increasing the dose of nebulized albuterol to 5 mg does not have a significant impact on spirometry or clinical outcomes. Similarly, continuously nebulized beta agonists have not been shown to confer an advantage. [110]

Subcutaneous injection of short-acting beta adrenergic agonists is reserved for situations in which inhaled administration is not possible. Parenteral use of these agents results in greater inotropic and chronotropic effects, which may cause arrhythmias or myocardial ischemia in susceptible individuals. [110]

Inhaled short-acting anticholinergic agents (e.g. ipratropium bromide) are used with inhaled short-acting beta adrenergic agonists to treat exacerbations of COPD. [46]This is based on several studies that found that combination therapy produces bronchodilation in excess of that achieved by either agent alone in patients with a COPD exacerbation, an asthma exacerbation, or stable COPD. [109, 111, 112] However, this finding has not been universal in patients having an exacerbation of COPD. [111, 112] Typical doses of ipratropium for this indication are 500 mcg by nebulizer every four hours as needed. Alternatively, 2 puffs (18 mcg per puff) by MDI with a spacer every four hours as needed.

3- Glucocorticosteroids:

Systemic glucocorticoid therapy improves lung function and treatment success, while reducing the length of hospital stay. [113-116] This was illustrated by a trial that randomly assigned 271 patients having a COPD exacerbation to receive either systemic glucocorticoids or placebo for up to two weeks.[115] Systemic glucocorticoid therapy significantly reduced the 30 day treatment failure rate (23 versus 33 percent), the 90 day treatment failure rate (37 versus 48 percent), and hospital stay (eight versus ten days), while improving lung function.[115]

Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD. [115, 117] Intravenous glucocorticoids should be given to patients who present with a severe exacerbation, who respond poorly to oral glucocorticoids, who are vomiting, or who may have impaired absorption due to decreased splanchnic perfusion (e.g. patients in shock). [115, 117]

Oral glucocorticoids are rapidly absorbed (peak serum levels achieved at one hour after ingestion) with virtually complete bioavailability and their efficacy is comparable to that with intravenous therapy. This was demonstrated in a double-blind trial in which 210 patients having a COPD exacerbation were randomly assigned to receive either oral or intravenous prednisolone (60 mg daily) for five days. [118] There were no differences between the two groups in treatment failure, length of hospital stay, improvement in spirometry, or improvement in quality of life. [118]

The efficacy of inhaled glucocorticoids on the course of a COPD exacerbation has not been studied in randomized trials. Thus, they should not be used as a substitute for systemic glucocorticoid therapy. [46]

The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Prolonged treatment does not result in greater efficacy and increases the risk of side effects (e.g. hyperglycemia, muscle atrophy). Lower doses (e.g. equivalent of 30 to 40 mg of prednisone) may be equally effective and safe. [46] Frequently used regimens include: Intravenous Methylprednisolone (60 to 125 mg, two to four times daily) or oral Prednisone (40 to 60 mg orally, once daily). [115]

The duration of systemic glucocorticoid therapy varies from patient to patient and exacerbation to exacerbation. As a rough guide, most exacerbations should be treated with full dose therapy for 7 to 10 days. [46] After this time, many pulmonologists taper over about seven days as a trial to see if continued glucocorticoid therapy is required. Tapering solely because of concerns about adrenal suppression is not necessary if the duration of therapy is less than three weeks (a duration too brief to cause adrenal atrophy). [46]

4- Antibiotics:

Randomized placebo controlled studies of antibiotic treatment in exacerbations of COPD have demonstrated mixed results of antibiotics on lung function,[116, 119] and a randomized controlled trial has provided evidence for a significant beneficial effect of antibiotics in COPD patients who presented with an increase in all three of the following cardinal symptoms: dyspnea, sputum volume, and sputum purulence.[98] There was also some benefit in those patients with an increase in only two of these cardinal symptoms.

A study on non hospitalized patients with exacerbations of COPD showed a relationship between the purulence of the sputum and the presence of bacteria,[120] suggesting that these patients should be treated with antibiotics if they also have at least one of the other two cardinal symptoms (dyspnea or sputum volume). However, these criteria for antibiotic treatment of exacerbations of COPD have not been validated in other studies. 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. [121]

Based on the current available evidence,[106, 122] antibiotics should be given to:

- Patients with AECOPD with the following three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence (Evidence B).
- Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C).
- Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive) (Evidence B).

The infectious agents in COPD exacerbations can be viral or bacterial. [123, 124] The predominant bacteria recovered from the lower airways of patients with COPD exacerbations are H. influenzae, S. pneumoniae, and M. catarrhalis.[123, 125-127] So-called atypical pathogens, such as Mycoplasma pneumoniae and Chlamydia pneumonia, [127, 128] have been identified in patients with COPD exacerbations, but because of diagnostic limitations the true prevalence of these organisms is not known.

Studies in patients with severe underlying COPD who require mechanical ventilation[129, 130] have shown that other microorganisms, such as enteric gram-negative bacilli and P. aeruginosa, may be more frequent. Other studies have shown that the severity of the COPD is an important determinant of the type of microorganism. [131, 132] In patients with mild COPD exacerbations, S. pneumonia is predominant. As FEV1 declines and patients have more frequent exacerbations and/or comorbid diseases, H. influenzae and M. catarrhalis become more frequent, and P. aeruginosa may appear in patients with severe airway limitation **(Table 12).** [106, 123]

The risk factors for P. aeruginosa infection are recent hospitalization (2 or more days' duration in the past 90 days), frequent administration of antibiotics (4 courses in the last year), severe COPD exacerbations (FEV1 <50 percent predicted), and isolation of P. aeruginosa during a previous exacerbation [133]or colonization during a stable period. [131, 132]

Table (12): Stratification of patients with COPD exacerbated for antibiotic treatment and potential microorganisms involved in each group[106, 123]

Group	Definition[a]	Microorganisms
Group A	Mild exacerbation: No risk factors for poor outcome	H. influenzae S. pneumoniae M. catarrhalis Chlamydia pneumoniae Viruses
Group B	Moderate exacerbation with risk factor(s) for poor outcome	Group A plus, presence of resistant organisms (β-lactamase producing, penicillin-resistant S pneumoniae), Enterobacteriaceae (K.pneumoniae, E. coli, Proteus, Enterobacter, etc)
Group C	Severe exacerbation with risk factors for P. aeruginosa infection	Group B plus: P. aeruginosa

a. Risk factors for poor outcome in patients with COPD exacerbation: presence of comorbid diseases, severe COPD, frequent exacerbations (>3 /yr), and antimicrobial use within last 3 months).

Table (13) [106, 123, 134] provides recommended antibiotic treatment for exacerbations of COPD, although it must be emphasized that most of the published studies related to the use of antibiotics were done in chronic bronchitis patients. The route of administration (oral or intravenous) depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred; if the IV route must be used, switching to the oral route is recommended when clinical stabilization permits. Based on studies of the length of use of antibiotics for chronic bronchitis,[135-137] antibiotic treatment in patients with COPD exacerbations could be given for 3 to 7 days (Evidence D).

Table (13): Antibiotic treatment in exacerbations of COPD [a,b](106, 123, 134)

	Oral Treatment (No particular order)	Alternative Oral Treatment (No particular order)	Parenteral Treatment (No particular order)
Group A	Patients with only one Cardinal symptom [c] should not receive antibiotics If indication then: • β-lactam • (Penicillin, Ampicillin/ • Amoxicillin [d]) • Tetracycline • Trimethoprim/Sulfamethox -azole	• β-lactam/ β-lactamase Inhibitor (Co-amoxiclav) • Macrolides (Azithromycin, Clarithromycin, Roxithromycin e) • Cephalosporins - 2nd or 3rd generation • Ketolides (Telithromycin)	
Group B	• β-lactam/ β-lactamase Inhibitor (Co-amoxiclav)	• Fluoroquinolones [e] (Gemifloxacin, Levofloxacin, Moxifloxacin)	• β-lactam/ β-lactamase Inhibitor (Co-amoxiclav, ampicillin/ sulbactam) • Cephalosporins - 2nd or 3rd generation • Fluoroquinolones e (Levofloxacin, Moxifloxacin)
Group C	In patients at risk for pseudomonas infections: • Fluoroquinolones e (Ciprofloxacin, Levofloxacin - high dose [f])		• Fluoroquinolones e • (Ciprofloxacin, Levofloxacin - high dose f) or • β-lactam with P.aeruginosa activity

a. All patients with symptoms of a COPD exacerbation should be treated with additional bronchodilators ± glucocorticosteroids.
b. Classes of antibiotics are provided (with specific agents in parentheses). In countries with high incidence of S. pneumoniae resistant to penicillin, high dosages of Amoxicillin or Co-amoxiclav are recommended. (See Figure 5-4-6 for definition of Groups A, B, and C.)
c. Cardinal symptoms are increased dyspnea, sputum volume, and sputum purulence.
d. This antibiotic is not appropriate in areas where there is increased prevalence of β-lactamase producing H. influenzae and M. catarrhalis and/or of S. pneumoniae resistant to penicillin.
e. Not available in all areas of the world.
f. Dose 750 mg effective against P. aeruginosa

5- Other therapies:

a) Mucoactive agents:

There is little evidence supporting the use of mucoactive agents (e.g. N-acetylcysteine) in acute exacerbations of COPD.[101, 138, 139] Some mucoactive agents may worsen bronchospasm. The lack of efficacy of mucoactive agents in the treatment of COPD exacerbations was best demonstrated by a double-blind trial that randomly assigned 50 patients with a COPD exacerbation to receive N-acetylcysteine (600 mg, twice daily) or placebo for seven days. There was no difference in the rate of change of FEV_1, vital capacity, oxygen saturation, breathlessness, or length of stay between the two groups. [139]

b) Methylxanthines:

Aminophylline and theophylline are not recommended for the treatment of acute exacerbations of COPD. [101] Randomized controlled trials of intravenous aminophylline in this setting have failed to show efficacy beyond that induced by inhaled bronchodilator and glucocorticoid therapy. In addition to lack of efficacy, methylxanthines caused significantly more nausea and vomiting than placebo and trended toward more frequent tremor, palpitations, and arrhythmias. [101]

The potential efficacy of theophylline must be balanced against toxicity. This is particularly important because of theophylline's narrow therapeutic index. When compared to acute intoxication, chronic theophylline overmedication is associated with a greater frequency of major toxicity, occurs at relatively lower theophylline levels, and cannot be predicted by the peak serum theophylline concentration. [140] Seizures may occur at plasma theophylline levels of 14 to 35 mg/L, the risk of seizures is more likely in patients who are older or who have previous brain injury, severe pulmonary disease, or hypoalbuminemia.[141]

It has also been proposed that theophylline might have an adverse effect on the quality of sleep. Of four studies reviewed [142-145] only one found that theophylline disrupted sleep architecture. [142]These trials also showed that theophylline improved both morning lung function and overnight oxygenation. [142-145]

Theophylline may have an important anti-inflammatory mechanism of action. In a randomized crossover study of 16 patients with stable COPD, oral sustained-release theophylline reduced nitrative stress and neutrophil infiltration more than inhaled glucocorticoids at a mean serum concentration of only 6.32 mg/L.[146] It has been proposed that the anti-inflammatory effects of theophylline may be especially relevant to patients with COPD with steroid resistance and/or a clinical pattern of frequent exacerbations, and may reduce disease progression. [147]

c) Respiratory stimulants:

Respiratory stimulants are not recommended for acute respiratory failure. [100] Doxapram, a nonspecific but relatively safe respiratory stimulant available in some countries as an intravenous formulation, should be used only when noninvasive intermittent ventilation is not available or not recommended. [148]

6- Chest physiotherapy:

Mechanical techniques to augment sputum clearance, such as directed coughing, chest physiotherapy with percussion and vibration, intermittent positive pressure breathing, and postural drainage, have not been shown to be beneficial in COPD and may provoke bronchoconstriction. Their use in acute exacerbations of COPD is not supported by clinical trials. [46, 101, 138]

7- Ventilatory support:

The primary objectives of mechanical ventilatory support in patients with COPD exacerbations are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive intermittent ventilation using either negative or positive pressure devices and invasive (conventional) mechanical ventilation by orotracheal tube or tracheostomy.

Non-invasive mechanical ventilation:

Noninvasive intermittent ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80-85%.[149-152] These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases P_aCO_2), decreases respiratory rate, severity of breathlessness, and length of hospital stay. More importantly, mortality-or its surrogate, intubation rate-is reduced by this intervention. [152-155] However, NIV is not appropriate for all patients, as summarized in **(Table 14)**.[106, 149, 150, 156]

Table (14): Indications and Relative Contraindications for NIV[106, 150, 156]

Selection criteria
• Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
• Moderate to severe acidosis (pH ≤ 7.35) and/ or hypercapnia (P_aCO_2 > 6.0 kPa, 45 mm Hg)
• Respiratory frequency > 25 breaths per minute
Exclusion criteria (any may be present)
• Respiratory arrest
• Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
• Change in mental status; uncooperative patient
• High aspiration risk
• Viscous or copious secretions
• Recent facial or gastroesophageal surgery
• Craniofacial trauma
• Fixed nasopharyngeal abnormalities
• Burns
• Extreme obesity.

Invasive mechanical ventilation:

During exacerbations of COPD the events occurring within the lungs include bronchoconstriction, airway inflammation, increased mucus secretion, and loss of elastic recoil, all of which prevent the respiratory system from reaching its passive functional residual capacity at the end of expiration, enhancing dynamic hyperinflation and increasing the work of breathing. [157, 158] The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown in **(Table 15)**, [159] including failure of an initial trial of NIV. As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV.

Table (15): Indications for Invasive Mechanical Ventilation [159]

• Unable to tolerate NIV or NIV failure.
• Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
• Respiratory frequency > 35 breaths per minute
• Life-threatening hypoxemia
• Severe acidosis (pH < 7.25) and/or hypercapnia (P_aCO_2 > 8.0 kPa, 60 mm Hg)
• Respiratory arrest
• Somnolence, impaired mental status
• Cardiovascular complications (hypotension, shock)
• Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

The use of invasive ventilation in end stage COPD patients 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—an advance directive or "living will"—makes these difficult decisions much easier to resolve. Major hazards include the risk of ventilator acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.

Contrary to some opinions, acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non COPD causes. [160]Despite this, there is evidence that patients who might otherwise survive may be denied admission to intensive care for intubation because of unwarranted prognostic pessimism.[161]A study of a large number of COPD patients with acute respiratory failure reported in hospital mortality of 17-49%.[162] Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before ventilation (FEV1 < 30% predicted), had a non respiratory co-morbidity, or were housebound. Patients who did not have a previously diagnosed comorbid condition, had respiratory failure due to a potentially reversible cause (such as an infection), or were relatively mobile and not using long-term oxygen did surprisingly well with ventilatory support. [162]

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load. [163] By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD.[1, 41, 164] Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate.[2, 165, 166] In patients with COPD that failed extubation, noninvasive ventilation facilitates weaning and prevents reintubation, but does not reduce mortality. [167, 168] A report that included COPD and non-COPD patients showed that noninvasive mechanical ventilation in patients that failed extubation was not effective in averting the need for reintubation and did not reduce mortality. [169]

Ventilatory settings:

Optimal ventilator settings can minimize the work of breathing, but not eliminate it. Conversely, inappropriate settings can create work that is greater than that required for spontaneous breathing.[34, 170, 171]

The clinician must specify numerous settings when mechanical ventilation is initiated, including the inspired oxygen fraction, trigger sensitivity, inspiratory flow rate, tidal volume, ventilatory rate, pressure level, and positive end-expiratory pressure (PEEP).

1- Inspired oxygen fraction:

The fraction of inspired oxygen (F_iO_2) should be adjusted to achieve an arterial oxygen tension (P_aO_2) at least 60 mmHg; higher levels increase the risk of oxygen toxicity without substantially increasing tissue oxygenation. Arterial oxyhemoglobin saturation measured with a pulse oximeter (SpO_2) is often monitored instead of P_aO_2 because it is a noninvasive measure that can be followed continuously.

The target SpO_2 should be considered in the context of the patient's skin pigmentation because SpO_2 can be erroneously elevated in blacks.[172, 173] As an example, an SpO_2 of 92 percent predicts satisfactory oxygenation in white patients, but may be associated with hypoxemia in black patients. A higher target SpO_2 will prevent hypoxemia in black patients, but some patients may develop oxygen toxicity. It is prudent to correlate the SpO_2 and P_aO_2 before determining the target SpO_2.

In our clinical practice, we titrate the F_iO_2 of ventilator-dependent patients to an SpO_2 of 92 percent for white patients and 95 percent for black patients. [172]

2- Triggering:

Ventilators can be triggered by a change in alveolar pressure (i.e. pressure triggered) or flow (i.e. flow triggered): The trigger sensitivity is usually set at -1 to -2 cmH_2O when pressure triggering is used. This means that ventilator-assisted breaths will be triggered when the alveolar pressure decreases to 1 to 2 cmH_2O below atmospheric pressure. The pressure decrease that a patient must generate to trigger a ventilator-assisted breath may be greater than the settings indicate if the demand valve is poorly responsive. [36] Inappropriate breaths may be initiated if the trigger setting is too sensitive, which can cause respiratory alkalosis. Conversely, the work of breathing may be increased if the

trigger setting is not sensitive enough. The trigger sensitivity is usually set at 2 L/min when flow triggering is used. This means that ventilator-assisted breaths will be triggered once the patient's inspiratory effort generates a flow of 2 L/min. Total inspiratory effort is 30 to 40 percent less with flow triggering than pressure triggering in patients receiving intermittent mandatory ventilation (IMV). [174, 175]In contrast, inspiratory effort during triggering is only 10 percent less with flow triggering than pressure triggering in patients receiving pressure support ventilation (PSV). [176] This is of minimal clinical importance because the difference occurs during triggering only, which is a small part of the total inspiratory effort. [176, 177] Inspiratory work does not appear to be impacted by the triggering method during assisted controlled ventilation (ACV). [176]

In practice, flow triggering is used in patients receiving IMV and in a subset of patients receiving PSV, those who have increased inspiratory effort during triggering. We do not have a preference for pressure or flow triggering in patients receiving ACV. We initially set the trigger sensitivity to -2 cm H_2O when we use pressure triggering. We initially set the trigger sensitivity to 2 L/min when we use flow triggering. [176,177]

3- Auto-PEEP:

Intrinsic positive end-expiratory pressure (i.e. intrinsic PEEP or auto-PEEP) can be measured in a relaxed patient by occluding the expiratory port of the ventilator circuit. The pressure recorded on the manometer at end-expiration is the auto-PEEP. [27] It is common in patients with COPD. In a prospective cohort study of 13 patients with COPD who were being mechanically ventilated, all of the patients had measurable auto-PEEP (mean 9.4 cmH_2O), and seven had an auto-PEEP greater than 10 cmH_2O.[178]

Auto-PEEP is an impediment to triggering ventilator-assisted breaths because it increases the amount of respiratory effort that is required to lower the alveolar pressure to the trigger value. As an example, consider a patient whose trigger value is set to -2 cmH_2O. When the auto-PEEP is 10 cmH_2O, the patient must lower the alveolar pressure 12 cmH_2O to reach the trigger value. In contrast, when there is no auto-PEEP, the patient must lower the alveolar pressure only 2 cmH_2O to reach the trigger value. Patients who cannot generate sufficient negative pressure will fail to trigger ventilator-assisted breaths despite obvious respiratory efforts. [179]

The impact of auto-PEEP on triggering breaths was confirmed by a study that compared the breaths that preceded failed attempts to trigger ventilator-assisted breaths (i.e. non-triggered efforts) versus the breaths that preceded successfully triggered ventilator-assisted breaths (i.e. triggered breaths).[180] Those breaths that preceded non-triggered efforts had a shorter expiratory time and a higher tidal volume than triggered breaths, both of which can cause auto-PEEP. When measured directly, auto-PEEP was higher at the onset of the non-triggered efforts than the triggered breaths. Auto-PEEP can be responsible for up to one-third of the total work of breathing. [181]

Applied PEEP decreases the amount by which the patient must reduce the alveolar pressure to trigger ventilator-assisted breaths, which reduces the work of breathing **(Figure 5)**. [26, 182] When the trigger sensitivity is set at -1 to -2 cmH_2O, a ventilator-assisted breath will be triggered once the alveolar pressure decreases to 1 to 2 cmH_2O below atmospheric pressure without applied PEEP, or 1 to 2 cmH_2O below end-expiratory pressure with applied PEEP. As an example, consider a patient whose trigger value is set to -2 cmH_2O and whose auto-PEEP is 10 cmH_2O. A breath will be triggered at an alveolar pressure of 3 cmH_2O if there is applied PEEP of 5 cmH_2O, which requires the patient to decrease the alveolar pressure 7 cmH_2O. In contrast, a breath will be triggered at an alveolar pressure of -2 cmH_2O if there is no applied PEEP, which requires the patient to decrease the alveolar pressure 12 cmH_2O.

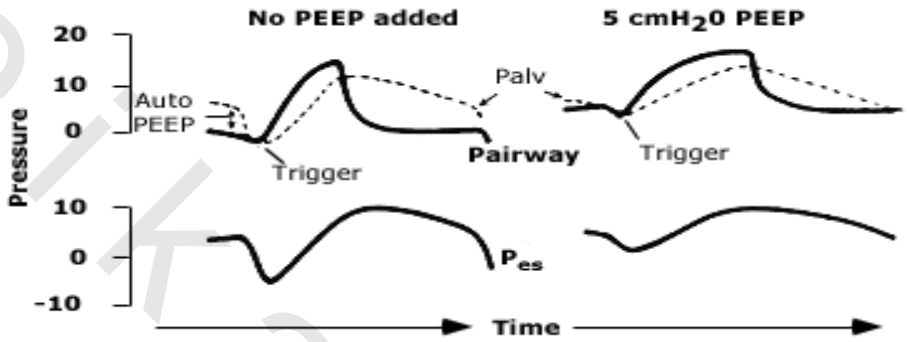

Figure (5): Impact of auto-PEEP on trigger sensitivity and inspiratory effort. [26, 182]

To trigger a breath, alveolar pressure (Palv) must decrease by the amount of auto-PEEP, plus the set trigger sensitivity. The large dip in esophageal pressure (Pes) reflects this effort. The addition of external PEEP reduces the Palv-Pes gradient and decreases the breathing workload, without a significant increase in end-inspiratory Palv.

Applied PEEP decreases the work of breathing without aggravating hyperinflation in patients who have an expiratory flow limitation. This can be illustrated using the analogy of a waterfall.[29] In this analogy, the water level upstream from the waterfall represents auto-PEEP, the height of the waterfall represents the closing pressure of the airways, and the water level downstream from the waterfall represents applied PEEP. Elevating the water level downstream has no influence on the height of the waterfall or the level of the water upstream, as long as the downstream water level remains lower than the height of the waterfall. When the downstream water level rises above the height of the waterfall, however, the upstream water level will rise. In other words, neither expiratory flow nor auto-PEEP will be altered by applied PEEP, as long as applied PEEP remains equal to or lower than the critical closing pressure. When applied PEEP surpasses the critical closing pressure, auto-PEEP will immediately increase and hyperinflation will be exacerbated. This usually occurs when applied PEEP is >80 percent of the auto-PEEP. [183]

4- Inspiratory flow rate:

A high inspiratory flow rate has several advantages in mechanically ventilated patients with COPD, including decreasing the work of breathing and decreasing the likelihood of hyperinflation. Mechanically ventilated patients with COPD generally have an increased respiratory drive, which requires a high inspiratory flow rate. The default inspiratory flow rate (usually 60 L/minute) is often inadequate. The inspiratory work

necessary to overcome pulmonary and ventilator impedance is markedly increased if the inspiratory flow is insufficient. [34, 184] Increasing the inspiratory flow rate will often satisfy this demand and decrease the work of breathing. A high inspiratory flow rate decreases the inspiratory time and increases the expiratory time. As a result, the likelihood of hyperinflation and auto-PEEP decreases.[185, 186]

In one prospective cohort study of 13 mechanically ventilated patients (seven with COPD), increasing the inspiratory flow rate from 40 to 100 L/min improved gas exchange, probably due to less gas trapping. [185]

A high inspiratory flow rate is occasionally associated with an increase in the respiratory rate.[186, 187] In one study of patients with COPD, increasing the inspiratory flow rate from 30 to 90 L/minute increased the respiratory rate from 16 to 20 breaths per minute. [186] The tendency of the high inspiratory flow rate to increase expiratory time outweighed the tendency of the high respiratory rate to decrease expiratory time. The net effect was an increase of the expiratory time (2.1 to 2.3 seconds) and a decrease of the auto-PEEP (7 to 6.4 cmH_2O).

As a general rule, we suggest that the initial inspiratory flow rate be set at 60 L/min. The inspiratory flow rate can then be increased to a level that satisfies the patient's demand if the patient appears to be struggling.

5- Tidal volume (VT):

There is growing recognition that large tidal volumes (e.g. 10 to 15 mL/kg) can cause alveolar over distension and lung injury, as well as increase the risk of hyperinflation and barotrauma. As a result, lower tidal volumes (e.g., 5 to 7 mL/kg) are increasingly being used during volume-assisted modes of ventilation.

6- Ventilator rate:

In the discussion that follows, the respiratory rate (RR) refers to the total number of breaths that the patient receives in one minute. The ventilator rate (VR) refers to the number of breaths per minute that is set by the clinician on the ventilator. In other words, it is the number of mandatory breaths that a patient will receive per minute of mechanical ventilation. The spontaneous rate (SR) refers to the number of breaths per minute that a patient receives beyond the ventilator rate (RR = VR + SR). The spontaneous rate reflects non-mandatory, patient-initiated breaths. The ventilator rate should be set approximately four breaths per minute less than the respiratory rate during ACV. As an example, the ventilator rate should be set at approximately 14 breaths per minute if the patient's respiratory rate is 18 breaths per minute. This ensures that the ventilator will continue to supply adequate minute ventilation even if there is a sudden decrease in respiratory center output. The patient should be monitored closely because a significant increase in the respiratory rate will decrease the expiratory time. This can cause hyperinflation, auto-PEEP, and/or inverse ratio ventilation. Inverse ratio ventilation exists when the inspiratory time is longer than the expiratory time. During IMV, the initial ventilator rate should be based upon the clinician's estimate of the required minute ventilation. There is an inappropriate tendency to adjust the ventilator rate according to the patient's acid-base status only.

The problem with this approach is that arterial blood gases give no information regarding the work of breathing, which may be excessive even when the ventilator rate is as high as 14 breaths per minute and the arterial blood gases are acceptable. [170] We

believe the ventilator rate should be adjusted according to the patient's acid-base status, respiratory effort, and comfort. A ventilator rate is not set during PSV. [170]

7- Pressure level:

During PSV, the pressure support level should be increased until the patient's respiratory rate is below 30 breaths per min because this respiratory rate indicates that the inspiratory effort has been reduced to a reasonable level. However, the expiratory effort of patients with COPD may increase when the pressure support is increased, which makes selection of the optimal pressure support level difficult.[170]

8- Applied PEEP:

In the past, applied PEEP was avoided in patients with COPD because of concern that applied PEEP could worsen hyperinflation. It is now recognized that applied PEEP is beneficial in patients with an expiratory flow limitation due to dynamic airway collapse.

9- Inhaled medications:

The administration of inhaled medications to mechanically ventilated patients is problematic because the medications accumulate in the ventilator tubing and the endotracheal tube. This can be overcome by delivering large amounts of bronchodilators via an in-line nebulizer.[188-190]

A metered dose inhaler (MDI) can also be used. As an example, one study demonstrated that the administration of four puffs of albuterol to mechanically ventilated patients produced similar bronchodilation as in-line nebulizers, but with greater efficiency and lower cost. [188, 189] Four puffs produced the maximal bronchodilating effect, but precise technique was required. The following has been proposed for using MDIs in mechanically ventilated patients: [190] Ensure that the tidal volume is greater than 500 mL during assisted ventilation, the inspiratory time (excluding the inspiratory pause) is greater than 30 percent of total breath duration, and the ventilator breaths are synchronized with the patient's inspiration. Shake the MDI vigorously. Place the canister in the actuator of a cylindrical spacer, which should be situated in the inspiratory limb of the ventilator circuit. Activate the MDI at the onset of inspiration. Institute a breath hold at end-inspiration, lasting three to five seconds. Allow passive exhalation. Repeat every 20 to 30 seconds until the total dose is delivered. [190]

Mechanical ventilation is frequently delivered to patients admitted to intensive care units to reduce the work of breathing (WOB), to improve oxygenation, or to assist ventilation. The interaction between patient and ventilator is complex with respect to a variety of variables including pressure, volume, flow, and time. Yet these variables can be adequately represented by a mathematical model, called the equation of motion for the respiratory system, which can be simplified as:

$$\text{Airway opening pressure} + P_{mus} = (\text{Flow x Resistance}) + (\text{Volume x Elastance})$$

Where P_{mus} is respiratory muscle pressure and is calculated based on the following general equation: P_{mus} = Elastic Pressure + Resistive Pressure. The equation shows that for any mode, only one variable (i.e., pressure, volume, or flow) can be controlled at a time. So we can simplify the modes to pressure control versus volume control.[188-190]