Acute Exacerbations and Respiratory Failure in Chronic Obstructive Pulmonary Disease

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Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) describe the phenomenon of sudden worsening in airway function and respiratory symptoms in patients with COPD. These exacerbations can range from self-limited diseases to episodes of florid respiratory failure requiring mechanical ventilation. The average patient with COPD experiences two such episodes annually, and they account for significant consumption of health care resources. Although bacterial infections are the most common causes of AECOPD, viral infections and environmental stresses are also implicated. AECOPD episodes can be triggered or complicated by other comorbidities, such as heart disease, other lung diseases (e.g., pulmonary emboli, aspiration, pneumothorax), or systemic processes. Pharmacologic management includes bronchodilators, corticosteroids, and antibiotics in most patients. Oxygen, physical therapy, mucolytics, and airway clearance devices may be useful in selected patients. In hypercapneic respiratory failure, noninvasive positive pressure ventilation may allow time for other therapies to work and thus avoid endotracheal intubation. If the patient requires invasive mechanical ventilation, the focus should be on avoiding ventilator-induced lung injury and minimizing intrinsic positive end-expiratory pressure. These may require limiting ventilation and "permissive hypercapnia." Although mild episodes of AECOPD are generally reversible, more severe forms of respiratory failure are associated with a substantial mortality and a prolonged period of disability in survivors.

Keywords: chronic obstructive pulmonary disease; pulmonary infections; respiratory failure; mechanical ventilation

DEFINITION AND IMPACT

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a clinical diagnosis made when a patient with COPD experiences a sustained (e.g., 24–48 h) increase in cough, sputum production, and/or dyspnea. AECOPD has clinical consequences ranging from a self-limited illness to progressive respiratory failure (1–4). AECOPD was responsible for 1.5 million emergency department visits, 726,000 hospitalizations, and approximately 119,000 deaths in 2000 (5, 6). The annual hospitalization rate for COPD in the United States increased from 9.7 to 24.5 per 10,000 population between 1988 and 1998, and the vast majority of these were due to AECOPD (5, 6). The average patient with COPD experiences two episodes of AECOPD per year, and 10% of these episodes require hospitalization (5). The average duration of an episode is 7 days, although it may take several months for the patient to return to baseline functional status (2, 3, 6). More recent data from the National Emphysema Treatment Trial show that patients with severe emphysema and who are eligible for lung volume reduction surgery have 6.1 days/year of hospitalization if they remain on medical therapy but only 3.2 days/year if given lung volume reduction surgery ($P = 0.005$) (7).

ETIOLOGY AND CONFOUNDING FACTORS

Bacterial infections are implicated in the majority of AECOPD episodes (2, 8–12). This is not surprising because the patient with COPD has airways that are prone to infections, with impaired local defenses and frequent bacterial colonization. Sputum and bronchoscopy data have shown that *Moraxella catarrhalis*, *Haemophilus influenza*, and *Streptococcus pneumonia* are the most common organisms associated with AECOPD episodes (8–11). Other bacteria (e.g., *Pseudomonas* and *Staphylococcus*) have also been implicated. Many of these bacteria may be chronic airway colonizers that progress to infection after a simple viral upper respiratory infection or an environmental stress. On the other hand, a significant number of AECOPD infections may come from bacterial strains that are new to the patient (8–11).

Infectious AECOPD can be caused by other agents. Rhinovirus and respiratory syncytial virus have been implicated as causes for AECOPD in several studies (13–17). During the influenza season, the prevalent strain of influenza virus may also be an important viral cause, especially in the elderly. Other viruses, such as parainfluenza virus, adenovirus, and picornavirus, may be important, but their role in AECOPD is less clear. Atypical microorganisms such as *Mycoplasma pneumoniae* and *Chlamydia* have been implicated in 5–15% and 5–10% of AECOPD cases, respectively (12, 16, 17). Patients with infectious exacerbations have longer hospitalizations and greater impairment of several measures of lung function than those with noninfectious exacerbations (8).

Air pollution is another important factor in AECOPD (18–23). Epidemiological research has linked increases in respiratory symptoms, admissions for exacerbations, and COPD-associated mortality with air pollutants such as particulate matter, sulfur dioxide, ozone, and nitrogen oxides. It has been estimated that up to 9% of admissions with AECOPD may be due to atmospheric pollution, especially during the summer months (23).

Cardiac dysfunction may be another important factor in AECOPD (24). Acute left heart dysfunction was present in 25–30% of patients with AECOPD (25–27). Congestive heart failure is an independent risk factor for survival in patients with COPD who had acute exacerbations requiring hospitalization (28). Decompensation of cardiac function may present as right heart failure (cor pulmonale) precipitated by hypoxia-induced pulmonary hypertension, pulmonary embolism, or pneumonia (29, 30). Left heart failure is common because many patients with COPD have coronary artery disease and hypertensive heart disease as comorbid conditions (24). Decreased cardiac output reduces oxygen delivery to respiratory muscles, contributing to respiratory

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decompensation in patients with COPD (1, 24). Pulmonary embolism is an uncommon trigger for acute exacerbation (31), although in patients with acute exacerbation of unknown origin, the prevalence may be as high as 25% (32). Other conditions, such as nonpulmonary infections and pneumothorax, can mimic an acute exacerbation or possibly act as triggers (1–3).

In about 30% of cases of AECOPD, no specific etiology could be identified. Many of these episodes may represent the fluctuating natural progression of COPD or noncompliance to maintenance treatment. It is possible that some of these episodes were triggered by infection, but the microorganisms are not identified due to the lack of sensitive technology.

Recent development in plasma biomarkers may help assess AECOPD and provide prognosis. For example, elevation of troponins was associated with increased severity of the exacerbation (25). Troponin T and amino-terminal pro-brain natriuretic peptide are elevated in patients with acute left heart failure and may be used to exclude left ventricular dysfunction as the cause of AECOPD (26, 27). Elevation of C-reactive protein, an acute-phase reactant, may help confirm the diagnosis of AECOPD, but it is nonspecific and cannot differentiate between infectious and noninfectious causes of AECOPD (33–35). D-dimer may also assist in diagnosing pulmonary embolism associated with AECOPD (31, 36).

CLINICAL PICTURE

The clinical manifestations of exacerbations of COPD are highly variable. Patients with AECOPD may present with symptoms and signs similar to those at baseline except with greater severity. Orthopnea and paroxysmal nocturnal dyspnea that are usually not present at baseline may become evident when congestive heart failure coexists. On physical examination, there may be increased expiratory wheezes and rhonchi. Breath sounds or wheezing may decrease if the airway obstruction is severe. There is usually more prominent use of accessory muscle. Signs of muscle fatigue, such as paradoxical breathing (an inward motion of the upper abdominal wall with inspiration) and respiratory alternans (a cyclic alternation between abdominal and rib cage breathing), may be present and should raise suspicion of impending respiratory failure.

With AECOPD, cough may become more severe and strenuous. Sputum volume may increase, and the color of the sputum may change from whitish to yellow or green. Hemoptysis is not uncommon during AECOPD and may consist of streaks or specks of blood mixed in purulent sputum. Occasionally, hemoptysis may be of larger quantity. In this case, other causes, including lung cancer, pneumonia, bronchiectasis, and heart failure, should be considered.

There may be signs of worsening right ventricular failure during AECOPD, including jugular venous distension, hepatic congestion, and lower extremity edema, especially in patients with advanced COPD and chronic hypoxemia. Many factors that trigger acute exacerbations typically increase ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch and hypoxemia (37, 38). This worsens pulmonary hypertension and produces right ventricular overload and, eventually, cor pulmonale (30, 39). The development of cor pulmonale is a particularly ominous sign in COPD and is a major cause of mortality (40, 41). In severe cases of acute exacerbation, muscle overload may occur, and hypercapnic respiratory failure may develop.

Central nervous system symptoms may be present, ranging from irritability to decreased responsiveness secondary to worsening hypoxemia, hypercapnea, or both. Central nervous system symptoms may precede respiratory symptoms or be the only recognizable clinical manifestation, especially in elderly patients with baseline hypercapnea.

STAGING AECOPD

The severity of AECOPD without respiratory failure can be classified according to several staging systems. The traditional system uses the Winnipeg criteria, which were derived from a double-blind, placebo-controlled trial that evaluated the role of antibiotics in patients with COPD with acute exacerbations (42). The three-stage system is based on three principal symptoms: increase in sputum volume, increase in sputum purulence, and increase in shortness of breath (Table 1). This staging system correlates well with the effectiveness of antibiotic treatment for AECOPD. In type 1 exacerbations, antibiotics reduce the risk of treatment failure, whereas the effects of antibiotics are virtually absent in type 3. The Canadian Medical Association recently published guidelines for the management of AECOPD based on a five-stage severity system (43). The system grades the severity based on the classic Winnipeg criteria and some of the factors known to correlate with poorer response to therapy, including age greater than 65 years, significant comorbid illness, FEV_1 less than 50% of predicted, and number of exacerbations per year. The antibiotic therapy is adjusted according to the severity of the exacerbation. Another three-level staging system for AECOPD has been proposed that incorporates symptoms criteria and history of the disease and comorbidity (44).

Although these more comprehensive severity-scoring systems may allow a more rational choice of antibiotics for AECOPD, they provide little guidance for nonantimicrobial therapies. In addition, none of these systems has been validated prospectively. Because of the array of different therapies aimed at different physiological derangements in acute exacerbations of COPD, no single severity scale will likely be sufficient to guide treatment decisions in an acute exacerbation of COPD. It may be necessary to have one scale related to likely microbial pathogens to guide antibiotic treatment, another to assess airway reactivity and likely response to different bronchodilator treatments, and another to assess ventilatory function and the need for mechanical ventilatory support and intensive care unit (ICU) care. Theoretically, these measures could be combined into one severity score system for the initial assessment of patients with AECOPD. Any such scoring systems would have to be tested formally before they could be used in clinical decision making.

It is important in the initial assessment of AECOPD to determine the need for hospitalization. Patients with more severe baseline disease are more likely to require hospital admission dur-

TABLE 1. THE WINNIPEG CRITERIA

Type of Exacerbations	Criteria
Type 1	All three of the following symptoms: increase in sputum volume, increase in sputum purulence, increase in shortness of breath
Type 2	Any two of the following symptoms: increase in sputum volume, increase in sputum purulence, increase in shortness of breath
Type 3	Any one of the following symptoms: increase in sputum volume, increase in sputum purulence, increase in shortness of breath, plus at least one of the following: upper respiratory tract infection lasting 5 d, fever; increase in wheezes, increase in cough, increase in heart rate $\geq$ 20%

TABLE 2. INDICATORS OF NEED FOR HOSPITALIZATION IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Older age
Severe underlying chronic obstructive pulmonary disease/already receiving long-term oxygen therapy
Marked increase in breathlessness
Poor or deteriorating general condition with little activity
Cyanosis or worsening peripheral edema
Impaired level of consciousness or confusion
Difficulty in coping at home
Significant comorbidities (particularly arrhythmias, heart failure, and insulin-dependent diabetes)
Failure to respond to initial medical treatment
Oxygen saturation $< 90\%$

ing acute exacerbations. Some indicators of the need for hospitalization are shown in Table 2 (45). Patients with AECOPD who have at least a few of these indicators should be admitted to the hospital for further management. When signs of respiratory failure or impaired consciousness occur, management in the ICU is needed.

PHARMACOLOGIC MANAGEMENT OF AECOPD

Bronchodilators

The use of short-acting β-agonists, theophylline, and anticholinergic bronchodilators is based on the concept that the smooth muscle reactivity, airway inflammation, and mucus production characteristics of AECOPD episodes should respond to these drugs. Numerous clinical trials have supported the use of these drugs (2, 46). In comparing β-agonists, albuterol given every 20 minutes seemed to provide an equal effect on FEV_1 as albuterol given every hour, and nebulized albuterol seemed comparable to subcutaneous terbutaline (46). Extrapolating from the asthma literature, a number of observational trials have shown efficacy for continuous albuterol nebulization (47). In a large meta-analysis of administration techniques, no difference was found in bronchodilator effect if the drugs were given in a metered dose inhaler or in a small-volume nebulizer (48).

Antiinflammatory (Corticosteroid) Therapy

The chronic airway inflammation in COPD becomes an acute airway inflammation during an AECOPD episode. As in an acute asthma flare, there is a rationale for corticosteroid (CS) therapy. Supporting this concept are a number of randomized clinical trials in AECOPD that showed that CS therapy improved pulmonary function testing more rapidly and shortened the length of the exacerbation period compared with placebo (49) (Table 3). Not all these studies were positive. In the largest of the positive studies, a regimen of 125 mg methylprednisolone every 6 hours for 72 hours followed by 60 mg prednisone daily tapered for 2 weeks was found to be most cost-effective.

The data supporting CS therapy in AECOPD episodes used oral or parenteral CS preparations. Whether inhaled corticosteroids (ICS) could provide a similar benefit is less clear. The effectiveness of ICS therapy depends heavily upon the patient's ability to properly perform the aerosol delivery maneuvers, something that may be difficult in the dyspneic patient with an AECOPD episode.

Antibiotics

Because of the importance of bacterial infection in most AECOPD episodes, the Global Obstructive Lung Disease and American Thoracic Society COPD guidelines recommend antibiotic use during these episodes (www.goldcopd.com, www.thoracic.org). Many studies have shown that routine antibiotics shortened the severity and/or the duration of an AECOPD episode, but this finding is not universal. A meta-analysis in 1995 demonstrated a statistically significant effect in favor of giving routine antibiotics (50). The choice of antibiotics depends on the likely organism. Treating an AECOPD episode early improves the speed of functional recovery.

Other Therapies

During an AECOPD episode, other modalities that are useful include mucolytics/chest physical therapy in selected patients who have copious retained secretions (51, 52). Supplemental oxygen may be helpful, but because oxygen therapy can be associated with worsening hypercapnia from combinations of ventilatory drive blunting, the Haldane effect in the red blood cell, and derangements in $\dot{V}/\dot{Q}$ relationships, oxygen therapy should be targeted to provide the minimal amount to maintain acceptable oxygenation (e.g., Sp_{O_2} values of $>89\%$) (37, 38). Airway clearance devices for patients with significant airway secretions range from simple airway vibratory/expiratory pressure devices to sophisticated airway or external percussors. Although these devices have been shown to increase sputum clearance, their effects on outcome have not been evaluated in clinical trials (52).

MECHANICAL VENTILATION ISSUES FOR HYPERCAPNIC RESPIRATORY FAILURE

Respiratory failure from airflow obstruction is a direct consequence of acute airway narrowing and critical increases in airway resistance. These lead to two important mechanical changes. First, the increased pressures required for airflow may overload respiratory muscles, producing a "ventilatory pump failure" with spontaneous minute ventilation inadequate for gas exchange (hypercapneic respiratory failure). Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal resting volume. This sometimes is called air trapping and produces elevated end-expiratory pressures (intrinsic positive end-expiratory pressure [PEEPi] or auto-PEEP). These regions of overinflation put inspiratory muscles at a substantial mechanical disadvantage, which further worsens respiratory muscle function (53). Overinflated regions may compress more healthy regions of the lung, impairing $\dot{V}/\dot{Q}$ matching. The high intrathoracic pressures may impair cardiac filling and contribute to overdistention lung injury (54). During spontaneous efforts, regions of air trapping and PEEPi can function as a threshold load to trigger assisted breaths, which can further overload ventilatory muscles (53, 55).

If short-term muscle rest could be achieved with noninvasive positive pressure ventilation (NPPV) through a nasal or oral mask, the pharmacologic agents given for AECOPD might be given time to work and thus avert a need for invasive mechanical ventilation. Evaluating this concept are a number of randomized and/or crossover studies using NPPV in the initial phases of severe AECOPD (56). Although there are mixed results, the two largest studies of NPPV in AECOPD (56) showed that NPPV reduced the need for invasive mechanical ventilatory support. The decision to discontinue NPPV and proceed to invasive mechanical ventilatory support is a clinical one usually driven by progressive respiratory acidosis and signs of patient fatigue/discomfort during NPPV.

In general, the overall goals of invasive mechanical ventilatory support in respiratory failure due to airflow obstruction are similar to the overall goals in other forms of respiratory failure, providing adequate gas exchange while minimizing lung injury.

TABLE 3. CORTICOSTEROID THERAPY DURING ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Study (yr)	Number of Patients	Design	Results
Albert (1980)*	44	RCT	Steroids improved FEV_1
Emmerman (1989)†	100	RCT	Steroids had no effect
Bullard (1996)‡	138	RCT	Steroids improved FEV_1, not hospitalization rates
Thompson (1996)§	27	RCT	Steroids improved FEV_1
Davies (1999)‖	56	RCT	Steroids improved FEV_1, not subsequent walk test or FEV_1
Niewoehner (1999)¶	271	RCT	Steroids reduced treatment failures, not long-term outcome

Definition of abbreviation: RCT = randomized controlled trial.

Data from Reference 40.

* Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med* 1980;92:753–758.

† Emerman CL, Connors AF, Lukens TW, May ME, Effron D. A randomized controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. *Chest* 1989;95:563–567.

‡ Bullard W, Burgi H, Landis E. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. *Am J Emerg Med* 1996;14:139–143.

§ Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996;154:407–412.

‖ Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;354:456–460.

¶ Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999;340:1941–1947.

Two particularly important considerations in respiratory failure from AECOPD are minimizing regional overdistention and managing PEEPi. Overdistention injury occurs when excessive end-inspiratory alveolar "stretch" physically damages alveolar structures and produces local and systemic inflammation (ventilator-induced lung injury [VILI]) (54). Clinically this occurs when the end-inspiratory stretching pressure (often estimated by the end-inspiratory airway plateau pressure) exceeds the normal physiological maximum of 30 cm H_2O (54). This stretch injury may be a consequence of excessive tidal volumes, even when the plateau pressure is less than 30 cm H_2O (57, 58). These effects have been most studied in patients with parenchymal lung injury, but protecting alveolar structures would seem to be a mechanical ventilation goal in virtually all forms of respiratory failure (59). This has led to recommendations to reduce tidal volumes (e.g., 5–7 ml/kg) to protect the lung in AECOPD. To avoid intrinsic PEEP buildup from resulting in patient tachypnea, moderate sedation may be required. The resulting reduction in minute ventilation may produce progressive hypercapnia (so-called permissive hypercapnia). However, accepting pH values in the 7.0–7.1 range may have little clinical effect on the patient and may be beneficial if the reduced volumes and pressures reduce the risk of VILI (60, 61). There is emerging evidence (although not universal) that a modest respiratory acidosis may ameliorate cellular injury (62, 63).

Narrowed airways produce a high resistance to flow that can result in very high peak airway pressures. Much of this pressure is dissipated in providing gas flow through obstructed airways and therefore does not overdistend distal alveoli. However, the heterogeneous distribution of airflow obstruction seen in most airway diseases means that less obstructed alveolar regions may transiently be exposed to these high peak pressures and thus may be at risk for overdistention injury. Because of this, a high peak pressure, even in the presence of acceptable plateau pressures, should be avoided.

The second important consideration in managing the patient with AECOPD who has respiratory failure involves PEEPi. PEEPi is a function of three variables: minute ventilation, inspiratory/expiratory (I/E) time ratios, and expiratory time constants (resistance $\times$ compliance) (64). An increase in any of these values increases the risk of PEEPi. Reducing PEEPi thus requires reductions in any or all of these—reducing minute ventilation (permissive hypercapnia), a shorter I/E that lengthens the expiratory time, or reductions in airway resistance using pharmacologic agents. If the PEEPi is causing a significant ventilator breath–triggering load on the patient, judicious amounts of applied circuit PEEP can equilibrate expiratory pressures and thereby reduce this triggering work (55, 65, 66). An esophageal balloon often can be helpful in detecting and managing this phenomenon. In severe airway obstruction, uses of low-density gases (e.g., 80:20, 70:30, or 60:40 helium/oxygen or heliox) can help reduce patient inspiratory work and facilitate lung emptying (driving pressure decreases and/or flow increases through a tube as gas density decreases) (67). If a helium/oxygen gas mixture is used, many flow sensors must be recalibrated to account for the change in gas density. Some ventilators cannot function in the presence of heliox.

Withdrawing mechanical ventilatory support after improvement in AECOPD respiratory failure should follow evidence-based guidelines for other forms of respiratory failure (68). In general, daily spontaneous breathing trials should be performed as patients recover, and patients should be managed with comfortable forms of assisted ventilation (e.g., pressure support, pressure assist, or proportional assist) in between the spontaneous breathing trials. There is some evidence that earlier extubations in patients with AECOPD might be facilitated with conversion to NPPV (69, 70). However, these trials are too small and insufficient to support broad recommendations for practice changes. In managing patients with airflow obstruction on a ventilator, techniques to deliver bronchodilator aerosols through the ventilator circuitry must be used. This generally involves in-line circuit nebulizers, although metered dose inhalers with inspiratory circuit-holding chambers are also effective (71, 72). Because endotracheal tubes significantly reduce aerosol delivery, doses usually are increased three- to fourfold (or aerosolized continuously) to ensure adequate drug effectiveness. Assessment of airway pressures (peak to plateau gradients) or flow–volume patterns can be used to monitor bronchodilator effectiveness.

OUTCOMES OF AECOPD

Most exacerbations in patients with COPD are relatively mild, requiring only outpatient care, but 3–16% of these require hospital admission, and some cases are severe enough to result

in respiratory failure requiring ICU intervention. AECOPD episodes have been shown to accelerate FEV_1 decline, to increase mortality (AECOPD episodes are the most common cause of death in COPD), and to have a profound influence on the decline in quality of life scores (4, 6, 73, 76).

One large survey found an in-hospital mortality rate of 11% and 1-year mortality rate of 43% in patients with COPD admitted for acute exacerbations (28). Another recent study found a similar in-hospital mortality rate (8%) and 1-year mortality rate (23%) (73). These mortality figures are much higher for patients requiring ICU admission (74–76).

Mortality is substantial in patients with COPD who require mechanical ventilation (although it is better than in patients with acute lung injury/acute respiratory distress syndrome) (74). In one large study, in hospital mortality in mechanically ventilated patients with AECOPD was almost 25%, 1-year mortality approached 40%, and 5-year mortality exceeded 70% (75). Survivors of respiratory failure from COPD tend to return to baseline lung function very slowly (i.e., weeks to months). In a large, multicenter study, the need for mechanical ventilation did not influence outcome in patients with COPD admitted to an ICU (41). However, the risk for rehospitalization and reintubation for patients with COPD is increased markedly after an episode of respiratory failure requiring mechanical ventilation (41).

CONCLUSIONS

AECOPD afflict millions of patients with COPD annually and account for substantial health care costs. Although bacterial infections are the most common causes of AECOPD, viral infections and environmental stresses are also implicated. AECOPD episodes can be triggered or complicated by other comorbidities. Pharmacologic management includes bronchodilators, corticosteroids, and antibiotics in most patients. Oxygen, physical therapy, mucolytics, and airway clearance devices may be useful in selected patients. In hypercapneic respiratory failure, NPPV may allow other therapies to work and thus avoid endotracheal intubation. If the patient requires invasive mechanical ventilatory support, the focus should be on avoiding VILI and minimizing intrinsic PEEP. These may require limiting ventilation and so-called permissive hypercapnia. Although mild episodes of AECOPD are generally reversible, more severe forms of respiratory failure are associated with a substantial mortality and a prolonged period of disability in survivors.

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