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Acute Lung Failure

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Abstract and Introduction

Abstract

Lung failure is the most common organ failure seen in the intensive care unit. The pathogenesis of acute respiratory failure (ARF) can be classified as (1) neuromuscular in origin, (2) secondary to acute and chronic obstructive airway diseases, (3) alveolar processes such as cardiogenic and noncardiogenic pulmonary edema and pneumonia, and (4) vascular diseases such as acute or chronic pulmonary embolism. This article reviews the more common causes of ARF from each group, including the pathological mechanisms and the principles of critical care management, focusing on the supportive, specific, and adjunctive therapies for each condition.

Introduction

Lung failure is the most common organ failure in the intensive care unit (ICU).[1] Approximately 56% of ICU patients suffer from acute respiratory failure (ARF), with one third of those subsequently dying.[2] The pathogenesis of ARF can be classified as (1) primarily neuromuscular in origin, (2) secondary to acute and chronic obstructive airway diseases, (3) alveolar processes such as cardiogenic and noncardiogenic pulmonary edema and pneumonia, and (4) vascular diseases such as acute or chronic pulmonary embolism. All mechanisms of ARF ultimately impair the ability of the alveolus to match ventilation with perfusion and impair gas exchange, either oxygen uptake, carbon dioxide excretion, or both (Fig. 1). Regardless of the cause of ARF, the physiological responses are often similar. Compensatory mechanisms, such as tachypnea and the use of accessory muscles of respiration, may initially preserve adequate gas exchange. Eventually, the work of breathing becomes excessive, exhaustion develops, and life-threatening respiratory decompensation follows with the development of hypoxia and hypercarbia. This article reviews the management of the more common causes of ARF, considering the pathological mechanisms by which respiratory failure develops. The article also focuses on the appropriate treatments for the different causes of ARF (Fig. 2).

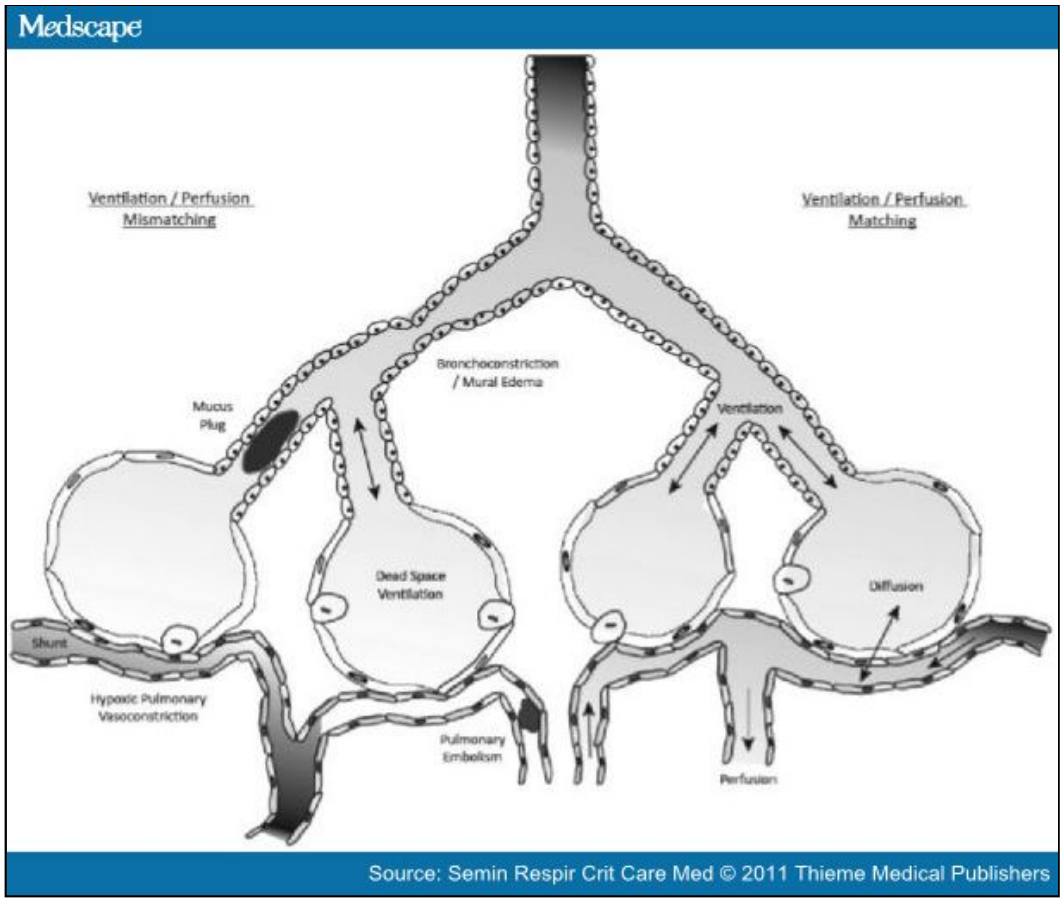

Figure 1. The four primary alveolar processes: ventilation, diffusion, perfusion, and their regulatory mechanism hypoxic

pulmonary vasoconstriction. All forms of lung failure result from a defect in one or more of these processes which culminates in V/Q mismatch, or its extreme variants shunt and dead space ventilation.

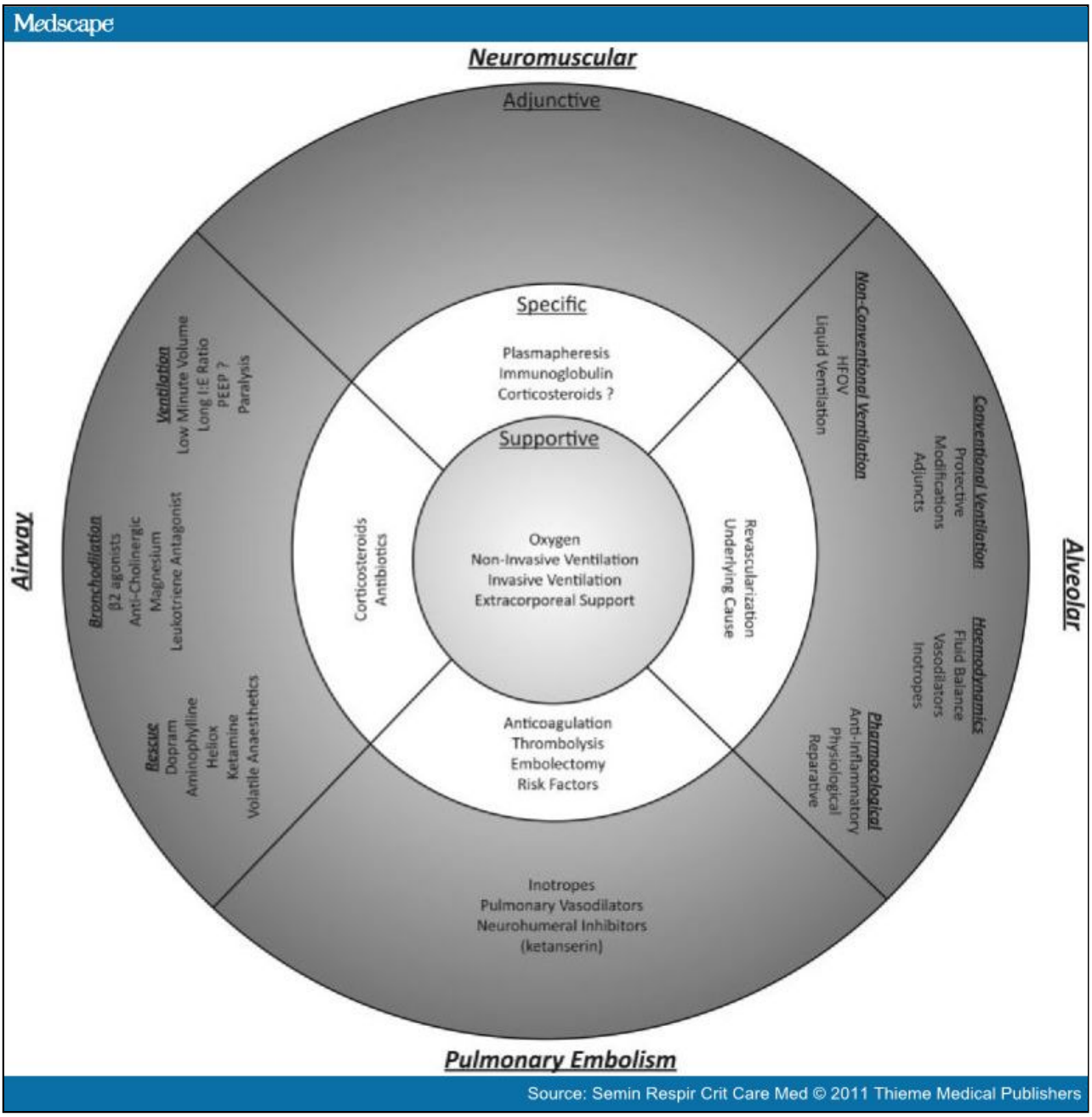

Figure 2. Comparison of therapies for different modes of lung failure. See text for details.

Neuromuscular Causes of Acute Respiratory Failure

Guillain-Barré syndrome (GBS) describes a group of acute inflammatory polyneuropathies resulting from demyelination or axonal degeneration.[3] The syndrome is probably autoimmune in origin, often occurring after a recent infection, and has a typical pathological finding of mononuclear cell infiltration of the peripheral nervous system.[4] The worldwide incidence is between 0.6 and 4 cases per 100,000 per year, rising with age, and there is a slight male preponderance.[4] GBS classically manifests as rapidly ascending symmetrical flaccid paralysis, either with or without sensory changes, and autonomic hyperreflexia.[5] It is most severe between 2 and 4 weeks after onset.[6] The diagnosis is dependent on typical clinical features, examination of cerebrospinal fluid, and neurophysiological studies.

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction, with autoantibodies directed against the postsynaptic nicotinic acetylcholine receptor, or other junctional proteins, resulting in failure of motor end plate transmission.[7] Characteristic findings are weakness, worsening with exercise, and recovery after a period of rest. MG is uncommon, with a

conservative worldwide incidence of 30 per million per year.[8] The American prevalence is 200 per million, giving an estimated 60,000 cases.[9] It is mainly a disease of young women and old men.[10] Diagnosis is based on clinical features and pharmacological, serological, and neurophysiological tests.[11] Myasthenic crisis is defined by the presence of respiratory failure requiring mechanical ventilation (MV).[12] Approximately 20% suffer a crisis, usually in the first 2 years after diagnosis.[12] Several risk factors have been associated with the development of a crisis, including infection, medication change, surgery, or trauma.[7] ARF may result from either a myasthenic crisis, due to therapeutic inadequacy, or from a cholinergic crisis, due to medication excess, with both crises being clinically indistinguishable.[7]

There are several mechanisms by which respiratory failure may develop in both GBS and MG.[13, 14] Bulbar dysfunction, recognizable by dysarthria, dysphonia, and dysphagia, leads to lingual, pharyngeal, and laryngeal muscle weakness. As a consequence, both upper airway patency and protective reflexes diminish, resulting in increasing airflow resistance and the vulnerability to aspiration.[15] The development of pneumonia may further compromise respiratory function. Inspiratory muscle weakness inhibits full lung expansion, predisposing to atelectasis, shunt, and hypoxia with compensatory rapid shallow breathing increasing the percentage of dead-space ventilation. Expiratory muscle weakness further limits coughing and secretion clearance, again inclining to lobar collapse, mechanical inefficiency, and ventilation/perfusion (V/Q) mismatch.

Subjective predictors of the need for MV include inadequate cough plus clinical signs of respiratory distress. Objective features include an arterial blood gas analysis and the memorable 20/30/40 rule, with MV likely to be required with a vital capacity <20 mL/kg, a maximum inspiratory pressure <30 cm H_2O, and a maximal expiratory pressure <40 cm H_2O,[13] although vital capacity measurements may be unreliable.[16] Predictive rules have also been developed.[17] The decision to implement MV is based on the rate of deterioration and ability to protect the airway. The requirement for MV in GBS varies between 25 and 50% of patients and lasts a median duration of 18 to 29 days.[14] All patients with myasthenic crisis are, by definition, in respiratory failure.[12]

MV may be either invasive or noninvasive (NIV). Few studies have addressed the use of NIV in acute neuromuscular respiratory failure. However, for NIV to be considered, the standard criteria for its implementation must be observed, including adequate level of consciousness and circulatory stability.[18] Bilevel positive airway pressure (BiPAP) has been used to avoid tracheal intubation in both GBS and MG, including four patients with bulbar dysfunction.[19–21] The presence of hypercapnea at baseline was predictive of NIV failure in MG. Failure of BiPAP in GBS has also been reported.[22]

No prospective evidence exists to guide tracheal intubation, but induction with the minimal amount of hemodynamic disturbance is required. The autonomic instability of GBS makes extremes of heart rate and blood pressure possible, rendering tracheal intubation hazardous.[13] The choice of intubation technique is dependent on the expertise of the clinician, with alternatives being fiberoptic intubation or formal rapid sequence intubation. Topical anesthesia may allow a further dose reduction in anesthetic agent. Etomidate can suppress adrenal function and has been associated with an increased mortality in sepsis in one report.[23, 24] It should be used with caution in the critically ill.[25] Although ketamine stimulates the circulatory system and is useful in hemodynamically unstable patients, it may not be a good choice in GBS.[26, 27] Suxamethonium has differing effects between the two conditions. Its use may result in hyperkalemia in GBS, whereas due to reduced acetylcholine receptor activity it may prove ineffective in MG.[28, 29] A larger dose may result in a phase II block, especially if prior plasmapheresis has induced a plasma esterase deficiency.[30] However, patients with both conditions may not require neuromuscular blockade due to their existing weakness. If paralysis is deemed necessary, a much reduced dose of a shorter-acting, nondepolarizing neuromuscular blocking agent is preferable.

Once tracheal intubation has been achieved the respiratory targets should be similar for most mechanically ventilated patients aiming for normal gas exchange. The use of sighs has been suggested, but the practice lacks prospective evidence.[31] Due to the potential requirement for tracheostomy, prediction systems have been developed to determine the likely duration of MV.[32, 33] Complications during prolonged MV are common, especially ventilator-associated pneumonia and bacteremia, but may be reduced by early tracheostomy.[34] Little evidence exists to guide weaning and extubation in these conditions. Reintubation is common, and preextubation blood gas values and pulmonary function tests do not correlate with extubation failure.[35]

Both plasmapheresis and intravenous immunoglobulin are established therapies for MG and GBS and are equally efficacious (Fig. 2).[36–39] Plasmapheresis has disadvantages, including its invasiveness, requirement for specialist personnel and equipment, and increased complication rate. Corticosteroids have no role in the acute management of GBS but may have a role in MG.[40, 41] Acetylcholinesterase inhibitors are not recommended during a myasthenic crisis due to the potential for both adverse effects, including bronchoconstriction, bradycardia, and asystole, and inaccurate diagnostic test results.[7, 42]

Although the outcome in GBS is subtype dependent, between 4 and 15% die, a further 7 to 20% remain disabled after a year, and many survivors are limited by fatigue and weakness.[4] The relapse rate is 3 to 5%.[43] For MG, the median duration of MV may be decreasing, from 13 days in the 1980s to 6 days in the late 1990s.[44] Between 27 and 44% fail extubation, with atelectasis the strongest predictor of this.[35, 45] A third of survivors will relapse.[46] Death rates from MG are lower than those for GBS at under 5%.[10]

Acute and Chronic Airway Obstruction Causes of Acute Respiratory Failure

Asthma and chronic obstructive pulmonary disease (COPD) share several pathological and therapeutic traits. They are, however, clearly distinguished by the chronic nature, poor reversibility, and associated comorbidities that characterize COPD.

Asthma is caused by reversible bronchial narrowing characterized by airway inflammation, smooth muscle contraction, and mucous plugging (Fig. 1).[47] Central airway narrowing, due to bronchoconstriction, may produce the spirometric features of severe asthma, whereas peripheral airway obstruction impedes local alveolar ventilation, with V/Q ratios falling to less than 0.1.[48] Dynamic hyperinflation causes both respiratory impairment (by placing the respiratory muscles at a mechanical disadvantage) and hypotension, via elevated intrathoracic pressure impeding venous return.[47, 49] Two fatal phenotypes have been described, one of slower onset with eosinophilic airway infiltration and luminal debris; the other, much less common, is characterized by rapid onset, neutrophilic bronchial infiltration without luminal debris.[50]

Asthma exerts an enormous health care burden. In the United States over 23 million suffer from asthma, with half having at least one attack per year, resulting in 3365 deaths in 2006.[51] Almost a quarter of asthmatic patients presenting to the emergency department (ED) have life-threatening asthma.[52] Ten percent of those admitted to hospital require ICU admission, and 2% receive invasive MV.[53] Three severe forms of asthma are currently described: acute severe, life threatening, and near fatal, each marking a progression from a state of physiological compensation to multisystem decompensation to emergent respiratory collapse (Table 1).[54]

Table 1. Features of Severe Asthma[54]

Near-Fatal Asthma	Life-Threatening Asthma	Acute-Severe Asthma
RESPIRATORY	RESPIRATORY	RESPIRATORY
Hypercapnea	Normocapnia	Inability to complete sentences
Need for ventilation with raised airway pressures	Hypoxia	Respiratory rate ≥25
	Cyanosis	Peak expiratory flow rate 30–50% best or predicted
	Silent chest	CIRCULATORY
	PEF (peak expiratory flow) 33% best or predicted CIRCULATORY	Heart rate ≥110
	Arrhythmia	
	Hypotension	
	NEUROMUSCULAR	
	Altered consciousness	
	Exhaustion	

Patients with life-threatening or near-fatal asthma should be managed in a critical care environment. The mainstay of asthma treatment is the use of pharmacological therapies aimed at bronchodilation and reducing bronchial inflammation (Fig. 2). Controlled humidified oxygen is provided, aiming for an oxygen saturation of 94 to 98%.[55] β_2 agonists are the mainstay of therapy, with salbutamol and terbutaline being of equivalent efficacy.[54] Oxygen-driven nebulization is the route of administration of choice and may be repeat, back to back, or continuous.[54] Intravenous β_2 therapy is not recommended due to a lack of superiority over inhaled administration plus increased complications and is reserved for refractory cases or where nebulized therapy is not possible.[56] To date, nebulized adrenaline has not been shown to offer any advantage over salbutamol.[57] The anticholinergic ipratropium bromide significantly improves bronchodilation and outcomes when given in conjunction with β_2 agonists.[58] Corticosteroids reduce mortality, and given their delayed onset of action should be administered as soon as possible.[59] In severe cases, parenteral therapy may be easier to administer than inhaled therapy, with a dose of hydrocortisone 100 mg every 6 hours as efficacious as higher doses.[59] Magnesium sulfate has an array of mechanisms through which it augments bronchodilation and reduces inflammation and is used if the initial therapeutic response is poor or features of life-threatening asthma are present.[55, 60] Aminophylline is not recommended because it is unlikely to increase bronchodilation over the aforementioned therapies and may induce unwanted side effects, including arrhythmias and vomiting.[61] Leukotriene receptor antagonists may improve outcomes in acute asthma, but further studies are warranted before widespread use.[62, 63] Oxygen-helium mixtures, in the form of heliox, have a density approximately one third that of air and may reduce the elevated work of breathing due to increased airway resistance.[64] At present, the evidence does not support heliox use in nonintubated patients, and little data exists for patients receiving MV.[65, 66]

NIV has been successfully used to avoid intubation, but further studies are required before it can be recommended.[67, 68] If invasive ventilation is required, the best pharmacological choice for tracheal intubation remains uncertain. Both ketamine and propofol possess bronchodilatory properties, whereas high-dose rocuronium and suxamethonium are rapid-onset neuromuscular blockers of similar efficacy.[69, 70] Suxamethonium suffers from many side effects and, with the advent of the reversal agent sugammadex, has arguably been superseded by rocuronium.[71] Atracurium is potentially associated with histamine release and is not recommended.[69, 72] Invasive MV can be complicated by dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP).[69] Use of low tidal volume (Vt), slow respiratory rate, and increased expiratory period, perhaps in conjunction with an increased inspiratory flow rate, should assist expiration.[73] The use of extrinsic PEEP has been suggested for spontaneous breathing modes to reduce the work to trigger the ventilator, but it is not normally recommended.[73] The mechanically ventilated asthmatic patient is at risk of several complications, including myopathy, critical illness polyneuropathy, further bronchospasm and barotrauma, and hypotension.[69] Ongoing paralysis may be required to control airway pressures, especially if there are difficulties with bronchospasm, cough, and patient-ventilator dyssynchrony.[69] For those patients who fail conventional MV, additional treatment options are available. Refractory cases may be treated with either the intravenous anesthetic agent ketamine or a volatile anesthetic agent such as isoflurane, although special adaptions are required for the ICU ventilator, and mucous plugging may limit agent delivery.[74–77] The use of extracorporeal oxygenation (ECMO) has been successfully described for those failing conventional MV.[78] Approximately 10% of survivors die within 1 year of a period of MV.[79]

COPD is a syndrome of progressive airflow limitation caused by chronic inflammation and destruction of the lung. Although the specific mechanisms differ, COPD has similarities to asthma, including airway inflammation, edema, and luminal secretions occurring in response to long-term noxious stimuli such as cigarette smoke, air pollution, and occupational noxious particles.[80–82] Unlike asthma, parenchymal destruction also occurs.[83] Pulmonary pathology includes dynamic hyperinflation, airflow obstruction, V/Q mismatch, and respiratory muscle fatigue.[84] Approximately 10% of the world's population are estimated to have COPD, with 14.8 million Americans diagnosed with this condition by 2009, and a further 12 million estimated to be undiagnosed.[51, 85] It is estimated that patients with COPD require 670,000 hospital admissions, form 2% of ICU admissions, and suffer 126,000 deaths annually in the United States.[51, 86, 87] Several factors have been implicated in the pathogenesis of acute exacerbations, including respiratory infection, air pollution, pulmonary emboli, and cardiac dysfunction, although in 30% no inciting event is identified.[88] Because the gross pathology of COPD overlaps with asthma, it follows that several of the same therapies are used.

Oxygen therapy is necessary to avoid the life-threatening effects of hypoxia and takes precedence over fears of hypercarbia.[89] However, uncontrolled oxygen administration may increase hypercarbia via increased hypoxic pulmonary vasoconstriction-induced dead space, the Haldane effect, and rarely the overly emphasized mechanism of diminished respiratory drive.[90] Therefore, a modest fraction of inspiratory O_2 (FiO_2) level to achieve safe oxygenation is suggested. Both salbutamol and ipratropium improve pulmonary mechanics, but whether they have an additive effect when administered concurrently is uncertain.[91–93] Corticosteroids also improve pulmonary function and hasten the resolution of exacerbations, with parenteral and oral administration proven to be equivalent.[94] Whether all exacerbations, or just those associated with purulent sputum, should be treated with antibiotics is uncertain. In a single study of patients requiring MV during an exacerbation, a course of antibiotics significantly reduced mortality, the duration of ventilation, and length of hospitalization.[95] If empirical antibiotics are utilized, they should treat the likely causative pathogens such as *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.[88] Current recommendations are that initial therapy should be with an aminopenicillin, a macrolide, or a tetracycline, depending on local microbiological flora.[96] Theophyllines are not recommended due to a consistent association with adverse effects and an inconsistent therapeutic effect.[97] Doxapram is effective as a respiratory stimulant but has been superseded by NIV and is only recommended if NIV is either unavailable or inappropriate.[96]

NIV should be implemented once clinical criteria have been met, although exclusion criteria, such as moderate acidemia, are important.[18] Numerous studies have proven the value of NIV in hypercapnic respiratory failure and demonstrated its superiority over invasive MV in terms of mortality, morbidity, and resource utilization.[98] NIV failure, however, occurs in 30% of patients and signifies a poor prognosis.[99] Early extubation to NIV has become a popular method of avoiding prolonged invasive ventilation and the need for tracheostomy.[100] Ventilatory practice is similar to that for asthma; however, the arterial target blood gas values should ideally be similar to the patient's usual values when stable, striving for a pH near the normal range and not trying to normalize the $PaCO_2$. Outcomes for COPD patients requiring MV are at least as good as for patients ventilated for other forms of ARF.[101] Indicators of worse outcome include increasing severity of the exacerbation, multiorgan dysfunction, and a poor premorbid state. Curiously, more patients with COPD die from cardiovascular disease, especially ischemic heart disease, than pulmonary disease.[102] This brings into focus the ongoing controversy over the potential increased mortality with β_2 agonist therapy in acute exacerbations of COPD, and with long-acting β_2 agonists in asthma.[103, 104] One study has reported that β antagonism was associated with improved outcomes in acute respiratory failure, possibly due to the cardioprotective effects of β blockers.[105]

Alveolar Causes of Acute Respiratory Failure

Acute lung injury (ALI) is a syndrome of increased permeability pulmonary edema characterized histologically by diffuse alveolar damage and clinically by severe hypoxemia refractory to oxygen therapy, decreased pulmonary compliance, and bilateral alveolar

infiltrates on the chest radiograph.[106, 107] It is common, with an incidence of 86 per 100,000 person-years, and equates to over 190,000 cases and 74,500 fatalities annually in the United States.[108] Although mortality has declined, recent studies still report an approximate 25% death rate.[109–111] Several conditions, both pulmonary and extrapulmonary, are associated with the development of ALI, with sepsis and liver failure-related ALI having particularly poor outcomes.[112, 113] Genetic predispositions for the development of ALI have been proposed, but no firm associations have yet been established.[114]

ALI has been described as passing through three pathological phases.[115] An initial exudative phase begins with neutrophil-mediated damage to the alveolus, causing epithelial and endothelial damage, leading to airspace flooding with protein-rich edema fluid and immune cells. A proliferative phase begins 3 to 5 days later, enabling epithelial regeneration via type II pneumocyte propagation and differentiation into type I pneumocytes. A third fibrotic phase may develop and is marked by transformation to a fibrosing alveolitis.

The diagnosis of ALI remains limited to the fulfillment of the American-European Consensus Conference Criteria but is not without uncertainties (Table 2).[116, 117] The definition does not take into account the ventilatory settings, with alterations in PEEP potentially changing the P_aO_2:F_iO_2 ratio.[118] Also, interpretation of the chest radiograph can be challenging, with mild infiltrates often being a source of confusion.[119] An elevated pulmonary artery occlusion pressure does not exclude a diagnosis of ALI because hydrostatic and increased permeability pulmonary edema may coexist, a fact compounded by a limited understanding of the pulmonary artery catheter.[120–122] Interestingly, the histological appearance of the lung at autopsy frequently does not show the diffuse alveolar damage that is pathognomonic of ALI.[123] Despite initial promising investigations, attempts to identify a biomarker for ALI have been not been successful thus far.[124]

Table 2. Diagnostic Criteria for Acute Lung Injury[116]

Acute Onset
Bilateral infiltrates on chest radiograph
Pulmonary artery pressure <18 mm Hg or no evidence of left atrial hypertension
PaO_2:FiO_2≤300 mm Hg (ARDS≤200 mm Hg)

Supportive therapy is indicated when endogenous respiratory function is, or is predicted to become, insufficient to maintain life. Once the pathological effects of reduced compliance, V/Q mismatch and hypoxia, and an increase in pulmonary dead space combine to increase the work of breathing above an achievable level, exogenous ventilation is required to support gas exchange (Fig. 1).[125] NIV has been investigated in ALI to a limited degree, with the evidence presently showing a high failure rate of 50%, particularly in the sickest patients.[126]

No one mode of invasive MV has been shown to be superior to another for respiratory support in ALI, although assist control makes it very straightforward to control the tidal volume.[127] The older modes, such as synchronized intermittent mandatory ventilation, are limited by a single control variable, either pressure or flow (or its surrogate volume).[128] These modes either guarantee minute volume, as in volume control, at the potential expense of airway pressure, or airway pressure, as in pressure control ventilation, at the potential expense of minute volume. Newer dual-control modes seek to combine the superiority of the descending flow waveform used in pressure control, with the guaranteed Vt of volume control.[129] This can occur in either a breath-to-breath fashion, such as in pressure-regulated volume control, or within a breath, such as volume-assured pressure control.[130, 131] Further novel methods of conventional ventilation have been developed and include airway pressure release ventilation, neurally adjusted ventilatory assist, and proportional-assist ventilation.[132–134] Future knowledge-based systems and other artificial intelligence designs may further improve our ventilatory ability.[128]

Although MV provides lifesaving respiratory support, if incorrectly employed, it also has the potential to cause further lung injury. Excessive airway pressure (barotrauma), excessive volume (volutrauma), and repetitive alveolar opening and closing (atelectrauma) can damage the lung both directly and indirectly via the generation of systemic proinflammatory cytokines (biotrauma).[135–138] Biotrauma can progress to multiorgan failure.[139] Ventilator-associated diaphragmatic dysfunction and oxygen toxicity complete the spectrum of ventilator-associated lung injury.[140–142] Using computed tomography (CT), the inhomogeneity of pulmonary consolidation in ALI has been demonstrated, suggesting Vt is delivered to a much smaller unit of lung than anticipated, a concept termed baby lung.[143]

The landmark National Heart, Lung, and Blood Institute ARDS Network ARMA study, published in 2000, reported a 9% absolute risk reduction in mortality in ARDS using reductions in Vt from a traditional 12 mL/kg to 6 mL/kg predicted body weight, and plateau airway pressures from 50 cm H_2O to 30 cm H_2O.[144] Analysis of several studies using similar lung protective ventilatory strategies reveals no safe upper airway pressure limit.[145] The "open-lung approach" uses PEEP to minimize atelectrauma.[146] At present there is no clear advantage with the use of either a standard higher or lower PEEP, although there is the suggestion that higher PEEP may be beneficial in the most severely ill.[147] Despite retrospective studies showing an association between larger Vt ventilation and the development of ALI in those initially without ALI, there remained widespread resistance to the implementation of

protective ventilation for all patients.[148] A very recent prospective, randomized, controlled trial has confirmed a fivefold increase in the development of ALI in those ventilated with Vt 10 mL/kg compared with 6 mL/kg.[149] In addition to using low Vt and low airway pressures, ventilated patients should also be positioned in a semirecumbent position to minimize the risk of ventilator-associated pneumonia.[150] The duration of MV is significantly reduced with both interrupted sedation and daily spontaneous breathing trials.[151, 152] For sedation, propofol may be superior to midazolam in facilitating earlier extubation.[153] While most patients spend two thirds of their ventilated period weaning, it remains difficult to predict successful extubation, with predictors such as the rapid shallow breathing index being imperfect.[101, 154, 155]

Modifications to MV include the use of permissive hypercapnea, which can be a central element of protective ventilation, but it is limited by its lack of applicability in conditions requiring a normal P_aCO_2, such as brain injuries.[156] Inverse-ratio ventilation allows a longer inspiratory time and may alleviate high peak airway pressures but requires deep sedation and paralysis and should not be routinely used.[157]

Several adjunctive therapies have been used in ALI (Fig. 2). Neuromuscular blockade can reduce airway pressure by eliminating patient effort but can be associated with myopathy. One recent clinical trial (the ACURASYS study) reported improved clinical outcomes with the use of early paralysis, without any increase in weakness.[109] The investigators used muscle paralysis early in the course of severe ALI (PaO_2:FiO_2 <150). The beneficial effect may have been explained by more effective implementation of a lung protective ventilation strategy. Prone positioning works through different mechanisms to improve V/Q matching.[158] Like many therapies, such as recruitment maneuvers, it may increase oxygenation but has no clear overall impact on mortality.[159, 160] It may, however, be beneficial in the more severely hypoxic patients.[161] By insufflating the distal trachea with either an intermittent or a continuous flow of oxygen, dead-space gas containing carbon dioxide (CO_2) may be eliminated, allowing a reduction in ventilatory requirements.[162] Rotational bed therapy is occasionally used to increase functional residual capacity and improve secretion clearance. Although it may reduce the incidence of ventilator-associated pneumonia, it has no effect on duration of ventilation or mortality.[163]

Modifying fluid balance has been moderately successful in reducing the duration of MV.[164] Diuresis to reduce both central venous and pulmonary capillary wedge pressures may also be helpful.[164, 165] Consistent with this finding, positive fluid balance is associated with increased mortality.[166]

Several pharmacological agents have been tested for the treatment of ALI. However, none has been shown to reduce mortality in a convincing phase 3 clinical trial, except for the use of neuromuscular blockade as already discussed. Pulmonary vasodilation has been tried with inhaled nitric oxide and intravenous prostacyclin, and pulmonary vasoconstriction attempted with almitrine.[167–170] Activated protein C has been tested without evidence of benefit, although the results of the current trial of activated protein C for very severe sepsis (PROWESS SHOCK) will include some patients with ALI.[171] Antiinflammatory effects have been tested with glucocorticoids, ketoconazole, pentoxyfylline, lisofylline, and fish oils;[172–176] miscellaneous agents include surfactant and β_2 agonists.[177, 178] All these trials have been negative, with the possible exception of corticosteroids, although their role remains uncertain at best.[179, 180] A newer therapeutic target is the regeneration of the injured alveolus, via either mesenchymal stem cells or growth factors, such as keratinocyte growth factor.[181, 182]

Nonconventional modes of ventilation have also been tried. High-frequency oscillatory ventilation (HFOV) utilizes a column of gas oscillated at high frequencies (180 to 1800/min) to achieve a narrower spectrum of airway pressures and avoid injuries associated with the extremes of airway pressure.[183] Alveolar ventilation is dependent on various novel mechanisms, including cardiogenic mixing, Taylor dispersion, asymmetric velocity profiling, and molecular diffusion.[184] Initial results are encouraging, and further large studies are ongoing.[185] Liquid ventilation utilizes perflurocarbons, which are highly soluble for oxygen and CO_2. By instilling such a carrier liquid into the lungs, air-liquid interfaces, which cause much of the damage of conventional MV, may theoretically be avoided.[186] However, studies of liquid ventilation have been disappointing to date.[187]

The recent H1N1 influenza epidemic, with its tranche of severely hypoxic ARDS patients, highlighted the major limitation of all forms of MV in very severe ARDS.[188] Extracorporeal gas exchange devices are based on cardiopulmonary bypass circuit technology and permit varying degrees of CO_2 removal and oxygenation.[189] Early studies utilizing this technology are now merely of historical interest because conventional MV has changed to such a degree.[190,191] Most recently, the CESAR study, albeit with some methodological limitations, reported a survival benefit of ECMO in patients with severe respiratory failure, although the clinical trial primarily demonstrated that, in the United Kingdom, referral of very ill patients with severe ARDS to a major tertiary center was beneficial.[192,193] Despite a small evidence base, worldwide over 2500 adults (and over 36,000 children) have received extracorporeal support, either for severe respiratory failure that has failed MV, severe cardiac failure, or both.[194]

One of the interesting features of ALI is that few patients die from refractory hypoxia; the underlying illness, sepsis, severity of acute organ dysfunction, and multiorgan failure cause most deaths.[195–197] Survivors suffer from pulmonary and neuromuscular disorders, and only 50% return to work.[108]

In contrast to ALI, cardiogenic pulmonary edema is characterized by no substantial structural damage to the alveolus and an edema fluid with a lower protein concentration.[198] Increased pulmonary capillary hydrostatic pressure, often aided by a low

plasma oncotic pressure, produces an imbalance in transcapillary fluid movement, as predicted by the Starling equation.[199] Substantial alveolar interstitial edema overwhelms the intrinsic safety factors, such as epithelial membrane impermeability, leading to airspace flooding.[200] Such increases in pulmonary hydrostatic pressure may occur via either a generalized increase in fluid volume or an acute redistribution of fluid, as occurs with acute heart failure.[201] Interestingly, the majority of patients with acute heart failure are normo- or hypertensive, and just 3% develop flash pulmonary edema.[202] Acute heart failure is the commonest cause of increased hydrostatic pressure and is very prevalent, with almost 658,000 emergency department visits in the United States per year.[203] Mortality from acute cardiogenic pulmonary edema ranges from 12 to 15% and is significantly worse than the overall 5% rate for acute heart failure.[204–206]

Diagnosis of cardiogenic pulmonary edema is dependent on the demonstration that the pulmonary edema has developed from cardiac dysfunction. Important prognostic clinical signs, such as raised jugular venous pressure or a third heart sound, may be difficult to appreciate in the critically ill.[199,207] Respiratory distress, exhibiting wheeze and widespread crepitations, occurs in any form of pulmonary edema, limiting their diagnostic value.[199] Chest radiography often shows a representative pattern but is limited in its ability to differentiate forms of pulmonary edema.[208,209] Approximately 20% of patients with acute heart failure lack radiological evidence of pulmonary congestion, possibly because a 30% increase in lung water is required for edema to show radiographically.[210,211] Elevated plasma levels of b-type natriuretic peptide (BNP) and N-terminal- proBNP occur in response to ventricular dilatation and pressure overload and have some value in determining the cardiac etiology of acute dyspnea.[212] A normal electrocardiogram is unlikely in the presence of heart failure, whereas an abnormal electrocardiogram can reveal an ischemic myocardium.[213,214] Ultrasonography can determine the presence or absence of cardiac dysfunction and may also distinguish between cardiogenic and noncardiogenic pulmonary edema.[215,216] Pulmonary artery catheterization may provide direct evidence of an elevated left atrial pressure by the measurement of an elevated pulmonary arterial wedge pressure and can also provide evidence regarding the cardiac output and systemic vascular resistance. However, routine use of the pulmonary arterial catheter does not improve outcome in most critically ill patients.[120,217] Measurement of the concentration of protein in pulmonary edema fluid along with the protein concentration in plasma is a noninvasive method to determine whether the pulmonary edema is hydrostatic or from increased permeability.[218]

Supportive therapy for acute cardiogenic pulmonary edema focuses on reducing pulmonary capillary hydrostatic pressure, with specific therapy aimed at the underlying cause. Supplemental oxygen is administered to target normoxia because hyperoxia may be associated with numerous unwanted effects in acute heart failure.[89,219] NIV provides several useful mechanisms, including increasing functional residual capacity, reducing myocardial preload and afterload, reducing oxygen consumption via a reduction in the work of breathing, and improving gas exchange permitting increased coronary oxygen supply.[220] A meta-analysis published in 2010, including the new large Three Interventions in Cardiogenic Pulmonary Oedema study (3CPO), has shown that continuous positive airway pressure (CPAP) and BiPAP are equally efficacious in reducing the need for invasive ventilation; however, only CPAP had a beneficial effect on mortality.[204,221] Morphine has numerous beneficial effects such as vasodilation, analgesia, and anxiolysis, but evidence of its benefit is lacking, and it may even be detrimental.[222] Cardiac preload may also be reduced with selective venodilators such as nitrates, and they are internationally recommended, although the development of hypotension can limit their usefulness.[223] Prospective, placebo-controlled evidence is lacking, although nitrates may be superior to diuretics.[223,224]

Diuretics are traditionally given for acute cardiogenic pulmonary edema, with their rapid relieving effect due to vasodilation rather than the later diuresis originally intended.[225] Although much accumulated evidence shows a beneficial short-term effect, again prospective placebo-controlled evidence is lacking.[223] Because diuretics are frequently used in nonhypervolemic patients with acute heart failure, due to multiple unwanted effects their place has been questioned.[226] Nesiritide is not recommended because it is associated with increased mortality when used in those with acutely decompensated heart failure.[227] Angiotensin-converting enzyme inhibition may be beneficial in acute cardiogenic pulmonary edema.[228,229] Further studies are awaited. Pharmacological support is required for the hypotensive or shocked patient, but the evidence base remains poor and does not support a clear superiority between catecholamines, phosphodiesterase inhibitors, and levosimendan.[230] An intraaortic balloon pump may be required to allow vital specific therapy such as coronary revascularization, or as a bridge to further supportive therapy such as a left ventricular (LV) assist device.[231–233] Extracorporeal support devices may similarly provide rescue therapy.[234]

Pulmonary Vascular Causes of Acute Respiratory Failure

Pulmonary embolism (PE) presents a severe impediment to arterial flow through the pulmonary vasculature, via mechanical obstruction, hypoxic pulmonary vasoconstriction, and the release of vasoactive neurohumeral factors, and it affects both cardiac and pulmonary function.[235] Although circulatory effects occur when 30 to 50% of the pulmonary vascular bed is occluded with thrombus, the size of the embolic burden is not the major determinant of outcome but, rather, whether right ventricular (RV) failure occurs.[236] As right-sided afterload increases acutely, the unconditioned thin-walled RV is unable to generate a pressure above 40 mm Hg; right heart output decreases, leading to decreased LV output and diminishing coronary blood flow.[236] The imbalance between increased RV workload with decreased coronary perfusion creates RV ischemia and predisposes to pulseless electrical activity and sudden cardiac arrest.[237,238] Respiratory effects result largely from V/Q mismatch, with vascular occlusion leading to dead space ventilation and also diverting excessive blood flow through patent vessels leading to shunt (Fig. 1).[235] Also, extreme right-sided pressures can open the foramen ovale, allowing intracardiac right to left shunting, further worsening oxygenation, and

predisposing to paradoxical emboli.[239] Oxygenation suffers more with the reduced systemic oxygen delivery producing relatively greater peripheral oxygen uptake leading to more desaturated venous blood entering the pulmonary vasculature.[235]

It has been estimated that 600,000 cases of PE occur annually in the United States and contribute either directly or indirectly to some 200,000 deaths.[240] Grading the severity of PE has changed recently from the size of the embolism (massive, submassive, nonmassive) to the risk of death (high, intermediate, low) for an individual.[241] An episode is considered to be high risk if shock or hypotension is present and occurs initially in 5% or less.[242] In contrast, non-high-risk PE is subdivided into intermediate-risk and low-risk PE, which are differentiated by the presence of RV dysfunction or myocardial injury. The mortality from an episode of PE is 8 to 15% if hemodynamically stable, 25 to 58% if hemodynamically unstable, and as high as 65% if cardiopulmonary arrests occurs.[242,243] Idiopathic PE is common, and 20% of persons with PE do not have an identifiable risk factor.[242] The most significant risk factors are trauma, orthopedic surgery, and general surgery, with odds ratios greater than 10.[244] PE represents one end of a spectrum of venous thromboembolism, highlighted by the fact that 70% of patients with PE have lower-limb deep venous thrombosis.[245]

Several rule systems for predicting the likelihood of PE have been developed, although simple clinical intuition may be just as good.[246–249] The mode of diagnosis depends on the severity of the syndrome.[241] Unstable patients with shock or arterial hypotension, in whom PE is considered likely, should undergo either CT, preferably multidetector CT (MDCT), or if too unstable for transfer, echocardiography (echo) in the ICU.[241,250] Echo signs of PE are mainly those of RV dysfunction and include RV dilatation and hypokinesis, increased RV:LV diameter ratio, increased velocity of the tricuspid regurgitation jet, and right-to-left shunt through the foramen ovale.[251,252] The presence of an RV thrombus virtually confirms the diagnosis and indicates an increased mortality.[253] Additionally, a normal RV on echo scan effectively excludes PE as the cause of circulatory compromise and allows a search for an alternative diagnosis such as pericardial tamponade.[241] If a multidetector CT scan is undertaken, thrombi may possibly be visualized as far as the fifth-order subsegmental pulmonary arteries.[254] Ventricular septal bowing and an RV:LV diameter ratio of greater than 1 are CT evidence of RV dysfunction. If the MDCT scan is negative the patient should have lower limb ultrasonography.[241,255,256] Other investigations are not considered here because they are inappropriate for the emergent management of high-risk PE.

Basic supportive therapy includes supplemental oxygen therapy to correct hypoxia and cautious fluid expansion to optimize RV filling without inducing RV ischemia.[257,258] Oxygen consumption can be reduced via the institution of MV to reduce the work of breathing, and sedation to diminish agitation.[259,260] Extreme care must be taken with the institution of anesthesia for tracheal intubation in a hemodynamically unstable patient. Ketamine's hemodynamic profile makes it an obvious, if evidence-light, choice.[27] Various pharmacological agents are available to support the circulation, either as vasodilators (isoprenaline, dobutamine, levosimendan, phosphodiesterase inhibitors), vasoconstrictors (dopamine, noradrenaline, adrenaline), or pulmonary vasodilators.[261–263] Because no randomized, controlled studies have evaluated these therapies, the evidence to guide practice is limited, with just a few physiological studies and case reports existing.[258] Two small case series investigating dobutamine in PE have shown increases in cardiac index and oxygen transport.[264,265] However, given its systemic vasodilatory properties it is uncertain if this is the ideal means of circulatory support. Sildenafil and both inhaled nitric oxide and prostacyclin may reduce pulmonary artery pressures but require larger evaluation before they can be recommended.[266–269] Ketanserin is a 5-HT blocker and in a small study slightly lowered pulmonary pressures in acute PE.[270]

Presently, specific therapy has two aims: the dissolution of the embolism and prevention of further embolism (Fig. 2). The embolism may be targeted by anticoagulation, thrombolysis, or embolectomy, either surgical or percutaneous. Prevention of further embolization requires anticoagulation or a vena caval filter, plus therapy for any risk factors. Unfractionated heparin is the anticoagulant of choice if thrombolysis is considered.[241,271] If there are not specific contraindications, high-risk PE should be treated with thrombolysis, with catheter-directed thrombolysis not being superior to systemic thrombolysis.[241,271,272] Over 90% of individuals treated with thrombolysis demonstrate clinical and echocardiographic improvements.[273] While a general mortality benefit has yet to be demonstrated with thrombolysis, it may be present in those with high-risk PE.[274,275] The optimal thrombolytic agent or regime is yet to be determined, but a short infusion period may achieve quicker thrombolysis with less bleeding complications.[271] If thrombolysis fails or is contraindicated, then surgical embolectomy or percutaneous embolectomy, via defragmentation and aspiration, may be considered and may have comparable outcomes.[276–278] ECMO may prove lifesaving until clot resolution is possible.[279]

After an acute episode, long-term anticoagulation is required, with the duration and depth determined by the causative factors specific to the case.[250] Chronic thrombotic pulmonary hypertension complicates up to 3.8% of patients at 2 years post-PE.[280]

Future Directions

Just as Ibsen heralded in a new era in respiratory support with the application of exogenous ventilation to replace failed endogenous ventilation during the Copenhagen polio epidemic of 1952, the emerging technology of extracorporeal lung support may herald a new era allowing severe respiratory failure to be assisted with an exogenous means of gas exchange in some patients with ARF. Management of lung failure now mirrors that of other organ failures, such as renal, cardiac, and, to a lesser degree, hepatic, in which the failed functional unit may be replaced at least temporarily. The greatest progress in the last 2

decades in the treatment of ARF has been the evidence that lung protective ventilation with smaller tidal volume and reduced plateau airway pressure markedly reduces mortality in patients with ALI and ARDS. With the rapid progression of growth factor and stem cell research, management of ALI and ARDS, and perhaps other causes of ARF, may become more directly treatable with the ability to improve healing of the injured organ.

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