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REVIEW

Critical care in the ED: potentially fatal asthma and acute lung injury syndrome

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Rick Hodder*

Divisions of Pulmonary and Critical Care, University of Ottawa and The Ottawa Hospital, Ottawa, Canada

*Dr Rick Hodder passed away on Tuesday April 17,2012. Please see the Dedication for more information on Dr Hodder.

Abstract: Emergency department clinicians are frequently called upon to assess, diagnose, and stabilize patients who present with acute respiratory failure. This review describes a rapid initial approach to acute respiratory failure in adults, illustrated by two common examples: (1) an airway disease – acute potentially fatal asthma, and (2) a pulmonary parenchymal disease – acute lung injury/acute respiratory distress syndrome. As such patients are usually admitted to hospital, discussion will be focused on those initial management aspects most relevant to the emergency department clinician.

Keywords: acute asthma, acute lung injury, ARDS, acute respiratory failure

Defining acute respiratory failure

A specific definition of what constitutes acute respiratory failure (ARF) is neither practical nor possible, as the individual patient's situation will always define the urgency of approach to management. It is, however, helpful to have an understanding of what constitutes a potentially dangerous gas exchange abnormality, so we can act to prevent or correct it.

Critical oxygenation

In general, hypoxemia as defined by an acute fall in PaO_2 to less than 50–55 mmHg, or an arterial oxyhemoglobin saturation (SaO_2% or SpO_2% if measured by pulse oximetry) less than 85%–88%, is important, because it signals a significant loss of oxygenation homeostasis and defines a status of minimal oxygenation reserve for the patient. Of course, oxygenation is critically dependent on oxygen delivery and utilization, both of which can be compromised in acute illness (eg, heart failure, sepsis, etc).

Critical PCO_2 and pH levels

The presence of acidemia, whether respiratory or metabolic, also indicates a loss of physiologic homeostasis and the presence of disease or dysfunction. However, hypercapnia is usually more of a marker than a cause of disease severity, and the safety of hypercapnic acidosis is fairly well documented in the critical care literature,[1] even with pH levels well below 7.20 (an exception might be the harmful consequences of hypercapnia in the setting of raised intracranial pressure). Indeed, it is interesting to note that the time-honored concept of so-called CO_2 narcosis has been challenged,[2,3] as commonly observed clinical PCO_2 levels are insufficient alone to induce a reduced level of consciousness, which is more likely reflective of patient fatigue and hypoxemia,

Correspondence: Pierre Cardinal
501 Smith Road, Ottawa,
ON K1H-8L6, Canada
Email pcardinal@royalcollege.ca

at least in the setting of isolated ARF. Nevertheless, an acute rise in PCO_2 causing a fall in pH to less than 7.20–7.30 cannot be ignored because it indicates a potentially dangerous loss of ventilatory reserve and capacity, and equally importantly, probably a fatiguing patient. Less commonly, sustained severe hypocapnia (eg, $PCO_2 < 20–25$ mmHg) can be harmful by reducing cerebral blood flow.

Classifying respiratory failure

Traditionally, respiratory failure is divided into a primary failure to oxygenate (hypoxemic failure), or a primary failure to ventilate (hypercapnic or hypoventilatory failure). Examples of primarily hypoxemic failure include severe pneumonia, pulmonary edema, and acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Quite often, early on in the course of hypoxemic failure, there is a high drive to breathe (stimulated by hypoxemia, various lung and airway receptors, and the disease process itself), so that the spared and relatively healthy lung regions can actually support alveolar hyperventilation and produce an initial hypocapnic respiratory alkalosis (reduced $PaCO_2$), despite significant hypoxemia. However, as the disease process advances and less healthy lung remains, or if central nervous system depression occurs, or if the breathing muscles lose their ability to cope with increasing ventilatory loads, alveolar hypoventilation may supervene and the $PaCO_2$ begins to rise, culminating in secondary hypercapnia. For this reason, a normal or rising $PaCO_2$ is a cause for concern, as it indicates a loss of patient ventilatory reserve that may require urgent intervention.

Primary hypercapnic respiratory failure can be further subdivided into failure of the respiratory centers (central failure), or failure of the ventilatory pump (peripheral failure). The ventilatory pump consists of the chest wall, diaphragm, and accessory muscles of breathing. Patients with peripheral failure of the ventilatory pump often work very hard to breathe (eg, kyphoscoliosis, myopathy, hyperinflation in chronic obstructive pulmonary disease [COPD]), but cannot breathe effectively and so develop hypercapnia. Ventilatory pump failure also commonly occurs if primary hypoxemic failure is sustained and the diaphragm begins to fail due to high breathing loads. Patients with central respiratory failure usually show no signs of distress and have a decreased respiratory rate (eg, narcotic/sedative overdoses, brain tumor). These patients may have healthy lungs, and hypoxemia is secondary to the hypercapnia. The pathophysiologic interrelationships of ARF are shown in Figure 1, illustrating that acute lung failure can lead to failure of the vital pump and vice versa.

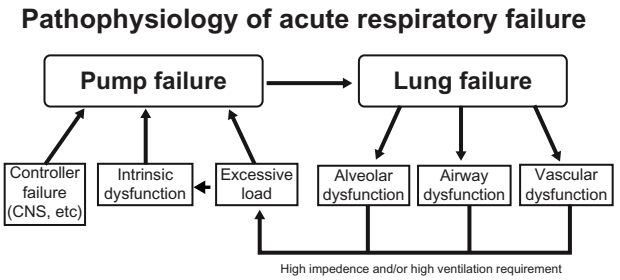

Figure 1 Pathophysiologic inter-relationships in acute respiratory failure.
Abbreviation: CNS, central nervous system.

Monitoring respiratory failure

An arterial puncture is not always necessary to assess the adequacy of gas exchange. Compared to arterial sampling, pulse oximetry, supplemented by venous blood gases are easier to obtain and less traumatic for the patient. The SpO_2% from a pulse oximeter placed on a well-perfused region (digit, nose, earlobe, etc), that is accurately tracking the patient's pulse, provides the essential information on arterial oxygenation required, as arterial oxygen content is primarily dependent on oxyhemoglobin saturation rather than arterial PO_2. Pulse oximeters are accurate to ±2%–3% over the usual range of clinical interest, and tend to be less reliable if the true SaO_2% is <80%, but if the reading is that low, the details are not important, because you know your patient has a serious oxygenation problem.

Under most circumstances, there is good correlation between the pH and PCO_2 values obtained by venous ($PvCO_2$) and arterial sampling,[4,5] and so the acid-base status of any patient can be quickly obtained from a venous blood gas sample, which can be taken by anyone skilled at venipuncture (eg, when inserting an intravenous line). In general, regardless of the absolute value, the $PvCO_2$ will always be about 5 mmHg higher than the corresponding arterial PCO_2, and the venous pH only slightly lower. The normal $PvCO_2$ is 45 mmHg, and any increase signifies some degree of hypercapnia. Obviously, the PvO_2 cannot be used to assess the state of arterial oxygenation and should be ignored. Because of ventilation dead space issues, end-tidal CO_2 monitors do not accurately reflect arterial PCO_2 in sick patients with lung disease.[6,7]

There are some important clinical respiratory warning signs that should not be ignored in assessing the patient with potential ARF. Although nonspecific, a high respiratory rate is one of the most sensitive signs of respiratory failure (for example, in the setting of community-acquired pneumonia, a breathing rate above 30 per minute correlates with an increased risk of dying).[8]

Observation for central cyanosis (bluish discoloration of the warm mucous membranes) is often sought as a sign

of ARF, but it is important to realize that to appreciate cyanosis at the bedside, there must be at least 50 g of reduced hemoglobin in the capillaries (not arterial blood).[9] It follows that the patient's hemoglobin level will influence when we can appreciate cyanosis in the course of ARF. For example, in a typical intensive-care unit (ICU) patient whose hemoglobin is 120 g/L, the observation of central cyanosis would be associated with an arterial PO_2 of about 45 mmHg and arterial SaO_2% about 80%. Clearly the observation of central cyanosis is only a late sign of significant ARF.

The breathing muscles have been called the "vital pump" and can experience fatiguing stress during ARF.[10] Use of accessory breathing muscles, in particular use of the inspiratory sternocleidomastoid muscles and of the abdominal muscles on expiration, indicates excessive loading of these muscles and strongly suggests a serious underlying respiratory problem, which, if not remedied, may progress to respiratory muscle fatigue and failure with collapse of the patient from breathing exhaustion (Figure 1). So-called "paradoxical breathing" or "abdomen/thorax discoordination," in which the abdominal wall moves inward instead of outward during inspiration is another sign of possible impending collapse of the vital pump, because it signifies the presence of very high inspiratory loads and a weakened diaphragm and usually indicates that some form of assisted ventilation will soon be needed. Patients with neuromuscular disease such as myopathy or Guillain–Barré syndrome present a special problem in recognition of ARF, because they may not be capable of demonstrating the usual signs of respiratory distress of a failing vital pump. A high index of suspicion is required, as such individuals may only present with a rapid respiratory rate and a sense of air hunger, or dyspnea if asked (be careful not to simply ascribe this to "anxiety").

Table 1 Primary assessment in acute respiratory failure

Scan the room

- Is there help available (eg, nurse, respiratory therapist, another physician)?
- Has supplemental oxygen been started? Is it nourishing the patient or the pillow?
- Is an oximeter present? Is it on the patient or the bed? Is it tracking the pulse?
- Is there a noninvasive blood pressure cuff on the patient? Is it cycling often?
- Has an intravenous been started? Is it working? Is it compromised by the blood pressure cuff?
- Is the ECG being monitored? Is rhythm benign or malignant?
- Are family members or similar present?

Scan the patient

Once the scene has been quickly assessed, your attention should turn quickly to the patient. It is important to follow a logical approach to assessment:

- First examine for signs of upper airway obstruction. The ability to talk and the absence of inspiratory stridor usually excludes glottic or supraglottic upper airway pathology (of course, the ability to talk in an intubated patient tells you that the endotracheal tube has either migrated out of the larynx, or is in the esophagus!)
- The initial respiratory exam should be limited to a quick inspection, palpation and auscultation looking for the following:
  - respiratory rate (calm or labored?)
  - use of accessory muscles of inspiration and expiration
  - expiratory breath sounds continue up to the next inspiration (air trapping)
  - midline trachea
  - asymmetrical movement of both hemithoraces (eg, pneumothorax, large effusion)
  - asymmetry of breath sounds
  - absence of expiratory breath sounds (eg, extreme hyperinflation, bilateral pneumothoraces)
  - diffuse crackles (eg, pulmonary edema, fibrosis)
  - diffuse, musical wheezes (eg, asthma, COPD)
  - focal, monophonic wheezes (eg, large airway obstruction)
  - signs of failure of the "vital pump" (see text)
  - is the skin, cool, mottled, cyanotic?
  - is the patient calm, agitated, seizing, fatigued?

Initial management of respiratory failure: the primary assessment

When confronted with a patient with possible respiratory failure, the experienced clinician begins an instinctive, coordinated combination of assessment and concurrent initial management, based on basic principles and past experience. This primary assessment involves a rapid (~1–2 minutes) initial evaluation for danger signs and the simultaneous institution of therapy, even before a diagnosis is reached. An example of a general approach to primary assessment in ARF is outlined in Table 1. Simultaneously with this brief initial examination, which should always include an assessment of the "vital pump" for signs of excess ventilatory loads, an oximeter should be placed for measurement of the SpO_2%. If an assistant is present, blood should also be drawn for initial biochemistry, hematology, and venous blood gas assessment.

Empiric oxygen therapy

When respiratory failure is highly likely, administration of empiric oxygen is the most prudent course, and comprehensive guidelines for emergency oxygen therapy have been published by the British Thoracic Society.[11] Except in the closed system of the intubated patient or the patient receiving noninvasive positive pressure ventilation (NPPV) by mask or hood, the precise amount of oxygen being delivered to the patient (fraction of inspired oxygen – FIO_2) cannot be known

with certainty. Even though the oxygen delivery device may indicate "100% O_2," this will never reflect the FIO_2 in the patient's trachea, as all delivery devices allow varying degrees of entrainment of "room air" by the patient, which will be greater (ie, reduced tracheal oxygen concentrations) the higher the patient's minute ventilation. In fact, it can be argued that the estimated FIO_2 is irrelevant, because what really matters is the effectiveness of oxygen administration as reflected in the SpO_2%. The goal should ideally be an $SpO_2\% \geq 92\%$, but in difficult situations, an SpO_2% of 85%–88% will at least confer a reasonable arterial oxygen content in patients with normal hemoglobin levels.

In patients who are severely hypoxemic (eg, $SpO\% < 85\%$), particularly if the problem is acute asthma or primary hypoxemic failure (eg, pulmonary edema, pneumonia, ALI/ARDS, etc), it is best to start with an inspired oxygen concentration of as close to 100% as possible, because the greatest danger is uncorrected hypoxemia. This can be administered by simple oxygen mask, by a non-rebreather mask with oxygen reservoir, or by new high-flow nasal cannulae that deliver heated, saturated oxygen at rates of up to 50 L/min.[12] For reasons noted above, 100% oxygen cannot actually be delivered to the lower airways unless the patient is intubated, and so there should be minimal concern about normobaric oxygen toxicity in the acute setting. Tissue damage from reactive oxygen species, for example, begins on the endothelial side of the lungs and so requires high local arterial PO_2 levels, which by virtue of the presence of respiratory failure are difficult to achieve. However, if patients are not initially severely hypoxemic, starting a very high oxygen concentration can have significant undesirable consequences that are not generally appreciated.[13,14] One of these is the observation that intrapulmonary shunt can worsen with unnecessarily high FIO_2 levels due to provocation of absorption atelectasis.[15] Another poorly appreciated, potentially harmful consequence of administering unnecessarily high oxygen concentrations as a "precaution" or to provide a "margin of safety" is that this does just the opposite and leads to delayed recognition of deteriorating lung function.[13,14,16] If the lung disease is not so severe, so that a high SpO_2% is easily obtained using high oxygen concentrations, the flat slope of the oxyhemoglobin dissociation curve will mean that considerable changes in gas exchange, including significant hypoventilation, could occur while the pulse oximeter still reads an $SpO_2\% > 90\%$, thus masking real physiologic deterioration. Furthermore, with excessive oxygen dosing, it will take longer for this deterioration to be recognized by a significant fall in SpO_2%. Thus, if there is severe hypoxemia, enough oxygen to raise the $SpO_2\% > 92\%$ is justified, but in the face of lesser degrees of hypoxemia (eg, SpO_2% 85%–90%), beginning with a lower FIO_2 to achieve an $SpO_2\% \geq 92\%$ is preferred, as it will permit earlier recognition of pulmonary deterioration (fall in SpO_2%) should this occur. This emphasizes the need for frequent and comprehensive reassessment of all patients with ARF. The special case of oxygen-induced hypercapnia is discussed below.

On the other hand, in patients with only modest hypoxemia, and in particular those with an acute COPD exacerbation, it is probably prudent to begin with low-flow oxygen delivered by standard nasal cannulae at 2–4 L/min, or low FIO_2 venturi masks, and to follow the SpO_2% response closely and often. Particularly in the setting of COPD, concern is frequently expressed that empiric administration of high concentrations of oxygen may result in a dangerous rise in $PaCO_2$, and "CO_2 narcosis." Studies in patients with COPD have shown that when PCO_2 rises in response to oxygen therapy, the causes are multifactorial and not solely due to suppression of hypoxic drive to breathe.[3,17] Furthermore, the existence of so-called CO_2 narcosis has been questioned,[3] and it must be emphasized that uncorrected hypoxemia is far more dangerous than hypercapnia. In one classic study, when 100% oxygen was given to hypoxemic COPD patients experiencing an exacerbation, even though PCO_2 rose on average 23 mmHg over 15 minutes, no changes in the patients' level of consciousness were noted.[3]

The response to oxygen therapy may provide important clues to the etiology of the respiratory failure. The hypoxemia of patients with central hypoventilatory failure, or with an exacerbation of COPD and often asthma, will usually easily correct with relatively low concentrations of oxygen. On the other hand, failure to rapidly correct hypoxemia suggests diseases that produce a severe intrapulmonary shunt (ie, alveoli that are perfused but not ventilated), such as a pneumonia, ALI/ARDS, or a right-to-left intracardiac shunt, as is occasionally seen in the patient with a patent foramen ovale and pulmonary hypertension. Failure to correct the hypoxemia despite a high inspired concentration of oxygen should be recognized early and should trigger the physician to consider alternative therapies, such as assisted ventilation, either invasive or noninvasive.

Acute potentially fatal asthma

The case

A 32-year-old man with chronic, poorly controlled asthma has been in the emergency department for 1 hour with only partial response to aggressive bronchodilator therapy and a single intravenous dose of corticosteroids. He is considered

to be at high risk for potentially fatal asthma because of the following clinical features: he is a smoker and has a history of depression; he was admitted to hospital for asthma 8 months previously, and during that stay, 1 day of mechanical ventilation in the intensive care unit was required; his most recent asthma exacerbation occurred 2 months ago; he has a poor understanding of how to control his asthma and has been relying exclusively on salbutamol for relief of symptoms.

Recognizing potentially fatal asthma

Management of acute potentially fatal asthma is the subject of frequent reviews and guidelines.[18–20] Most asthma exacerbations treated in the emergency department (ED) with first-line standard care resolve within 2 hours of presentation, and overall the mortality rate from acute asthma exacerbations is low (<0.1%), with most deaths occurring before arrival at a hospital.

Effective and efficient treatment of acute asthma in the ED requires prompt recognition of the patient at risk for potentially fatal asthma, so that appropriately aggressive therapy and monitoring can be assured. Some of the historical features and signs/symptoms predictive of high-risk patients are listed in Table 2. An evaluation for these risk factors is important, because when stable, patients who have survived a near-fatal episode of asthma are indistinguishable from other patients with asthma, at least on clinical grounds.[21] The strongest predictor of potentially fatal asthma is a history of previous admission to hospital or ICU for asthma.[22,23] Patients with such a history should be identified and monitored closely for 1–2 hours after arrival in the ED, regardless of apparent stability or improvement in response to initial therapy. Appropriate management of the patient whose distress persists despite aggressive initial asthma therapy also requires an awareness of conditions that may mimic an acute asthma attack, such as upper airway obstruction, foreign body aspiration, vocal cord dysfunction syndrome,[24] hysterical conversion reaction, and Münchausen syndrome.

Table 2 Risk factors for potentially fatal asthma

(1) Historical features:

Asthma control and severity
- Poor asthma control
- History of admission to hospital, or ICU for asthma
- History of multiple emergency department visits for asthma
- Pattern of sudden attacks
- History of previous hypercapnic asthma attack

Medication use
- Poor adherence with asthma medications
- Increasing reliance on β_2-adrenergic bronchodilators
- Underuse of inhaled corticosteroids
- History of need for oral corticosteroids
- Monotherapy with a long-acting β_2-adrenergic bronchodilators
- Asthma that is aggravated by acetylsalicylic acid or nonsteroidal anti-inflammatory drugs

Psychosocial profile
- Poor perception of breathlessness
- Psychological dysfunction (psychosis, anxiety, depression, denial)
- Socioeconomic factors (family discord, low income, ethnicity)
- Continued smoking
- Failure to use a written asthma action plan

Physician factors
- Failure to initiate (or delay in initiating) appropriately aggressive therapy
- Failure to objectively evaluate the severity of airflow obstruction in ED
- Failure to recommend appropriate strategies for avoidance of allergens, irritants, and work-related factors
- Failure to provide a written asthma action plan

(2) Signs and symptoms that may suggest a potentially fatal asthma attack

Signs:
- Use of accessory muscles
- Heart rate > 120/minute, or increasing
- Respiratory rate > 25–30/minute
- Difficulty speaking due to dyspnea/fatigue
- Altered level of consciousness
- Quiet chest in a patient with dyspnea or reduced level of consciousness
- Diaphoresis
- Inability to lie in the supine position because of breathing distress
- Peak expiratory flow <30% of predicted or forced expiratory volume in 1 second <25% of predicted 1–2 hours after initial therapy
- Oxygen saturation < 90%
- Cyanosis

Symptoms:
- Sense of progressive breathlessness or air hunger
- Sense of fear or impending doom
- Progressive agitation or anxiety

Managing acute asthma

Both patients and physicians tend to inaccurately gauge the level of airflow obstruction, which can lead to undertreatment and hence unacceptable risk of relapse.[25,26] Therefore, airflow obstruction must be measured objectively whenever possible, using either spirometry to record the forced expiratory volume in 1 second (FEV_1), or simple peak expiratory flow. Measurements of airflow obstruction can significantly help to guide therapy for acute asthma, and in one study more than 90% of patients presenting to the ED with acute asthma had valid spirometry measurements when the test was administered by trained personnel.[27] A peak expiratory flow <200 L/minute or <30% of predicted, or FEV_1 <1.0 L or <25% of predicted at any time during the asthma exacerbation indicates a high degree of airflow obstruction and suggests the presence of an elevated PCO_2 and the

potential for fatigue of the respiratory muscles.[28] Structured management plans and care maps for acute asthma have been shown to improve the use of objective measurements of airflow obstruction, increase the frequency of reevaluation and reassessment, and reduce admission rates and length of stay in both the ED and hospital.[29,30] Early response of FEV_1 or peak expiratory flow at 30–60 minutes after initial treatment is the best predictor of outcome.[31,32]

Recommended pharmacotherapy for acute asthma in varying stages will vary with local custom, but an approach that is representative of that found in most guidelines[18,20] is listed in Table 3. In general, the inhaled route for bronchodilators is as good as, or better than, giving the same drugs intravenously,[33,34] and there is only minimal data supporting the use of intravenous salbutamol in acute asthma in adults (more popular in pediatrics).[35] However, it may be considered for refractory cases in nonintubated patients in whom the inhaled route seems unlikely to succeed due to patient fatigue. Aminophylline is not recommended for acute asthma, as systematic reviews have consistently concluded that it confers no additional benefits over β_2-adrenergic bronchodilators alone. Rapid-acting inhaled β_2-adrenergic bronchodilators are thus first-line therapy for acute asthma. The optimal doses necessary to achieve maximal bronchodilation have not been defined, so dosing is empiric and should be titrated using an objective measure of airflow obstruction, such as FEV_1 or peak expiratory flow and clinical response. Use of a pressurized metered dose inhaler, preferably used with a valved holding chamber or spacer, is at least as effective as wet nebulization in acute asthma[18,36] and has the advantages of lower cost and the ability to provide sequential doses more quickly (four to eight puffs in 2 minutes vs 10–20 minutes for a single nebulization). When nebulization is used in severe asthma, continuous nebulization appears superior to intermittent nebulization for improvements in airflow obstruction and reduction in the need for admission to hospital.[37] Although ipratropium bromide, a short-acting anticholinergic bronchodilator, has a slower onset of action than the β_2-adrenergic bronchodilators, randomized controlled trials and a meta-analysis have shown that combining these two agents results in greater improvements in lung function and a significant reduction in the need for admission to hospital than use of β_2-adrenergics alone, particularly for patients with severe airflow obstruction ($FEV_1 \leq 30\%$ predicted).[38,39]

A dose of systemic corticosteroids should be administered within the first hour of treatment for acute asthma for all but those patients with the mildest form of the disease.[40] This therapy is particularly important for patients with a history of poorly controlled asthma and those already receiving oral corticosteroids. A recent large prospective study of asthma care in Canadian (Ontario) emergency departments has clearly demonstrated that the need for hospital admission for acute asthma was inversely related to the time to administration of

Table 3 Pharmacotherapy for acute asthma

Mild and moderate asthma

- Supplemental oxygen to keep $SpO_2 \geq 92\%$
- Frequent reassessment with objective measures (FEV_1 or peak expiratory flow)
- Frequent/continuous β_2-adrenergic bronchodilators
  - Salbutamol pMDI + spacer (100 mcg/puff): 4–8 puffs, q 15–20 minutes × 3; or
  - Salbutamol nebulizer (5 mg/mL): 5 mg (1 mL) in 3 mL 0.9% sodium chloride, q 15–20 minutes × 3; or
  - Salbutamol continuous nebulizer as necessary
- Anticholinergic bronchodilators
  - Ipratropium bromide pMDI + spacer (20 mcg/puff): 4–8 puffs, q 15–20 minutes × 3; or
  - Ipratropium bromide nebulizer (250 mcg/mL): 250–500 mcg (1–2 mL) in 3 mL 0.9% sodium chloride q 15–20 minutes × 3; or
  - Ipratropium bromide continuous nebulizer as necessary

All patients with FEV_1 or peak expiratory flow < 60% predicted or with moderate/severe dyspnea (consider venous or arterial blood gas)

- Corticosteroid
  - Prednisone PO: 50 mg tablet × 1 dose; or
  - IV methylprednisolone: 40–125 mg; dilute in 50 mL D5 W or 0.9% sodium chloride × 1 dose over 15–30 minutes, if there is concern about reliability of the oral route
- Consider
  - In addition to systemic corticosteroid, consider high-dose inhaled fluticasone 500 mcg (or equivalent) q 10 minutes × 1 hour
- Consider
  - IV magnesium sulfate (0.5 g/mL): usually 2 g (4 mL) in 100 mL D5 W over 20 minutes × 1 dose

If unresponsive to treatment, consider:

- Increase frequency of above inhaled bronchodilators
- High concentration O_2 (>60% if possible) with continuous oximetry
- Repeat IV magnesium sulfate (0.5 g/mL)
- Epinephrine IM (1:1000 solution = 1 mg/mL): 0.3–0.5 mg (0.3–0.5 mL) every 20 minutes as necessary
- Epinephrine IV injection: dilute 1 mL of 1:1000 solution (1 mg/mL) with 9 mL of 0.9% sodium chloride (=1:10,000 dilution) and give 0.1 mg (1 mL) IV over 5 to 10 minutes
- Epinephrine IV infusion: dilute 2 mL of 1:1000 solution (1 mg/mL) in 250 mL of D5W (=8 mcg/mL) and infuse at 1–4 mcg/min (=7.5–30 mL/hour)
- IV salbutamol 500 μg bolus followed by IV infusion at 5–20 μg /minute. Patients unresponsive to treatment may benefit from IV ketamine, aminophylline, or inhalational anesthetic agent (eg, isoflurane)
- IV ketamine 0.2–1 mg/kg load followed by infusion: 0.1–1 mg/kg/h
- Note: aminophylline not recommended as bronchodilator in the first 4 hours of treatment
  - Load: 3–6 mg/kg IV over 30 minutes (reduce dose by 50% if already taking aminophylline or theophylline) and follow with infusion: 0.2–1 mg/kg/hour (follow levels)

systemic corticosteroids.[41] Short-term administration of high-dose inhaled corticosteroids appears to accelerate recovery from acute asthma relative to systemic corticosteroids alone, particularly for patients with prolonged attacks and severe airflow obstruction.[42,43] The rapid effect of inhaled corticosteroids in this setting may reflect a mechanism of action different from their traditional anti-inflammatory effects, and it is postulated that high-dose inhaled corticosteroids have topical nongenomic effects on the airway epithelium, including vasoconstriction and mucosal decongestion. There is, however, insufficient evidence to suggest that inhaled corticosteroids should replace systemic corticosteroids for the treatment of severe acute asthma.[44]

There is no support for the routine use of intravenous magnesium sulfate for acute asthma, but there is evidence that it is effective in patients with no response to first-line initial therapy and those with initial, severe airflow obstruction (FEV_1 or peak expiratory flow <25%–30% predicted).[45] Despite the biological plausibility for modulation of turbulent airflow, systematic reviews have concluded that there is no role for the routine use of helium–oxygen mixtures in the initial treatment of acute asthma.[46] There may, however, be benefit for patients with more severe airflow obstruction in whom aggressive first-line therapy has failed.

The case continued

Despite repeated cycles of salbutamol plus ipratropium bromide by continuous nebulization, the patient remains in obvious breathing distress, with oxygen saturation 88% on a 100% non-rebreather mask. His level of consciousness begins to deteriorate as he becomes exhausted and somnolent from the high work of breathing. Repeat measurement of peak expiratory flow or FEV_1 is not possible because of his distress, and repeat venous blood gas analysis reveals pH of 7.23 and PCO_2 of 60 mm Hg. A colleague wonders whether a trial of noninvasive ventilation by mask should be started, as a potential means of avoiding intubation and invasive mechanical ventilation.

Noninvasive positive pressure ventilation for acute asthma

NPPV for acute disease is best delivered using a tight-fitting full-face mask, although other delivery forms are available. However, although NPPV is a promising modality, and works well for acute exacerbations of COPD and cardiac pulmonary edema, its routine use for acute asthma cannot currently be recommended.[47] Published anecdotal experience documenting the use of NPPV for adults with acute asthma is limited,[48–50] with only three small randomized controlled trials supporting its use in this setting.[48,51,52] In these controlled trials, the patients had significant airflow obstruction (FEV_1 < 60% predicted) but did not have hypercapnia. These patients also had good oxygenation (SpO_2% > 90% on room air) and were alert, cooperative, and able to perform spirometry. No evidence-based guidelines are available on the selection of patients with acute asthma for whom NPPV may be suitable, but suggestions for potential candidates are listed in Table 4.

Bronchodilators can be administered during brief periods when the NPPV is interrupted and the mask is removed, or by introducing either a nebulizer or a metered-dose inhaler into the ventilation circuit. The dosing of bronchodilators should be empiric and titrated to simple clinical outcomes such as slower, more comfortable breathing. Indeed, the main goal of NPPV for acute asthma is to avoid the need for intubation and invasive ventilation by reducing the load on the respiratory muscles, thus allowing the patient to rest and buying time for other aspects of therapy to have an effect. Accordingly, if the patient does not visibly relax within 30–60 minutes in response to the institution of NPPV, the setup and technique should be reassessed to ensure correct use. If the setup is appropriate but the patient is still in distress, judicious sedation with short-acting opiates and sedatives may be considered (but only in a high-dependency area staffed by personnel skilled at airway control and assisted ventilation) and the patient assessed for possible intubation and invasive ventilation. In most cases of respiratory failure complicating acute asthma, the safest approach is to administer sedation, intubate and start invasive mechanical ventilation.

Intubation for acute asthma

The decision to intubate in asthma is more an art than a science, and ideally should be made electively, before the patient suffers catastrophic respiratory collapse. There is no evidence to support a specific pH or a specific value of PCO_2 as a trigger for intubation, and worrisome initial blood gas levels often improve substantially in response to first-line therapy for acute asthma. There are, however, certain clinical criteria that suggest instability and failure to respond to initial therapy (Table 4), and patients meeting these criteria should be considered for immediate intubation. Endotracheal intubation of a patient with acute asthma who is exhibiting agitation and whose clinical condition is unstable can be difficult. Associated complications include hypotension and heightened risk of gastric aspiration caused by distension of the stomach because of swallowed air, either preexisting or from bag-and-mask ventilation. Adequate

preoxygenation is essential, but may be difficult in an agitated or delirious patient who is rapidly deteriorating.[53] Expert help from an anesthetist, intensivist, or other physician skilled at intubation in this setting should be called for immediately. If such help is not available, rapid-sequence intubation is recommended (Table 5), with the use of ketamine being preferred by some experts for its combined sedative and bronchodilator properties.[19]

Mechanical ventilation for acute asthma

Many patients requiring assisted ventilation for acute asthma are mainly exhausted but still have moderately preserved lung function and so are relatively easy to ventilate. However, others have extreme degrees of airway obstruction and hyperinflation that make mechanical ventilation very challenging, and may require input from an intensivist or other experienced individual. Adopting a ventilatory strategy that will prevent or help to reverse severe dynamic hyperinflation may reduce excessive morbidity and the high mortality rate associated with mechanical ventilation for acute asthma, although the greatest benefits will come from appropriate treatment of the underlying airway obstruction.[54] The basic principles of mechanical ventilation for acute asthma and suggestions for initial ventilator setup are listed in Table 5.

Patients with acute and potentially fatal asthma experience dynamic hyperinflation because obstruction of the expiratory airflow leads to air trapping. This is made worse when the inspiratory cycle is allowed to begin before the preceding exhalation and expiratory flow have finished. Conditions favoring the development of air trapping and dynamic hyperinflation include excessively rapid breathing rates (for both spontaneous breathing and machine ventila-

Table 4 Indications for assisted ventilation in acute asthma

Potential candidates for a trial of noninvasive ventilation

- Clinical judgment suggesting that asthma is likely to respond to treatment in a few hours or less
- High work of breathing
  - Breathing rate >30 breaths per minute
  - Use of accessory muscles of breathing
  - Obvious dyspnea
- Progressive fatigue
- Patient alert, cooperative
- Patient able to perform spirometry or peak expiratory flow measurement
- Oxygen saturation >90% on room air
- PCO_2 <45 mmHg
- No excessive coughing or phlegm
- No vomiting
- Hemodynamic stability

Clinical observations indicating probable need for elective intubation and mechanical ventilation

- Exhaustion
- Decreasing level of consciousness
  - drowsiness
  - confusion
  - unresponsiveness
- Signs of respiratory muscle fatigue
- Weak breathing efforts
- Silent chest
- Onset and progression of hypercapnia
- Progressive or refractory acidemia (pH < 7.10)
- Inability to maintain oxygenation by mask (oxygen saturation <90%)
- Cyanosis
- Cardiac instability
  - severe hypotension
  - severe cardiac dysrhythmia or ischemia

Table 5 Intubation and mechanical ventilation for acute asthma

Rapid sequence intubation for acute asthma

Prepare:

- Assemble equipment and verify functioning: suction, self-inflating bag and mask, oxygen source, laryngoscope, endotracheal tubes in varying sizes, stylet
- Ensure reliable IV access
- Assistant present

Induction:

- Ketamine 1.5 mg/kg IV (give as a bolus and may be an effective bronchodilator at doses of 2–3 mg/kg)
  or
- Propofol 2.0–2.5 mg/kg IV (start with 1.0 mg/kg);
- May add midazolam 0.1–0.3 mg/kg IV

Preoxygenate:

- 100% oxygen and follow SpO_2%

Paralysis:

- Succinylcholine 1.5 mg/kg IV; or
- Rocuronium 1.0 mg/kg IV

Pass the tube and begin assisted ventilation

- Ventilatory management should be supervised by a physician experienced with this therapy in a critical care area
- Intubated/ventilated patients may require ongoing sedation ± paralysis

Principles of initial mechanical ventilation for acute, potentially fatal asthma

1. Attempt to maintain oxygen saturation ≥92%
   - Use 100% oxygen initially
2. Have patience with the process of reducing PCO_2
   - Keep pH > 7.20 (give bicarbonate intravenously as needed)
3. Minimize dynamic hyperinflation
   - Modest rate of assisted ventilation (8–12 breaths per minute)
   - Low to normal tidal volume (6–8 ml/kg)
   - Inspiratory flow rates >60 L/min, or inspiratory time ≤ 1–1.5 sec
   - Peak inflation pressure <50 cm H_2O
   - Plateau pressure <35 cm H_2O
4. Begin with low applied positive end-expiratory pressure levels initially (eg, 2–5 cm H_2O)
5. If necessary, use intravenous opiates to suppress breathing drive and pharmacologic paralysis to prevent dysynchrony between patient and ventilator

tion) leading to inappropriately short exhalation times, and the setting of too large a tidal volume on the ventilator when there is insufficient time for exhalation.[54,55] If the waveform of the expiratory flow rates can be displayed on the ventilator, the presence of dynamic hyperinflation can be inferred by observing that expiratory flow persists right up to the onset of the next machine or spontaneous breath (Figure 2). Dynamic hyperinflation should also be suspected if exhalation sounds are heard (via a stethoscope over the trachea) right up until the next inspiration.[56] If exhalation has not stopped before the next inspiration starts in a patient who is breathing spontaneously, the adequacy of bronchodilator therapy should be reassessed and additional sedation may be required. If exhalation ends before the next inspiration begins, inducing slower breathing rates will not further reduce the risk of hyperinflation.[54]

The low tidal volume and low respiratory rates recommended to minimize the risk of new or worsening air trapping and dynamic hyperinflation in acute asthma are usually associated with some degree of reduced minute ventilation leading to varying degrees of hypercapnia. This approach, called controlled mechanical hypoventilation or permissive hypercapnia, has reduced the high mortality rate previously reported for patients with asthma undergoing ventilation.[57,58] Indeed, initially, it may not be possible to raise alveolar ventilation sufficiently to lower the PCO_2 without substantially worsening dynamic hyperinflation and causing dangerously high inflation pressures and hypotension through an increase in intrathoracic pressure. Therefore, it is often safest to accept a PCO_2 that is higher than normal and to control arterial or venous pH with intravenously administered bicarbonate if necessary (pH above 7.20 being a reasonable initial goal).[59] As the patient's fatigue, bronchospasm, mucosal edema, and airway plugging gradually resolve in response to bronchodilators and corticosteroids, minute ventilation will increase naturally, and PCO_2 and respiratory acidosis will improve. These changes indicate that weaning from mechanical ventilation may soon be possible.

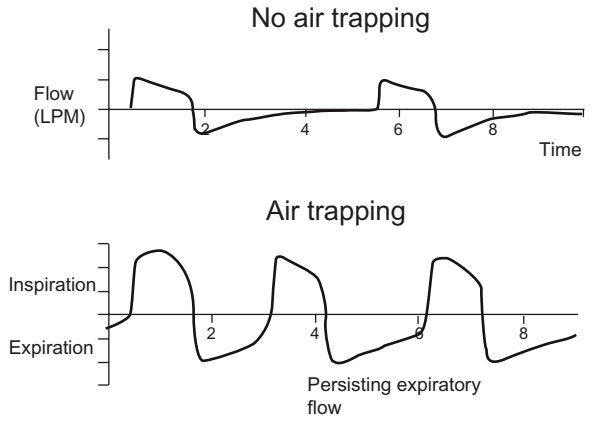

Figure 2 Ventilator flow-time tracing showing normal conditions (top) and persisting expiratory flow indicative of air-trapping and dynamic hyperinflation (bottom).

During invasive ventilation, bronchodilators can be administered by either wet nebulization or metered-dose inhaler with a holding chamber or spacer. The effects of turbulent flow dictate that if a metered-dose inhaler and spacer combination is used, multiple puffs (usually four to eight) timed with the patient's inspiration should be administered individually.[60] The dosing of bronchodilators should be empiric and should be titrated to simple outcomes, such as reduction of air trapping, increase in exhaled tidal volumes, and for patients who are breathing spontaneously, slower, more comfortable breathing.

Most patients with asthma will improve quickly after a period of ventilation and rest, and the endotracheal tube can be removed without a prolonged weaning phase, especially if fatigue was the main problem and the patient's lung mechanics were not too adversely affected. However, if the patient's lung mechanics and PCO_2 are slow to improve, weaning can be difficult, and a more gradual process is required, possibly involving consultation with experts.

The case continued

He is not felt to be a candidate for NPPV and is intubated. Shortly after mechanical ventilation begins, you notice that the tidal volumes delivered by the ventilator are falling, and soon the ventilator's high-pressure alarm begins to sound. The patient is still asleep and pharmacologically paralyzed with the drugs given before intubation. The postintubation chest radiograph shows extreme hyperinflation but no signs of barotrauma (ie, no pneumothorax and no mediastinal or subcutaneous air), nor opacities that might suggest pneumonia. It is quickly determined that in a misguided attempt to rapidly lower the patient's PCO_2 (which had a measured value of 60 mmHg), the ventilator has been set to deliver tidal volumes of 10 mL/kg at a breathing rate of 16 breaths/minute, which has worsened air-trapping and dynamic hyperinflation. The tidal volume is decreased to 7 mL/kg and the ventilator rate to 8 breaths/minute. The air trapping stops, as does the high-pressure alarm, indicating a safer ventilatory pattern.

Adverse effects of mechanical ventilation for acute asthma

Complications of invasive mechanical ventilation commonly occur, often immediately after intubation. Deterioration soon

after intubation, characterized by hypotension, hypoxemia, hemodynamic instability, or hypoventilation, may have several potential causes, including the sedative drugs used for intubation; preexisting intravascular volume depletion (dehydration); misplacement of the tube, such as intubation of the right main stem bronchus or esophageal intubation; sudden worsening of a preexisting but unrecognized pneumothorax coincident with initiation of positive pressure ventilation; substantial worsening of dynamic hyperinflation caused by excessive handbagging; or inappropriate setup of the ventilator.

Appropriate sedation to temporarily blunt the patient's drive to breathe is usually needed initially, to ensure the patient's comfort and safety and to maintain synchrony between patient and ventilator. Intravenously administered opiates, ketamine,[61] or propofol[62] are suitable for this purpose, but vigilance for drug-induced hypotension is necessary. Occasionally, sedation alone is inadequate, and consideration must be given to a period of pharmacologic paralysis to achieve safe and effective mechanical ventilation. Without adequate sedation and/or pharmacologic paralysis, the patient may become agitated and may physically interfere with mechanical ventilation or cause other problems by biting down on the endotracheal tube or even removing the endotracheal tube. Dysynchrony between the patient and the ventilator ("fighting the ventilator") should be dealt with initially by disconnecting the ventilator and assisting the patient's ventilation by means of a self-inflating bag with 100% oxygen.

The case continued

The patient's condition continues to improve, and ventilation is switched to a spontaneous mode consisting of continuous positive airway pressure plus pressure support. The next morning, the sedation is discontinued, and the endotracheal tube is removed. The patient is referred to a respirologist and an asthma educator to discuss ways to improve overall control of his asthma and to prevent another episode of potentially fatal asthma.

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS)

The case

A 59-year-old man with advanced alcoholic liver cirrhosis presents to the ED with several days of increasing abdominal girth, abdominal pain, and progressive shortness of breath. He is afebrile, peripherally edematous, mildly hypotensive, BP 100/45 mmHg, has sinus tachycardia at 120/minute, and is tachypneic at 20 breaths per minute without wheeze or cough. His initial chest radiograph is interpreted as showing some pulmonary edema (Figure 3A), perhaps from suspected (but unproven) alcoholic cardiomyopathy or possibly pancreatitis. Initial laboratory tests reveal: white blood cell count 17.7×10^9/L; venous $PvCO_2 = 28$ mmHg; $SpO_2\% = 90\%$ while breathing supplemental oxygen via nasal cannulae at 2 L/min. He is given IV furosemide and the oxygen is increased to 6 L/min, and initially he seems to stabilize. He is observed in the ED and given a second dose of furosemide, but 4 hours later he is worse. His breathing rate has increased to 32/minute; he is more dyspneic; $PvCO_2$ has risen to 40 mmHg and the $SpO_2\% = 88\%$ despite being on a non-rebreather oxygen mask at 15 L/min. A repeat chest radiograph shows widespread interstitial opacities characteristic of worsening pulmonary edema (Figure 3B).

Defining ALI/ARDS

Intensivists and researchers have defined ALI as being a milder form of acute hypoxemic failure than ARDS, but neither the common definition nor the distinction is very helpful for the ED clinician. Both conditions are defined as acute hypoxemic respiratory failure with bilateral pulmonary opacities/infiltrates on the chest radiograph, in the absence of left atrial hypertension.[63,64] ARDS is considered to be more severe, requiring a PaO_2/FIO_2 ratio ≤ 200, whereas ALI requires a PaO_2/FIO_2 ratio ≤ 300 (a healthy person breathing room air has a PO_2/FIO_2 ~ 450–480). However, from a practical perspective, these criteria for definition are impractical for several reasons: the FIO_2 can only be accurately determined in the intubated, mechanically ventilated

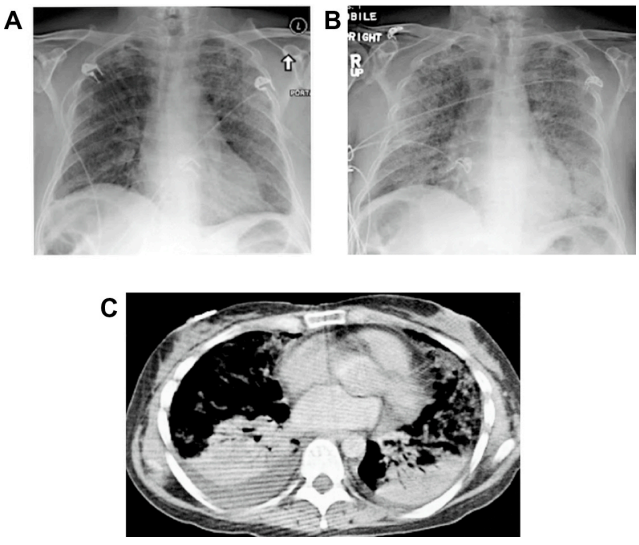

Figure 3 Early ALI/ARDS showing mild interstitial pulmonary edema (Figure 3a), progressing over several hours despite diuretic therapy (Figure 3b). Computed tomography of established ALI/ARDS showing dependent (dorsal) congestive atelectasis and relative sparing in non-dependent anterior zones.

patient, and it is not always easy to exclude an element of left atrial hypertension in the acutely hypoxemic patient without either invasive measurement of central venous or pulmonary artery occlusion pressures, or at least echocardiography, all of which are usually impractical during the initial ED assessment. Furthermore, ALI as formally defined, does not necessarily progress to ARDS, and these consensus definitions of ALI/ARDS, being purely clinical, do not predict the typical pulmonary pathology of diffuse alveolar damage seen in advanced ARDS. For these reasons, I will refer to ALI/ARDS as a single entity without specific distinction and develop a practical approach that is more meaningful for the practising ED clinician.

ALI/ARDS is not a specific disease, but rather a syndrome with many potential causes.[63,65] It is an inflammatory process involving the lungs, which results in disruption of the alveolar-capillary membrane, causing an accumulation of protein-rich and cellular fluid in the pulmonary interstitium and alveoli (noncardiogenic pulmonary edema). An initial exudative phase is associated with neutrophil invasion, washout of surfactant, alveolar edema and collapse (atelectasis), and very low lung compliance (ie, "stiff lungs").[63] This results in high degrees of intrapulmonary shunting causing often, resistant hypoxemia in lungs that are difficult to ventilate safely. The inflammation of ALI/ARDS is similar to that associated with the cytokine storm characteristic of severe sepsis (a common cause of ALI/ARDS) and includes microvascular thrombosis and inflammation, and widespread oxidative damage. If the patient survives the initial insult, a proliferative lung-repair phase may begin in a few days, which can lead to eventual lung destruction and fibrosis causing extreme pulmonary debilitation or even death from refractory hypoxemia. When ARDS lungs are biopsied at this stage, the finding is invariably nonspecific diffuse alveolar damage.

Risk factors for ALI/ARDS are multiple,[65] and some are listed in Table 6. The injury to the lungs may be direct to the airway epithelium, as in pneumonia, near drowning, trauma, inhaled toxins, gastric aspiration, burns, etc (so-called pulmonary ALI/ARDS), or indirect from a systemic source such as shock, sepsis, pancreatitis, drugs, fat embolism, etc, that initially injures the vascular endothelium via the generation of proinflammatory cytokines (so-called extrapulmonary ALI/ARDS). Even when the initial injury is directly to the lungs, proinflammatory cytokines are generated, which can spill over into the systemic circulation, causing ALI/ARDS to evolve into a systemic illness. Thus, ALI/ARDS can both result from multisystem organ failure (MOF) and cause MOF.[66]

Table 6 Common risk factors for ALI/ARDS

Direct lung injury (Pulmonary ALI/ARDS)	Indirect lung injury (Extrapulmonary ALI/ARDS)
• Pneumonia	• Sepsis
• Aspiration	• Shock
• Pulmonary trauma/contusion	• Pancreatitis
• Near drowning	• Burns
• Inhalational injury	• Crush injury
	• Fat embolism syndrome
	• Reperfusion injury

Despite much research and evidence of improved clinical outcomes from lung-protective and low-tidal-volume ventilation strategies, reported mortality from established ALI/ARDS remains high,[63,66,67] ranging from 26% to over 60%. Several factors influence reported mortality, including the nature of the inciting injury (lowest with trauma, highest with sepsis), the timing of recognition and specific treatment, and whether studies were simply observational (higher reported mortalities), or randomized controlled trials done in specialized referral centres (lower mortalities). The systemic nature of ALI/ARDS is exemplified by the fact that death from ARDS is more commonly due to MOF (30%–84%) than due to refractory respiratory failure (13%–19%).[66] Many patients who survive ALI/ARDS return to near-normal life, but others are left with somewhat reduced exercise capacity, emotional and psychological sequelae, and reduced quality of life.[68]

Differentiating ALI/ARDS from other causes of acute respiratory failure

ALI/ARDS usually presents to the ED physician as a case of acute hypoxemic respiratory failure, quite distinct from an exacerbation of COPD. A key initial decision facing the ED clinician is whether the patient's presumed pulmonary edema is cardiogenic or not. Acute cardiac pulmonary edema is much more common than ALI/ARDS in the ED, and so is the appropriate usual initial working diagnosis in patients with obvious cardiac-disease risk factors (elderly, diabetes, hypertension, smoking, abnormal ECG, etc), even if there is concomitant evidence for possible ALI/ARDS risk factors (Table 6). Furthermore, it has been observed that up to 30% of patients with ALI/ARDS may have some volume overload,[69] and of course, ALI/ARDS can occur in patients with concomitant heart failure (the standard consensus definitions are inadequate in this regard). Some investigators have attempted to use B-type natriuretic peptide (BNP) to differentiate cardiogenic from noncardiogenic pulmonary edema in

acutely dyspneic patients (BNP < 100 pg/mL – cardiogenic edema unlikely; BNP > 500 pg/mL – cardiogenic edema likely), but in patients with or at risk for ALI/ARDS, there is considerable overlap making this blood test unreliable as an isolated parameter.[70]

Thus initial empiric therapy with intravenous diuretics, etc, can often be justified when there is uncertainty about combined ALI/ARDS and cardiac disease. One clue to the possible presence of significant ALI/ARDS and noncardiogenic pulmonary edema is the speed of response to treatment. Patients with pure cardiogenic pulmonary edema are generally fairly easy to oxygenate and usually respond to appropriately aggressive specific therapy quickly. On the other hand, patients with ALI/ARDS are unlikely to respond significantly to diuresis (they may in fact deteriorate with hypotension), because the distinct pathophysiology of their noncardiogenic pulmonary edema dictates that it takes much longer (often several days) to respond to treatment.

Although ALI/ARDS is relatively uncommon at the time of presentation to the ED,[71,72] it is important to identify patients with acute respiratory failure who are at risk for progressing to ALI/ARDS as soon as possible, because this defines a group of patients at high risk of poor outcome who merit aggressive preventative, supportive, and specific therapy.[71–73] Patients coming to the ED with acute respiratory failure who eventually declare themselves to have ALI/ARDS usually do so within a few hours of presentation,[71,73] suggesting that there is often time for the ED clinician to narrow down the diagnosis and institute specific preventative (eg, low tidal volume ventilation, etc) or rescue therapy. Therefore, depending on local resources, it may be possible to obtain additional data via BNP measurement (with appropriate caveats), central venous pressure monitoring and echocardiography in cases where the cause of presumed pulmonary edema is in doubt. Clinical risk factors supporting a potential diagnosis of ALI/ARDS (Table 6) should not be ignored. One group of investigators has attempted to develop a lung injury prediction score to identify patients at risk for ALI/ARDS.[72] They studied only patients considered to be at risk of ALI/ARDS by virtue of having sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma (eg, lung contusion, smoke inhalation), or high-risk surgery (orthopedic spine, cardiothoracic, etc), who had already been hospitalized (ie, transferred out of the ED). The lung injury prediction score verified the validity of these risk factors for ALI/ARDS, but had only a low positive predictive value (0.14–0.23). Its negative predictive value on the other hand was high (0.96–0.98). The incidence of at-risk patients who developed ALI/ARDS in this study was relatively low (6.8%). On the other hand, other investigators have suggested very simple guidelines for early identification of patients at risk for ALI/ARDS in the ED or on the hospital ward.[71] Using only basic clinical data readily available in the ED, they observed a 33% incidence of ALI/ARDS in patients who met the entry conditions of bilateral radiographic opacities in the absence of overt right atrial hypertension and who needed supplemental oxygen therapy >2 L/minute (odds ratio for ALI/ARDS requiring assisted ventilation 8.1, 95% CI 2.7–24.5), with sensitivity and specificity of 73% and 79%, respectively, and positive and negative predictive value of 63% and 85%, respectively. Patients with ALI/ARDS risk factors who meet such criteria should be identified and closely monitored for progression that would require aggressive intervention. Clinical features that may help in identifying patients with acute respiratory failure who are at risk of progressing to ALI/ARDS are listed in Table 7.

Managing ALI/ARDS

In approaching the patient with potential ALI/ARDS, it is important to treat pathophysiology rather than presumptive labels (ALI/ARDS, CHF, pneumonia, etc), and so initial supportive management of ALI/ARDS follows the general approach to ARF outlined earlier. Because ALI/ARDS is a syndrome rather than a specific disease, the clinician must search for an underlying cause and aggressively treat the inciting event (pneumonia, sepsis, etc). Not infrequently, some

Table 7 Clinical features identifying patients likely to progress to acute lung injury/acute respiratory distress syndrome (ALI/ARDS)[a]

Patient characteristics
- Abnormal chest radiograph
  - Bilateral opacities/infiltrates
  - Interstitial opacities
  - Basilar opacities consistent with atelectasis or consolidation
  - Pleural effusions with adjacent consolidation
- SIRS
- Immunosuppression
- Need for supplemental oxygen >2 L/min

Absence of distracting conditions
- Absence of obvious left atrial hypertension
  - RAP ≤14 mmHg, PAOP ≤18 mmHg
  - No echocardiographic evidence of left ventricular dysfunction
  - BNP ≤400 pg/mL
  - Absence of acute coronary syndrome
- Absence of respiratory failure due to chronic lung disease or neuromuscular disease

Abbreviations: SIRS, systemic inflammatory response syndrome; RAP, right atrial pressure; PAOP, pulmonary artery occlusion pressure; BNP, B-type natriuretic protein.

element of shock (often septic) is involved with ALI/ARDS, and so an aggressive approach to so-called early goal-directed therapy of severe sepsis[74] is warranted in an attempt to prevent progression to full-blown ARDS with its high mortality rate. It is important to keep in mind that the noncardiogenic pulmonary edema characteristic of ALI/ARDS takes much longer to respond to treatment than typical congestive heart failure, and so the ED clinician must resist the temptation to be overly aggressive with attempted diuresis, as this may worsen underlying shock and help precipitate MOF.[74,75] On the other hand, initial resuscitation with early goal-directed therapy may require significant fluid administration, and it is well established that alveolar fluid clearance is impaired in ALI/ARDS and that wet lungs contribute to the mortality of this syndrome.[75] This can make ALI/ARDS therapy tricky, requiring close attention by experts in an ICU setting. Once the patient with ALI/ARDS has been resuscitated, there is some evidence showing improved survival from gentle diuresis and a conservative fluid therapy approach.[75]

Assisted ventilation for ALI/ARDS

Once ALI/ARDS has been established as the working diagnosis, the ED physician should consult colleagues expert in the management of this syndrome and arrange for admission to the ICU, or some similar high-dependency area. Although there are anecdotal reports and small case series reporting success with NPPV for ALI/ARDS,[76,77] its routine use cannot be recommended.[76] On occasion, the ED clinician may be charged with managing the initial phases of assisted ventilation for the patient until a transfer can be made. In this regard, it is important to emphasize that inappropriate application of positive pressure ventilation to patients with ALI/ARDS may actually worsen the disease process and provoke systemic MOF, through a phenomenon that has been called ventilator-induced lung injury (VILI).[78]

The pathology of ALI/ARDS is unevenly distributed throughout the lungs, with some areas being relatively spared (usually the nondependent regions), while the more dependent (usually dorsal) regions suffer severe congestive atelectasis with high degrees of intrapulmonary shunting of blood, causing often refractory hypoxemia (Figure 3C). Sustained high oxygen concentrations necessary to achieve satisfactory oxyhemoglobin saturations can also lead to lung injury from oxygen toxicity, likely primarily in the relatively spared lung regions. Inappropriate attempts to open up the atelectatic regions by employing high tidal volumes and/or high ventilating pressures will injure not only the diseased areas but also those relatively spared areas, which may experience local damage and inflammation and even pulmonary barotrauma, such as pneumothorax and pulmonary interstitial emphysema. Repetitive opening and closing of atelectatic lung units throughout the ventilation cycle can generate shear forces that lead to physical disruption of the alveolar-capillary membrane, generating proinflammatory cytokines that further injure the lung and spill over into the systemic circulation and contribute to the development of MOF (so-called biotrauma).[66,78]

There are many ventilation modes that can be used with ALI/ARDS (eg, volume-limited ventilation, pressure-limited ventilation, volume-assured pressure-limited ventilation, high-frequency oscillation, airway pressure release ventilation, etc), all designed to open up the lungs while limiting additional lung damage.[79–81] Despite the fact that various clinician experts will favor one ventilation mode or strategy over others (often vigorously!), no one mode has proven to be superior to any other. In an attempt to reduce the aforementioned cyclic opening-closing injury to alveoli, clinicians apply positive end-expiratory pressure (PEEP) or continuous positive airway pressure during the ventilator cycle to prevent end-expiratory closure of atelectatic-prone lung units, thereby lessening the potential for injury. This also helps to keep lung units open, thus reducing shunt, improving oxygenation and the need for high oxygen concentrations, and will increase overall lung compliance. In general, if an FIO_2 of 1.0 is required to keep the $SpO_2\% > 88\%–90\%$, in my opinion it is probably best to begin with relatively high levels of positive end-expiratory pressure (18–24 cm H_2O), than to start too low and gradually work up if oxygenation remains poor,[82] although there is no unanimity on this point.[83] Additional ventilation strategies designed to recruit atelectatic lung units and improve oxygenation in ALI/ARDS have included intermittent prone positioning of the patient, so-called recruitment maneuvers (intermittent sustained high inflation pressures – 40 cm H_2O for 40 seconds) and extracorporeal membrane oxygenation.[79–81,84] Although such maneuvers can improve oxygenation in difficult cases, they have not been shown to predictably reduce the high mortality associated with ALI/ARDS. A potentially useful tip for the ED clinician faced with temporarily managing established ALI/ARDS in a patient who is also in shock is to attempt aggressively to improve cardiac output, for in so doing, the blood returning to the lungs will be less desaturated, thus reducing the impact of intrapulmonary shunt and improving overall oxygenation.

It is remarkable that despite decades of research, the only therapy proven to reduce mortality in ALI/ARDS is low tidal

volume ventilation, which seeks to minimize the effects of VILI.[85] In attempting to minimize further lung damage by employing low tidal volume ventilation (6–8 mL/kg is typical), the patient's alveolar ventilation may suffer and the PCO_2 will rise. Although opinions differ, most experts agree that a modest level of hypercapnia and respiratory acidosis in this setting is an acceptable compromise (in the opinion of some, it may actually be beneficial in modulating lung injury itself).[86] Table 8 lists a basic initial ventilator setup designed to minimize the risk of VILI in patients with ALI/ARDS.

Pharmacotherapy for ALI/ARDS

Much research has been done on various pharmacotherapies for established ALI/ARDS, including activated protein C, beta-2 adrenergics, inhaled vasodilators, corticosteroids, etc, and virtually all such investigations have not produced positive results, at least in terms of mortality. While an argument for treatment with low-dose systemic corticosteroids has been made,[87] the ED clinician should resist the temptation to start these drugs early, as at best the timing of such therapy should be reserved for established ALI/ARDS that is not improving after a few days of intensive support in patients who have been transferred from the ED. Currently, the only enthusiasm for specific drug therapy to assist the management of ALI/ARDS may be for early institution of neuromuscular blockade to reduce patient/ventilator dysynchrony, thus facilitating the delivery of noninjurious mechanical ventilation and so helping to prevent VILI.[88]

Table 8 Initial ventilator set-up for acute lung injury/acute respiratory distress syndrome (ALI/ARDS)

Volume-targeted mode

1. Inspired oxygen concentration (FIO_2)
   - Start with $FIO_2 = 1.0$
   - Goal: $FIO_2 < 0.40$ with an $SpO_2\% > 88\%–90\%$, ($PO_2 > 55–60$ mmHg)
2. Tidal volume
   - 6–8 ml/kg
3. Frequency or respiratory rate
   - 8–12 breaths/minute
4. Positive end expiratory pressure (PEEP)
   - Initial value depends on FIO_2 required to meet oxygenation goal
   - For $FIO_2 = 1.0$, set PEEP = 18–24 cm H_2O and titrate down as possible
5. Inspiratory pressure alarms/limits
   - Peak inspiratory pressure <40 cm H_2O
   - Plateau pressure <35 cm H_2O
6. Inspiratory flow rate
   - 40–80 L/minute
7. Pressure support
   - Used in conjunction with spontaneous breathing modes
   - Pressure set to achieve normal V_T (6–8 mL/kg)
8. Practise "permissive hypercapnia" to keep tidal volume low if necessary
   - Accept PCO_2 50–70 mmHg and if necessary titrate pH to > 7.20 with bicarbonate
9. Monitor cardiac output and oxygen delivery success

Dedication

Dr Rick Hodder passed away on Tuesday April 17, 2012. Dr Hodder joined the Ottawa Hospital in 1982 as a staff Respirologist and Intensivist. He established the Critical Care Program at TOH and was the first Chief of the Department of Critical Care. He served as Professor of Medicine at the University of Ottawa, and was past President of the Ontario Thoracic Society. In 2005, Dr Hodder was appointed as Canada's first Chief Examiner for Critical Care Medicine by the Royal College of Physicians and Surgeons of Canada (RCPSC). In 2010, the RCPSC appointed him with Founder Status in Critical Care Medicine.

It is clear that the world of Critical Care and Respirology have been touched by Dr Hodder in countless ways and will truly miss his valued contributions.

Disclosure

The author reports no conflict of interest in this work.

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