Management of Acute Respiratory Distress Syndrome

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Case Presentation

A 53 year old woman with a history of alcohol abuse, pancreatitis, hypertension and COPD presented with 3 days epigastric pain, nausea, vomiting and decreased oral intake in addition to respiratory symptoms which included a week of cough with white sputum. At the time of presentation to the hospital her alcohol level was 207, lipase was 838, white blood cell count was 12.8 K. She was started on IV hydration and received benzodiazepines for incipient alcohol withdrawal when her mental status became delirious. Over the course of the next 12 h her oxygenation progressively deteriorated and she was intubated. Post intubation chest x-ray and a representative image from the CT scan performed are below (Figs. 21.1 and 21.2).

Question What approach should guide this patient's ventilator management?

Answer Lung Protective Ventilation

All patients with the acute respiratory distress syndrome should be treated with lung protective ventilation in order to avoid ventilator associated lung injury (VALI). This patient was started on assist control mechanical ventilation with a tidal volume of 350 ml and 100 % FiO_2. Neuromuscular blockade with cisatracurium was initiated. The depth of paralysis was monitored with train of four nerve stimulation and the depth of sedation with midazolam and fentanyl was assessed via bispectral analysis. Over the next 12 h her PEEP was increased to 16 cm H_2O and her FiO_2 was decreased to 40 %. During this time the patients plateau airway pressure ranged between 26 and 28 cm H_2O. She was treated with broad spectrum antibiotics, vancomycin, pip-tazo and azithromycin. Results of a culture obtained from a mini-BAL specimen failed to grow any pathogenic organisms. Cisatracurium was discontinued after 48 h. At that time, solu-medrol was begun at a dose of 1 mg/kg body weight. The patient had had already been on an insulin drip but the glucose target range was changed to less than 110 mg/dL from the usual less than 150 mg/dL at that time. Daily sedation holidays were instituted to assess mental functioning and a physical therapy consult was initiated to promote mobility. The patient remained hemodynamically stable with good renal function and diuresis with furosemide was initiated, resulting in a negative fluid balance of 2400 ml on the third ICU day and about 1–2 L/day subsequently. Gas exchange remained satisfactory such that on the fourth ICU day PEEP was decreased to 5 cm H_2O. By that time the patient was able to march in place at the bedside and take

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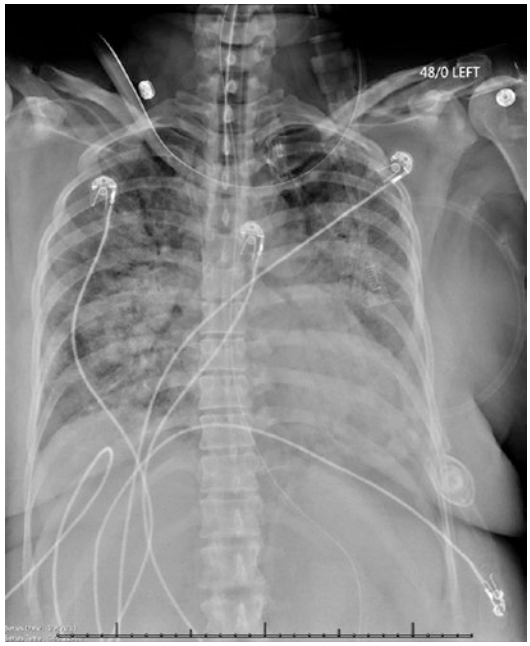

Fig. 21.1 Chest x-ray of patient with ARDS from case study showing bilateral alveolar infiltrates

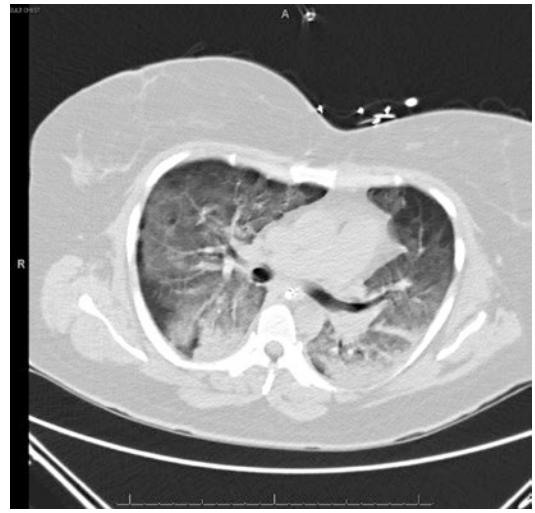

Fig. 21.2 Representative section of chest CT from patient in case study demonstrating bilateral alveolar infiltrates with mild compressive atelectasis in the dependent lung zones

a brief walk into the hall outside of her room. Later that day the patient was weaned and extubated. She was transferred out of the ICU to the general medical ward the following day.

Principles of Management

Risk Factors for ARDS and Diagnosis

Several risk factors for the development of ARDS have been identified. The lung injury prediction score (LIPS) is a model which incorporates know risk factors and predicts the likelihood of developing ARDS accordingly [1] (Table 21.1). Many patients with multiple risk factors do not develop ARDS as even patients with a LIPS score of more than 7 only develop ARDS less than half of the time. In the case presentation above the patient's history of chronic alcohol ingestion was a predisposing risk factor for the development of ARDS in what was likely to have been an aspiration pneumonia, which itself in another risk factor.

The PaO_2 to FiO_2 (P/F) ratio, a measure of oxygenation impairment was part of the old American European Consensus Conference diagnostic criteria for acute lung injury and ARDS. Although easily calculated the P/F ratio did not account for the effect of mean airway pressure on oxygenation. The Berlin criteria for ARDS, published in 2012 [2], did away with the concept of acute lung injury (ALI) in favor of classifying ARDS as mild, moderate or severe. ARDS severity is based on oxygenation criteria which also accounts to some extent, for the application of positive airway pressure. The diagnosis of ARDS is based on clinical presentation and physiology. Diffuse alveolar damage is usually seen histopathologically, but may be absent even in cases of severe ARDS [3].

Berlin Definition of ARDS

Timing

- Within 1 week of a known clinical insult or new or worsening respiratory symptoms

Chest Imaging

- Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules

Origin of Edema

- Respiratory failure not fully explained by cardiac failure or fluid overload
- Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present

Table 21.1 Lung injury prediction score (LIPS)

	LIPS points	Examples
Predisposing conditions		(*1*) Patient with history of alcohol abuse with septic shock from pneumonia requiring $FI_{O2} > 0.35$ in the emergency room: Sepsis + shock + pneumonia + alcohol abuse + $FI_{O2} > 0.35$ 1 + 2 + 1.5 + 1 + 2 = 7.5
Shock	2	
Aspiration	2	
Sepsis	1	
Pneumonia	1.5	
High-risk surgery[a]		
Orthopedic spine	1	
Acute abdomen	2	
Cardiac	2.5	
Aortic vascular	3.5	
High-risk trauma		(*2*) Motor vehicle accident with traumatic brain injury, lung contusion, and shock requiring $FI_{O2} > 0.35$ Traumatic brain injury + lung contusion + shock + $FI_{O2} > 0.35$ 2 + 1.5 + 2 + 2 = 7.5
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	
Multiple fractures	1.5	
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI > 30)	1	(*3*) Patient with history of diabetes mellitus and urosepsis with shock Sepsis + shock + diabetes 1 + 2–1 = 2
Hypoalbuminemia	1	
Chemotherapy	1	
$FI_{O2} > 0.35$ (>4 L/min)	2	
Tachypnea (RR > 30)	1.5	
$Sp_{O2} < 95\%$	1	
Acidosis (pH < 7.35)	1.5	
Diabetes mellitus[b]	−1	

From Gajic et al. [1]
The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society
Definition of abbreviations: *BMI* body mass index, *RR* respiratory rate, Sp_{O2} oxygen saturation by pulse oximetry
[a]Add 1.5 points if emergency surgery
[b]Only if sepsis

Oxygenation

- Mild ARDS – The PaO_2/FiO_2 is >200 mmHg, but ≤300 mmHg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O.
- Moderate ARDS – The PaO_2/FiO_2 is >100 mmHg, but ≤200 mmHg, on ventilator settings that include PEEP ≥5 cm H_2O.
- Severe ARDS – The PaO_2/FiO_2 is ≤100 mmHg on ventilators setting that include PEEP ≥5 cm H_2O

Lung Protective Ventilation

Avoiding over distension of the lung during mechanical ventilation of ARDS patients is called lung protective ventilation (LPV). LPV reduces

hospital and 28 day mortality [4], presumably by decreasing lung inflammation and avoiding the fibrinoproliferative phase of this condition. The largest trial to date demonstrating this was done by the NIH sponsored ARDS Network, whose results were published in 2000 [5]. The approach undertaken in this trial, the utilization of a tidal volume of less than 6.5 cc/kg of ideal body weight (IBW) (but at least 4 cc/kg) and maintaining a plateau pressure of less than 30 cm of H_2O has become the standard treatment to provide mechanical ventilation to patients with ARDS. The calculation of ideal body weight is based on height:

$$\text{Male IBW}\,(\text{kg}) = 50 + 0.91(\text{cm height} - 152.4)$$
$$\text{Female IBW}\,(\text{kg}) = 45.5 + 0.91(\text{cm height} - 152.4)$$

Plateau airway pressure is not a threshold variable [6] and it should be maintained as low as realistically possible, even though in the ARDSNet trial tidal volume was allowed to increase up to 8 cc/kg as long as plateau pressure remained under 30 cm H_2O. The ARDS Network approach is the standard approach to lung protective ventilation. However, multiple other approaches have been championed, each ostensibly offering a refinement of the basic lung protective ventilation approach of the ARDSNet. In a retrospective analysis of several of the large trials, a low driving pressure (ΔP) was found to be better correlated with ARDS mortality than tidal volume or plateau pressure [7]. Driving pressure is the pressure being applied by the ventilator to distribute gas to the recruited portion of the lungs which are not collapsed from compressive atelectasis caused by the weight of the lung in the dependent lung zones. In a patient not making spontaneous respiratory efforts ΔP can be estimated as plateau pressure minus PEEP in cm H_2O.

Open Lung Ventilation

Avoiding alveolar overdistension with a low tidal volume is the established mechanism of avoiding ventilator-associated lung injury. In the supine ARDS patient delivered gas is distributed to non-dependent lung zones. Dependent lung zones are not ventilated due to the weight of the lung, i.e. compressive atelectasis. In between the two zones is an area of lung which distends and collapses with each delivered ventilator breath, a phenomenon termed cyclic atelectasis. In animal models cyclic atelectasis produces lung injury. Optimizing the recruitment of additional areas of collapsed lung with PEEP in order to mitigate the effect of cyclic atelectasis is the rationale behind open lung ventilation. Meta-analysis of several large clinical trials demonstrated a mortality benefit to open lung ventilation [8]. However, each of the three large trials used for this analysis individually failed to demonstrate a mortality benefit. To the extent that the large clinical trials did not demonstrate harm with higher levels of PEEP, such as an increased rate of pneumothorax, clinicians may choose to use the open lung approach in their patients. Several approaches to performing open lung ventilation are available. A study evaluating the effect of PEEP on lung recruitment, as evaluated by CT scan, suggested the best tradeoff between lung recruitment while simultaneously avoiding lung overdistension was obtained via a high PEEP strategy similar to that utilized in the Lung Open Ventilation Study (LOVS) [9] (Table 21.2).

Prone Ventilation

A large randomized, multi-center trial, PROSEVA, demonstrated an impressive mortality benefit to patients who underwent prone ventilation 18 h per day [10]. Prone ventilation can be considered to be a form of open lung ventilation. This trial addressed criticisms of earlier, negative trials of prone ventilation in that the study subjects with ARDS had a severe oxygenation defect, were proned for long periods of time daily and a protocolized lung protective approach was used in the control group, the original ARDS network approach [11]. Using the low PEEP ARDS Network approach in the control group, while appropriate, leaves open the question as to whether proning adds incremental benefit to patients who are already receiving higher levels

Table 21.2 Example of open-lung high positive end-expiratory pressure (PEEP) strategy

FIO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5–10	10–18	18–20	20	20	20–22	22	22–24

of PEEP (see open lung ventilation, below). In addition, patients underwent neuromuscular blockade, which itself may have a beneficial effect on outcome. Despite these concerns, prone ventilation has assumed an important place as a rescue modality in the treatment of severe ARDS patients who have not responded to a conventional lung protective strategy.

Fluid Management

Volume removal via diuretic administration can shorten the duration of mechanical ventilation in patients who are recovering from ARDS. The Fluid and Catheter Therapy Trial of the ARDS Network demonstrated an average of 2.5 day increase in ventilator free days with a fluid conservative approach [12]. In addition, in patients in whom the total protein is less than 6.0 g/dL, the addition of albumin for 72 h helped promote fluid loss in ARDS patients and improved oxygenation [13].

Supportive Care

Other important aspects of care pertain more generally to the care of all patients receiving invasive mechanical ventilation. These include the early and successful use of enteral alimentation, a daily sedation awakening trial, delirium screening and management, early mobility, and treating the underlying illness such as pneumonia.

Evidence Contour

Several aspects of management in the patient with ARDS remain without consensus in the face of available clinical trials. Several of these are extensions of basic lung protective ventilation and essentially are attempts to find the optimal approach.

Additional Risk Factors

Vitamin D supplementation in critically ill patients who are severely deficient has been shown to decrease hospital mortality [14]. Low prehospital levels of vitamin D are associated with an increased risk of respiratory failure [15], and may be common in patients at risk for or having ARDS [16]. The NIH PETAL Network in conducting a randomized trial of high dose vitamin D in deficient patients at risk for ARDS.

Cytomegalovirus reactivation (CMV) is common in critically ill immunocompetent patients and portends a worse outcome in patients compared to CMV negative patients [17]. In one series, immunocompetent patients with ARDS were found to have a histologic evidence of CMV pneumonia on open lung biopsy in 18 of 37 cases of ARDS [18]. A NIH sponsored trial is examining whether the administration of ganciclovir improves outcomes in CMV antibody positive patients with acute respiratory failure and ARDS [19].

Subgroups and Subphenotypes

Because ARDS is a clinical syndrome, with an array of risk factors, and not a disease per se, attempts have been made to evaluate ARDS subgroups from several standpoints. Sepsis induced ARDS has a worse outcome than that due to other causes [20]. As is evident from lung biopsy and autopsy series clinical classification as either pneumonia or ARDS is frequently at odds with tissue findings [3, 21]. In addition the histopathology likely evolves over time, with pneumonia and/or diffuse alveolar damage yielding to fibrotic changes. Rather than determining which subcategory of ARDS a patient manifests on the basis of causal risk, more relevant to treatment and outcome may be subclassification based on clinical manifestations. ARDS patients demon-

strate different amounts of recruitable lung with administered PEEP [22]. Patients showing improvements in oxygenation due to lung recruitment with PEEP may have a lower mortality than those who do not [23]. Additionally, ARDS patients with a hyperinflammatory subphenotype have a higher mortality regardless of the ascribed cause for ARDS [24]. It remains to be determined identification of subgroups based on recruitability or hyperinflammatory subphenotypes represent different histopathologies (pneumonia versus diffuse alveolar damage versus fibrosis) or will lead to improved outcomes by varying the approach to therapy on that basis.

Helmet Ventilation

Noninvasive ventilation with a helmet interface, rather than the more conventional face mask, was shown in a pilot randomized trial of ARDS patients to decrease the rate of intubation. This observation awaits confirmation in a larger trial [24a].

Transpulmonary Pressure

Plateau airway pressure, measured after a delivered tidal volume, reflects lung and chest wall compliance. The contribution of the chest wall, which includes the abdominal compartment, can confound the utilization of plateau pressure as a guide to lung protective ventilation by suggesting the lung is being overdistended when in fact this is not the case. By subtracting an estimation of pleural pressure made by readings taken by an esophageal balloon (P_{es}) from the measured plateau pressure (P_{plat}) an estimate of transpulmonary pressure (P_L) may be determined and used to guide lung protective ventilation.

$$P_L = P_{plat} - P_{es}$$

A mortality benefit was observed in a single center randomized trial which used this approach [25]. The results may have been influenced by the enrollment of more than 60 % post abdominal surgery patients, a population in whom the abdominal compartment is likely to make a significant contribution to the chest wall and thereby P_{plat}. An accompanying editorial suggested, in reality, this approach was a means to justify the use of higher PEEP levels than customarily employed (i.e. > 22 cm H_2O). Also, the validity of using esophageal pressure as an estimate of pleural pressure has been questioned [26]. A larger, multi-center trial is being conducted to confirm these results [27]. This approach can be considered in patients in whom the chest wall is likely contributing to alveolar pressure, such as patients who are post-operative from abdominal surgery, are morbidly obese, have ascites or have a chest wall deformity such as scoliosis, provided the necessary equipment and expertise are available.

Pressure Limited Mechanical Ventilation

Pressure-limited modes of mechanical ventilation, including airway pressure release ventilation (APRV), bi-level, and pressure-controlled inverse ratio ventilation are all ways of providing lung protective ventilation. Ostensibly, pressure limited modes offer an advantage of less variation in transpulmonary pressure and a lower tidal volume to functional residual capacity alveolar strain ratio, which would be offer a salutary effect on VALI [28]. Additionally, APRV and bi-level ventilation offer the additional putative benefit of allowing spontaneous breathing, which might help prevent ventilator-induced respiratory muscle weakness [29] and more completely ventilate lung zones near the diaphragm. Despite adherents, to date, the superiority of this approach to volume cycled ventilation has not been demonstrated [30].

Neuromuscular Blockade

A large, multicenter randomized trial demonstrated a mortality benefit in patients who received 48 h of neuromuscular blockade following the onset of ARDS [31]. Less barotrauma was observed in the paralysis group, whereas a greater incidence of neuromuscular weakness was not. Because the Kaplan-Meier

survival curves did not separate until 14 days, the mechanistic benefit of this approach has been challenged. In addition this study has been criticized for lacking a more rigorous approach to the assessment of neuromuscular weakness. Some support is given to this study by a database analysis study which demonstrated a mortality benefit in patients with a pulmonary source of sepsis and respiratory failure who underwent neuromuscular blockade within the first 48 h for reasons other than intubation [32]. Additionally, in an animal model spontaneous breathing caused regional alveolar overdistension near the diaphragm due to Pendelluft ventilation which did not occur in paralyzed animals [33]. Hence the notion that spontaneous breathing provides "better" ventilation to lung zones near the diaphragm may not be valid. The NIH sponsored PETAL (Prevention and early treatment of acute lung injury) Network is conducting a clinical trial to re-evaluate whether neuromuscular blockade benefits patients with severe ARDS.

High Frequency Oscillatory Ventilation (HFOV)

Two large, randomized multi-center trials published in 2012, OSCILLATE and OSCAR, failed to show benefit to this clearly open-lung approach [34, 35]. Critics suggested that concerns regarding volume status and effects on the right ventricle may have contributed adversely to the findings. To the extent that the OSCILLATE trial showed an increased mortality in the HFOV group this approach cannot be recommended at present for adults with ARDS.

Extra Corporeal Membrane Oxygenation (ECMO)

A mortality benefit was observed in the British CESAR trial among patients randomized to be transported to the specialty center to receive ECMO on an intent-to-treat basis [36]. As the mortality benefit was accounted for by patients randomized to ECMO who did not receive ECMO, concerns regarding whether the benefit seen in this study represents the modality itself or the benefit of regionalization of care to a specialty hospital is a concern. Use of ECMO has been prevalent during recent H1N1 outbreaks, when young patients with few if any comorbidities developed ARDS refractory to more commonplace ventilator approaches to oxygenation [37]. Another randomized trial of ECMO in ARDS patients is currently underway in Europe [38].

Corticosteroids

Most meta-analyses have not suggested confirmed a mortality benefit to the use of corticosteroids in patients with ARDS. The LaSRS study performed by the ARDS Network is the largest trial to date examining whether corticosteroids benefit ARDS patients [39]. No mortality benefit was ultimately observed although a significantly greater of patient days alive and off assisted breathing ("ventilator-free days"). An initial mortality benefit in favor of the steroids may have been lost among the 20 patients who returned to assisted breathing, as opposed to 6 in the control group. Whether this was due to tapering steroids after weaning or the development of neuromuscular weakness is unclear. Although an increased morality was seen in LaSRS among patients who were started on corticosteroids beyond 14 days of mechanical ventilation for ARDS the confidence intervals were large. This has resulted in some authors warning against starting corticosteroids beyond 14 days. If given, corticosteroids should be administered at a dose of 1 mg per kg body weight twice per day with a taper over 28 days. Tight glycemic control may play a role in minimizing the risk of neuromuscular weakness [40]. Corticosteroid administration may result in prolonged viral replication in patients with ARDS due to H1N1 influenza. A higher mortality has been reported in observational series in these patients and corticosteroid administration is best avoided early on in the care of influenza patients with ARDS [41].

Inhaled Vasodilators

Trials of inhaled nitric oxide have failed to yield positive results. Meta-analyses have suggested that while oxygenation improves not mortality benefit accrues from the use of this agent [42]. Iloprost (synthetic PGI2) also increases pO_2. However, no large clinical trials have been performed to determine if improvements are also seen in a clinically meaningful outcome such as mortality or ventilator-free days [43].

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