**Introduction**

Acute respiratory distress syndrome (ARDS) is a serious medical condition characterized by widespread inflammation in the lungs leading to life-threatening respiratory failure. It affects approximately 200,000 patients each year in the United States with a mortality rate approaching 30-40% (1). ARDS continues to be a major cause of morbidity and mortality among critically ill patients, underscoring the need for prompt recognition and optimal management by healthcare providers, including pharmacists. Key aspects in caring for patients with ARDS include lung protective ventilation strategies, conservative fluid management,targeted pharmacologic therapies, and interventions like prone positioning. Recent research has focused on identifying more personalized therapies based on ARDS subphenotypes. This chapter will provide an in-depth overview of ARDS to prepare pharmacists for caring for this complex patient population.

**Clinical Presentation**

The clinical manifestations of ARDS include:

* Severe hypoxemia characterized by an elevated alveolar-arterial (A-a) oxygen gradient and decreased PaO2/FiO2 ratio
* Bilateral pulmonary opacities on chest imaging not fully explained by effusions, lobar collapse, or nodules
* Decreased lung compliance and stiff lungs that are difficult to ventilate
* Respiratory distress such as tachypnea and increased work of breathing

Some risk factors include:

* Sepsis
* Pneumonia
* Aspiration,
* Trauma
* Shock
* Pancreatitis

Patients may initially present with symptoms related to the inciting condition. ARDS often develops within 72 hours of an acute insult but usually manifests clinically within 5-7 days (2). Common early signs are tachypnea and hypoxemia that is refractory to supplemental oxygen delivery. Chest imaging reveals diffuse infiltrates and opacities. Misdiagnosis as heart failure or volume overload is possible if objective evidence of elevated left atrial pressures is not pursued. Point-of-care lung ultrasound demonstrating diffuse B-lines supports the diagnosis.

**Pathophysiology**

ARDS is characterized by widespread inflammation leading to increased pulmonary vascular permeability, interstitial and alveolar edema, and loss of aerated lung tissue. This manifests clinically as stiff, noncompliant lungs with severe hypoxemia. The pathophysiologic phases include:

* **Exudative phase:** Activation of inflammatory and coagulation cascades leads to damage of the alveolar-capillary barrier, flooding the alveolar space with proteinaceous edema fluid. This manifests as clinical acute lung injury.

* **Proliferative phase:** Type II alveolar cells proliferate and attempt to restore the epithelial barrier. Fibroblasts deposit extracellular matrix. The lung begins repair and recovery.

* **Fibrotic phase:** Widespread fibrosis occurs in some patients leading to long-term lung dysfunction. This is associated with prolonged mechanical ventilation.

Injury to both the alveolar epithelium and pulmonary capillary endothelium results in an influx of protein-rich fluid into the interstitium and alveoli (3).

Pro-inflammatory cytokines like interleukin-1, TNF-alpha, and platelet-activating factor perpetuate inflammation and recruit neutrophils which release toxic mediators causing further injury (4).

Reactive oxygen species, proteases, and eicosanoids contribute to cellular damage. This impairs surfactant production and clears the path for uncontrolled neutrophil migration into airspaces.

Vascular congestion raises hydrostatic pressures.

The loss of the alveolar-capillary barrier allows the large influx of proteinaceous fluid characteristic of ARDS. Patients often develop complications like ventilator-induced lung injury, pneumonia, pulmonary embolism, and multiple organ failure.

**Diagnostic Approach**

ARDS is defined according to the Berlin Criteria which includes (5):

* Onset within 1 week of a known clinical insult or new/worsening respiratory symptoms
* Bilateral opacities on chest imaging not explained fully by effusions, lobar collapse, or nodules
* Respiratory failure not fully explained by cardiac failure or fluid overload
* Impaired oxygenation defined by the P/F ratio:
* Mild: 201-300 mmHg
* Moderate: 101-200 mmHg
* Severe: ≤100 mmHg

At minimum 5 cm H2O PEEP must be applied to make the diagnosis. Chest x-ray or CT scan reveals diffuse bilateral opacities but lung ultrasound at bedside may also be useful. Echocardiography helps rule out heart failure. Diagnosing ARDS requires a multimodal approach combining clinical signs and symptoms, radiographic findings, and oxygenation metrics.

**Management - Overview**

The key principles in managing ARDS include:

* Treating the underlying cause, whether sepsis, pneumonia, pancreatitis etc.
* Lung protective ventilation strategies using low tidal volumes (4-8 mL/kg ideal body weight) and limiting plateau pressures under 30 cm H2O
* Conservative fluid management after initial resuscitation to limit edema
* Consideration of pharmacologic therapies like steroids, muscle relaxants, and vasopressors
* Rescue therapies for refractory hypoxemia like prone positioning and extracorporeal support

A multidisciplinary approach is essential to providing guideline-concordant care for ARDS patients. Pharmacists play a critical role in developing the pharmacologic plan of care and advising on ventilator management.

**Pharmacotherapy**

Multiple pharmacologic agents may be utilized in patients with ARDS (6):

**Corticosteroids**

* Inflammation is a core component of ARDS pathophysiology providing rationale for steroids
* Role remains controversial but most recent guidelines provide recommendations (6):
* Use low dose steroids in moderate to severe ARDS (Grade 1B)
* Do not routinely use high dose steroids (Grade 2C)
* Dexamethasone 20 mg daily x 5 days, then 10 mg daily x 5 days used in recent trial with mortality benefit

**Sedation**

* Required to facilitate mechanical ventilation
* Choices: propofol, dexmedetomidine, benzodiazepines

**Neuromuscular blocking agents (NMBAs)**

* Prevent patient-ventilator dyssynchrony
* Most evidence for early use in moderate-severe ARDS to improve oxygenation
* Agents: cisatracurium, vecuronium
* Monitor for weakness with electromyography and peripheral nerve stimulation

**Vasopressors**

* Used to maintain adequate perfusion pressures
* Agents: norepinephrine, vasopressin, epinephrine
* Titrate to MAP 60-65 mmHg or higher if chronic hypertension

**Diuretics**

* Furosemide to promote negative fluid balance after hemodynamic stabilization
* Avoid in hypotensive patients
* Monitor electrolytes, renal function

**Inhaled Vasodilators**

* Inhaled nitric oxide, prostacyclin analogs (inhaled epoprostenol)
* Select use for severe refractory hypoxemia and pulmonary hypertension
* No mortality benefit proven

Neuromuscular blockade, steroids, and conservative fluid management have the strongest evidence basis for routine use. All other pharmacologic therapies should be used judiciously based on individual patient factors.

Non-Pharmacologic Interventions

Beyond medications, other evidence-based interventions are a key part of management:

* **Lung protective ventilation (7)**
* Low tidal volume (4-8 mL/kg ideal body weight)
* Limit plateau pressures (<30 cm H2O)
* Allow "permissive" hypercapnia
* Consider retrograde PEEP titration to optimize driving pressure

* **Conservative fluid management after initial resuscitation (8)**
* Balance fluids once hemodynamic stability achieved
* Consider diuresis

* **Prone positioning (9)**
* Physically placing patient in prone orientation
* Recommended for moderate-severe ARDS with PaO2/FiO2 <150
* Improves mortality outcomes
* Must be done safely and consistently (at least 12-16 hours per day)

* **Extracorporeal membrane oxygenation (ECMO) (10)**
* Form of modified cardiopulmonary bypass used as rescue therapy
* Consider for most severe cases not responding to conventional therapies
* Improves outcomes when initiated early at expert centers

These interventions help mitigate ventilator-induced lung injury and refractory hypoxemia which are major contributors to ARDS mortality. Protocolized, step-wise application guided by severity of illness optimizes outcomes.

**Key Guidelines and Evidence**

Several major guidelines inform the clinical management of ARDS, including:

* American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline on mechanical ventilation for ARDS (2017) (6)
* Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) (2021) (7)
* WHO Guidelines for Clinical Management of ARDS (2022) (8)

Major recommendations for ARDS management:

|  |  |
| --- | --- |
| **Recommendation** | **Level of Evidence, Strength of Recommendation** |
| Low tidal volume (4-8 mL/kg) ventilation (6) | 1A, Strong |
| Limit plateau pressures <30 cm H2O (6) | 1B, Strong |
| Moderate PEEP strategy (6) | 1B, Strong |
| Conservative fluid management (6) | 1C, Strong |
| Prone positioning for severe ARDS (6) | 1B, Strong |
| NMBA use in moderate/severe ARDS (6) | 1A, Strong |
| Low-dose steroids in early ARDS (7, 8) | 1B, Strong |
| Avoid routine high-dose steroids (6) | 2C, Weak |

These guidelines synthesize current evidence to provide clear recommendations for managing ARDS. The table summarizes the key pharmacotherapy and ventilation recommendations with the strength of evidence. This information should guide clinical decision making and protocol development for ARDS.

**Clinical Scenarios**

Clinical Scenario 1:

A 65-year-old male with past medical history of hypertension, diabetes, and COPD presents with bilateral pneumonia leading to sepsis and shock. He was admitted to the ICU, started on broad spectrum antibiotics, and vasopressors were initiated for hypotension. He progressed to develop acute hypoxemic respiratory failure rapidly requiring intubation and mechanical ventilation by hospital day 2. Chest x-ray showed diffuse bilateral opacities and PaO2/FiO2 was 110 on an FiO2 of 90% and PEEP of 10 cm H2O. Plateau pressures were 28-30 cm H2O on a set tidal volume of 6 mL/kg ideal body weight. His pH was 7.22 and pCO2 60 mm Hg. He meets diagnostic criteria for moderate ARDS.

Q: What would be the optimal management for this patient based on evidence-based guidelines?

: Key steps would include:

* Ensuring lung protective ventilation with plateau pressures <30 cm H2O by decreasing tidal volume. FiO2 and PEEP can then be adjusted to balance oxygenation and pressures.
* Starting low-dose steroids for moderate ARDS. Dexamethasone 20 mg daily x 5 days is a reasonable regimen.
* Conservative fluid management and even diuresis once he is hemodynamically stable to prevent worsening pulmonary edema.
* Consider prone positioning and/or neuromuscular blockade to optimize ventilation and oxygenation.
* Treating the underlying sepsis is essential as well.

Clinical Scenario 2:

A 45-year-old female developed ARDS following major abdominal surgery and septic shock requiring vasopressors. She was intubated for respiratory failure. She had no prior lung disease. On hospital day 6, she remained ventilator dependent with PaO2/FiO2 of 85 and plateau pressures 33-35 cm H2O on assist control ventilation. Her sedation was weaned but she remained hypoxemic. She was bolused and started on cisatracurium. After 12 hours, her oxygenation improved to a P/F ratio of 120 and plateau pressures decreased to 28 cm H2O on the same ventilator settings.

Q: What key points does this scenario demonstrate regarding neuromuscular blockade in ARDS?

A: This case illustrates how neuromuscular blockade can improve patient-ventilator synchrony by preventing respiratory muscle activity and contractions against the ventilator. This allowed the set tidal volume to be delivered appropriately. Her oxygenation improved and plateau pressures decreased, indicating improved lung compliance. It demonstrates how paralysis facilitates optimal lung protective ventilation, a key priority in managing ARDS.

**Tips for Board Exam Questions**

* Low tidal volume (4-8 mL/kg ideal body weight) ventilation is the cornerstone of lung protection in ARDS. Plateau pressures should be maintained <30 cm H2O.
* Conservative fluid management and even diuresis should be considered after hemodynamic stabilization to prevent worsening pulmonary edema.
* Prone positioning, neuromuscular blockade, and low-dose steroids can significantly improve mortality and should be used in moderate-severe ARDS.

**Summary**

ARDS is characterized by an acute inflammatory lung injury leading to hypoxemic respiratory failure. Diagnosis is made using clinical, radiographic, and oxygenation criteria. Management focuses on lung protective ventilation, conservative fluids, targeted pharmacologic therapies, and interventions like prone positioning for refractory hypoxemia. Protocolized, evidence-based care is critical. ARDS continues to have high mortality so pharmacists play a pivotal role within the multidisciplinary team to optimize patient outcomes.

**References**

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