PHARMACY TO DOSE
THE CRITICAL CARE PODCAST

Acute Respiratory Distress Syndrome (ARDS)

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What is the history of ARDS and why are we talking about this today?

- Microcosm of all of critical care
  - Relatively common, high mortality, hard to define and study
  - Faced everyday with how to treat these patients
- Approximately 10% of ICU patients develop ARDS
  - 25% of mechanically ventilated patients develop ARDS
  - Severe ARDS has a 50% mortality rate
- First described by Ashbaugh and colleagues in 1967 in a 12 patient case series
  - Describe a rapid development of respiratory distress with acute onset of tachypnea, hypoxia, and loss of lung compliance
  - First described the use of positive end-expiratory pressure (PEEP), which was NOT the standard of care at that time
- American-European Consensus Conference (AECC) created the first ARDS definition in 1994
  - Severe hypoxemia including PaO_2/FiO_2 ratio less than 200 mm Hg
  - Bilateral infiltrates on chest x-ray
  - No evidence of cardiogenic pulmonary edema

What is the current definition to diagnose ARDS currently?

- Criticisms of previous definition:
  - High rate of inter-observer error when reading a chest x-ray
  - Hypoxia criteria (PaO_2/FiO_2) can be altered by the ventilator settings
  - Low specificity for ARDS
- Berlin Definition:
  - Onset within 7 days
  - Bilateral opacities consistent with pulmonary edema
  - Hypoxia including $PaO_2/FiO_2 \leq 300$ mm Hg with PEEP ≥ 5 cm H_2O
    - Stratified mild, moderate, and severe ARDS based on PaO_2/FO_2 ratio

What are criticisms of the Berlin definition of ARDS?

- Kigali modification
  - Other parts of the world may not have access to a ventilator, how do we define ARDS there?
- Emphasis on having no cardiac source for pulmonary edema
  - Heart failure patients can also have ARDS, how can we evaluate and diagnose ARDS in those patients?
- Presence of diffuse alveolar damage (DAD)
  - Examining 712 autopsy results of patients with ARDS based on Berlin definition
  - Only 45% had DAD which is supposedly the hallmark pathophysiology of ARDS

Have we identified any common causes or risk factors for ARDS?

- Risk factors:
  - Pneumonia
  - Non-pulmonary sepsis
  - Aspiration
  - Trauma
  - Age
  - Non-white race
  - Genetic
- Even though we know age is a risk factor, it isn't associated with excess mortality
- We know there is a genetic component (just not 100% sure what it is) because not everyone with pneumonia develops ARDS

What is the typical time course of ARDS with respect to its pathophysiology?

- Acute, exudative phase
  - Occurs over the first 7 days of ARDS
  - Characterized by diffuse alveolar injury and capillary endothelial injury
  - Neutrophils adhere to the pulmonary capillaries and boring those little holes through the basement membrane
    - Those holes then allow large plasma proteins to cross into the interstitial fluid

        - This disrupts Starling's Equilibrium causing diffuse pulmonary edema and reduced gas exchange and lung compliance
        - Neutrophils and T cells migrate into the inflamed lung amplifying the damage
            - The underlying cause for this altered behavior isn't fully known
    - Alveolar epithelium cells
        - Type 1
            - Gas exchange surface of the lung
            - Look similar to flat plates
                - Take the brunt of the damage
        - Type 2
            - Produce surfactant and are the progenitor cells for lung lineages
                - Not as much damage as Type 1 cells
- Proliferative Phase
    - Repair process
    - Essential for recovery
        - Reabsorption of the fluid
- Fibrotic Phase or "Recovery" Phase
    - Associated with prolonged mechanical ventilation
- Don't have a good understanding of when these phases take place clinically

What are ARDS treatment goals?

- Three principles of critical care
    - Treat the underlying cause
    - Provide supportive therapy
    - Do not harm the patient in the process of the first two
- Treatment is largely focused on supportive care with ARDS

Overview (or pod-torial) of mechanical ventilation for ARDS

- Goal is to oxygenate without harming the patient
- Try to avoid:
    - Volutrauma – excess volume that can harm the alveoli
    - Barotrauma – excess pressure that can harm the alveoli
    - Oxygen toxicity – free radical formation

- ARDSNet low tidal volume study
  - 6 cc/kg (IBW) v. 12 cc/kg standard tidal volume
  - Trial ended early due to ~10% reduction in mortality with low tidal volume ventilation strategy
- Ventilator mode
  - Three things that define a mode: trigger, target, and cycle
    - Trigger – what initiates the breath
    - Target – what the goal of the breath is
    - Cycle – what terminates the breath to go to exhalation
      - Answer is either time, pressure, or volume
  - Pressure regulated volume control (PRVC) – main ventilator mode in many ICUs
    - Allows pressure to be constant while also targeting a specific volume
    - "Breath to breath" mode
  - Volume control – target a specific tidal volume
    - The ARDS neuromuscular blockade studies all used volume control ventilation
  - Pressure control
    - This is referring to what is being controlled or targeted for that mode
- Advanced ventilator modes
  - Airway pressure release ventilation (APRV)
    - Inverse ratio
      - Only spend one second exhaling and the rest of the time inhaling
      - Historically, clinicians thought patients needed more sedation because it's an unnatural mode of ventilation
        - Spontaneous ventilation on APRV helps lung recruitment, so deep sedation or paralysis may negate the potential benefit
  - High frequency oscillatory ventilation (HFOV)
  - Proportional assist ventilation
- General terms
  - FiO_2 – Fraction of inspired oxygen
    - 21% is room air FiO_2

        - FiO_2 > 60% likely leads to oxygen toxicity
    - TV – Tidal volume
        - How big is the breath you inhale
    - PEEP – Positive end-expiratory pressure
        - Pressure that remains in your lungs after you exhale

How does prone positioning help improve ARDS outcomes?

- Lungs are bigger in the back than the front
- Laying on your back (supine positioning) can impede gas exchange through gravity and migration of substances within the lungs
- Prone positioning improves V/Q (ventilation/perfusion) mismatch
    - PROSEVA study reduced mortality by >50% with prone positioning (16% v. 32.8%)
- Challenges with implementing prone positioning for ARDS:
    - Logistics to actually flip a patient from supine to prone
        - Or $$$ to purchase the specialized bed that rotates (RotoProne)
    - Prone positioning for a minimum of 16 hours out of the 24-hour day
    - Can lead to changes with sedation, nutrition, line placement, etc.
        - Think about these as challenges rather than barriers due to the large mortality reduction from prone positioning

What is the current role of neuromuscular blockers for ARDS?

- Historically, we based recommendations from the ACURASYS trial
    - 48-hour infusion of cisatracurium while patients received volume control ventilation
        - Initial bolus and 37.5 mg/hr cisatracurium IV continuous infusion
        - No train-of-four monitoring
        - PaO_2/FiO_2 < 150 mm Hg
    - Cisatracurium reduced the 90-day adjusted mortality compared to placebo
        - No difference seen with crude mortality
- Based on the ACURASYS trial results, use of neuromuscular blocking agents increased in ARDS
- ROSE trial did their best to replicate the ACURASYS trial
    - Compared neuromuscular blockade and deep sedation to light sedation with neuromuscular blockade

  - No difference in mortality (study was stopped early due to futility)
  - Limitations:
    - Excluded patients who previously received a neuromuscular blocker IV continuous infusion
      - These are the sickest patients who may have benefited the most
    - Enrolled patients within 8 hours (compared to 16 hours in ACURASYS trial)
      - Modern phenotype called "rapidly improving ARDS" and those patients may be different than our classic ARDS patients
        - Possibly could have confounded the results
- Now the question is should we be using neuromuscular blockade or not?
  - Likely shouldn't be using as a standard of care for everyone
  - Limit to severe ARDS as there are patients who may benefit

Should you paralyze, switch to prone positioning, or do both for severe ARDS?

- Going back to the landmark studies, most patients were receiving both
- Goal should be to optimize care by using both
  - May need to alter based on resources at your institution

How do you apply the findings of the FACTT study to ARDS patients at your institution?

- Andrea does not follow the FACTT protocol to a T
- The moment the patient is hemodynamically stable and perfusing effectively, should shift focus to diuresis
  - No protocol in place, but try to aggressively diurese the moment we can
  - Look to minimize "hidden fluids"

Why is the use of corticosteroids in ARDS so controversial?

- Controversial because 1 investigator team (Meduri et al) have produced most of the positive studies that have not been replicated
  - Initial study by Meduri et al showed early corticosteroids reduced mortality, time on the ventilator, and time in the ICU
  - A repeat study in NEJM found no improvement in mortality

        - This same study demonstrated increased mortality if corticosteroids are started ≥ 14 days from the onset of ARDS
    - Still have the question of when is early v. late ARDS
        - The concern is that starting corticosteroids for ARDS at any point may be doing more harm than good (since we don't fully understand the ARDS time course)

What drugs have been studied and ultimately failed for the treatment of ARDS?

- A lot have been studied, but notable ones include:
    - Corticosteroids
    - Albuterol
    - Statins
        - Interesting literature looking at specific ARDS phenotypes
        - When re-evaluating statin studies, mortality benefit found in the more inflammatory phenotype
            - Hypothesis-generating for how we should be evaluating ARDS as a whole
    - Prostaglandins
    - Surfactant
        - Curious if some of these studies failed due to study design and power calculation
        - If we could remove the "rapidly improving" ARDS phenotype patients, some of these medications (e.g. statins) may have some benefit

What is the role of ECMO for severe ARDS?

- CESAR study was first to look at ECMO for ARDS
    - Did not show that ECMO was superior to conventional mechanical ventilation
    - Lots of criticisms of the CESAR study:
        - Almost 25% of patients transferred to an ECMO center didn't receive ECMO
        - Additionally, a wide variety of ventilation strategies were used
- EOLIA study was released in 2018 and there was no difference in 60-day mortality comparing ECMO to conventional mechanical ventilation

    - Post-publication Bayesian analysis did show a mortality benefit to ECMO from the EOLIA study
    - Bayesian analysis – statistical methodology using prior probability distributions
        - Use prior data to decide what is the percent chance of a benefit
- EOLIA control group received the highest standard of care
    - Likely can rest easy that if you are doing everything else correctly (e.g. prone positioning, low tidal volume, etc) you may not need ECMO
        - But if you aren't or can't do those things, ECMO may help
- Highest benefit for ECMO may be seen in the young critically ill patient with few comorbidities
    - ECMO may simply be harder to implement than other critical care interventions

What are the biggest upcoming research areas/topics for ARDS?

- Identify a disease modifying drug
- Evaluating response to therapy based on ARDS phenotypes and endotypes
    - Use biomarkers to help differentiate types of ARDS

What is the role of the Pharmacist when treating patients with ARDS?

- High quality critical care management
- More aggressive fluid stewardship
- Calculate ventilator settings to double-check
- Understand ventilator modes
- Be a medication expert