

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on “**Acute Respiratory Distress Syndrome (ARDS)**.” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

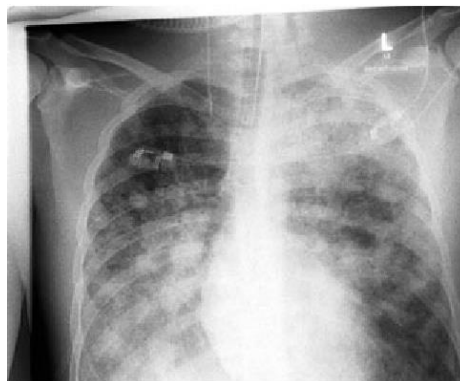
ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Developed by Dr. Michael Prodanuk, Dr. Tanya Holt, and Dr. Gregory Hansen for PedsCases.com.
August 4th, 2018.

Introduction

Michael: Welcome to PedsCases and thanks for tuning in to our podcast on pediatric acute respiratory distress syndrome. My name is Michael Prodanuk and I am a medical student at the University of Saskatchewan. Today I am joined by two pediatric intensivists from Royal University Hospital in Saskatoon, Saskatchewan; Dr. Tanya Holt, Head of the Division of Pediatric Critical Care and Pediatric Inter-Facility Transport, and Dr. Gregory Hansen, neurocritical pediatric intensivist. We will be discussing an approach to acute respiratory distress syndrome, or ARDS, in children. Dr. Holt, let's begin with a clinical case.

Dr. Holt: A 6-year-old previously healthy immunized boy with a 6-day history of cough, fever, and sick respiratory contacts is brought to hospital by his parents. In the emergency department, his physician notes increased work of breathing, hypoxemia, hypercarbia, and decreased level of consciousness, so promptly intubates him and arranges transfer to the PICU. The intensive care team places him on the Hamilton G5 conventional ventilator with the following settings: mode: volume control; rate 20; tidal volume: 5 mL/kg; PEEP 10 cm H₂O and FiO₂: 0.55. The initial blood gas shows hypoxemia with PaO₂ 70, and a respiratory acidosis with a pH 7.20; PaCO₂: 58 mmHg; HCO₃: 22 mEq/L; and lactate 2.3. His chest x-ray shows diffuse bilateral infiltrates. He is tachycardic and poorly perfused, so is resuscitated with 20 mL/kg of IV normal saline. His parents are worried and want to know what has caused their son's deterioration.



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Michael: Let's cover some background information first so we are better prepared to approach this challenging case. The learning objectives for this podcast are:

1. Define the criteria for pediatric ARDS.
2. Review the etiologies and pathophysiology of ARDS.
3. Delineate the basic management and lung protective ventilation strategies for ARDS.
4. Discuss the mortality of ARDS.

DEFINITION

Michael: This is clearly a complex condition. Dr. Hansen, let's start with a basic definition.

Dr. Hansen: Acute respiratory distress syndrome is a life-threatening lung condition involving non-cardiogenic pulmonary edema due to disruption of the alveolar-capillary barrier.¹ This results in hypoxemia, loss of aerated lung tissue, decreased respiratory compliance, and usually requires PICU admission for mechanical ventilation.

Michael: So, the hallmark features are an acute onset of pulmonary edema and hypoxemic respiratory failure requiring significant medical support. Are there specific diagnostic criteria for the pediatric population?

Dr. Hansen: Yes. For children, ARDS is diagnosed clinically using the PALICC definition.² PALICC stands for Pediatric Acute Lung Injury Consensus Conference. In 2015, this group of international critical care experts published the first pediatric specific definition of ARDS. This definition builds upon the previous Berlin definition that was developed for adult ARDS but was often applied in pediatrics as well.³

Michael: Could you break down the PALICC definition for us?

Dr. Hansen: Certainly. There are five categories in the PALICC definition: age of patient, timing of clinical insult, origin of edema, chest imaging, and oxygenation.

Michael: Lets address the first category. What are the age requirements?

Dr. Hansen: The PALICC definition applies to any person 17 years or younger. However, it is important to note that a child cannot be born with ARDS, rather it is acquired. Therefore, neonates are excluded as they may have a perinatally acquired condition, such as meconium aspiration syndrome.

Michael: So, the definition applies to any child except newborns. What about timing?

Dr. Hansen: The patient must have experienced a clinical insult within 7 days of the ARDS diagnosis. Examples of this include a near-drowning episode one day ago, being diagnosed with pneumonia three days ago, or developing sepsis 12 hours post-operatively.

Michael: What about the origin of pulmonary edema and imaging findings?

Dr. Hansen: Patients must have new pulmonary edema that is respiratory in origin. This means that the edema cannot be solely due to heart failure or fluid overload. On imaging, usually a chest x-ray or CT scan, they will have a new infiltrate or consolidation that may be unilateral or

bilateral. On chest x-ray, a consolidation may appear as a dense white lesion confined to a single lobe, while pulmonary edema may appear as fluffy white patches scattered throughout both lungs.

Michael: Now onto the last part of the PALICC definition, oxygenation.

Dr. Hansen: This is a key part of the diagnosis. The patient must have significant hypoxemia. However, it is not as simple as a specific oxygen saturation cutoff, as the type of respiratory support being used must also be considered. There are separate criteria for patients on non-invasive ventilation and those on mechanical ventilation. Examples of non-invasive ventilation include CPAP and BiPAP, where positive pressure is delivered by mask to a patient who is awake and breathing spontaneously. Mechanical ventilation means that the child is intubated and a ventilator is delivering or assisting their breaths. It is a step up in support from CPAP or BiPAP and means that a child's respiratory status is more severe. Let's focus on the criteria for mechanically ventilated patients, as the majority of children with ARDS will require this high level of support.

Michael: So how do we determine if a mechanically ventilated child's hypoxemia is significant enough to be classified as ARDS?

Dr. Hansen: PALICC uses the oxygenation index to define hypoxemia. The higher the oxygenation index, the more severe the hypoxemia and ARDS. FiO_2 and mean airway pressure are in the numerator, meaning that higher values of these variables will increase the oxygenation index and indicate more severe disease. This makes sense, as sicker patients often require a higher FiO_2 to maintain their oxygen saturation and may require higher pressures on the ventilator to recruit collapsed areas of lung. Meanwhile, the PaO_2 is in the denominator, so when patients' oxygen saturations drop the oxygenation index will increase, again indicating more severe disease. Once calculated, the oxygenation index is used to stratify the patient as having mild, moderate, or severe ARDS.

Michael: We have covered a lot of information. Let's do a quick recap of the PALICC definition of ARDS:

1. The patient is 17 or under, but not a neonate.
2. They have experienced a clinical insult within the last 7 days.
3. There is new pulmonary edema that is respiratory, not cardiac, in origin.
4. There are new infiltrates on chest imaging, which may be unilateral or bilateral.
5. The patient is significantly hypoxemic, as determined by the oxygenation index in mechanically ventilated patients.

Dr. Holt: Using our new knowledge of the PALICC definition, let's see if our patient meets criteria for ARDS. He meets the age criteria being 6-years-old; he experienced respiratory failure following 6 days of symptoms and exposure to infectious contacts, so the timing of the clinical insult is appropriate; the chest x-ray shows new diffuse bilateral lung changes with evidence of edema, and he is mechanically ventilated with an oxygenation index of 14. It's important to note that an oxygenation index of 4 or higher is abnormal. Therefore, our patient meets criteria for a diagnosis of ARDS.

ETIOLOGY AND PATHOPHYSIOLOGY

Michael: So, we determined that our patient meets the PALICC definition of ARDS. My next question is, how did this happen? What are the underlying mechanisms and pathophysiology of his lung disease?

Dr. Holt: The pathophysiology is complex and not yet fully understood, but let's focus on what we do know, starting with the causes. As we discussed earlier, ARDS is caused by an insult to the lungs. These insults are grouped as direct or indirect.

Michael: Could you tell us about the direct insults first?

Dr. Holt: A direct insult means that there was direct damage to the alveolar epithelium, impairing alveolar fluid clearance.⁴ This includes infections like pneumonia and bronchiolitis, aspiration, lung contusion, smoke inhalation, and even mechanical ventilation. It's important to note that aspiration can include any foreign material entering the lungs, such as gastric contents from vomiting, water from a drowning incident, or chemical ingestion, like a detergent pod.

Michael: What about the indirect insults?

Dr. Holt: Indirect insults describe damage to the capillary endothelium.⁴ This damage increases the permeability of the capillary, which results in movement of fluid into the alveoli. Many indirect insults are mediated via the blood. They include sepsis, blood transfusions (think TRALI, transfusion-related acute lung injury), pancreatitis, polytrauma, burns, and ischemic reperfusion injuries.

Michael: So, there are direct insults which damage the alveolar epithelium, such as pneumonia and aspiration, and indirect insults which damage the capillary endothelium, such as sepsis and reactions to blood transfusions. Overall, what would the most common cause be?

Dr. Holt: The number one cause of ARDS in children is viral respiratory infections.⁴ This is not surprising given that viral infections are commonplace in childhood. While most kids with viral lower respiratory tract infections recover spontaneously as outpatients, an unfortunate few develop ARDS and require hospitalization.

Michael: Let's talk about the pathophysiology now.

Dr. Holt: Let's break the pathophysiology down into five main mechanisms of lung injury. This includes disrupted alveolar fluid clearance, inflammation, surfactant inactivation and loss, apoptosis, and coagulation dysfunction.

Michael: Could you tell us more about how alveolar fluid clearance is disrupted?

Dr. Holt: The cells of the alveolar epithelium and capillary endothelium form the alveolar-capillary barrier. Its large surface area and thinness make it excellent for gas exchange, but also prone to injury. Direct injuries damage type 2 alveolar cells, which normally produce surfactant and resorb excess alveolar wall liquid. Indirect injuries increase capillary permeability, overwhelming the ability of the type 2 cells to remove fluid. Thus, there are two different mechanisms that disrupt fluid clearance but lead to a similar result: the accumulation of fluid within the alveoli.¹

Michael: Are there other consequences of the disrupted alveolar-capillary barrier?

Dr. Holt: The disrupted barrier allows large molecules such as albumin to enter the alveoli, creating a protein-rich edema fluid.⁴ This proteinaceous fluid inactivates surfactant, which normally provides surface tension at the air-liquid interface and prevents alveolar collapse. Surfactant production is also decreased due to type 2 cell damage. Thus, surfactant is both inactivated and/or lost in ARDS, making regions of lung prone to atelectasis. These collapsed areas no longer take part in gas exchange and contribute to hypoxemia.

Michael: So far, we know about disrupted alveolar fluid clearance leading to pulmonary edema, and surfactant dysfunction leading to atelectasis. What about the other mechanisms of lung injury?

Dr. Holt: Another key part of the pathophysiology is inflammation, both local and systemic, which is mediated by white blood cells, cytokines, and chemokines.⁴ When alveolar macrophages are activated in response to a clinical insult, they release inflammatory mediators which draw neutrophils and circulating macrophages into the alveoli. This leukocytic infiltration is a pathologic hallmark of ARDS. Systemic inflammation is mediated by circulating cytokines and chemokines, which activate the capillary endothelium and promote apoptosis of epithelial and endothelial cells. An additional feature of ARDS is coagulation dysfunction. Capillary endothelial injury releases tissue factor and von Willebrand factor, creating a prothrombotic state. Microthrombi form in the pulmonary vasculature, decreasing perfusion to often already poorly ventilated alveoli.

Michael: So, inflammation, apoptosis, and coagulation dysfunction also contribute to lung injury in ARDS. How do these disturbances affect patient's overall respiratory physiology?

Dr. Holt: Taken together, the atelectasis, edema, and inflammation seen in ARDS define it as a restrictive lung disease.¹ ARDS lungs have low compliance, meaning that they are stiff - higher pressures are needed to reach the same volumes as healthy lungs. They also have low functional residual capacity, the volume remaining at the end of tidal expiration. For this reason, ARDS lungs are sometimes referred to as "baby" lungs, as they are effectively of lower volume.⁵ It is important to note that the respiratory physiology of ARDS is highly heterogeneous. One region may be collapsed, while others may be edematous or even hyperinflated. In other words, the lung experiences significant V/Q mismatching.

Michael: The pathophysiology of ARDS is clearly complex, but it seems that the key points are that a clinical insult impairs alveolar fluid clearance, leading to pulmonary edema, inflammation, and poor compliance. This results in heterogeneous V/Q mismatch and hypoxemia.

MANAGEMENT

Michael: So far, we have reviewed the PALICC definition, etiology, and pathophysiology of pediatric ARDS. Now let's discuss the management.

Dr. Hansen: Sure. Unfortunately, there are no specific treatments for ARDS, as it is a clinical syndrome. Instead management is supportive, focused on treating the underlying condition and a mechanical ventilation strategy that minimizes risk of ventilator-induced lung injury.⁴ In general, there is little evidence on managing pediatric ARDS, so clinical practice is often based on expert opinion, clinical experience, or adult data.

Michael: Could you begin by explaining some mechanical ventilation basics?

Dr. Hansen: Mechanical ventilation involves a ventilator circuit that delivers positive pressure breaths to the patient, usually via an endotracheal tube.⁶ There are many indications for mechanical ventilation, but in the case of ARDS it is usually because of respiratory failure. This means the patient either has inadequate oxygenation, ventilation, or both.

Michael: What are the parameters that can be set on a ventilator?

Dr. Hansen: There are many, however mode, tidal volume, and PEEP are probably the most important considerations. First let's talk simply about modes. The two basic modes are volume control and pressure control.⁶ In volume control, the clinician sets the tidal volume, but the pressures required to deliver that tidal volume change based on lung compliance. Pressure control is essentially the opposite. The clinician sets an inspiratory pressure, but the resultant tidal volume changes based on lung compliance. For example, let's pretend there are two identical patients in terms of age and size, but one has healthy compliant lungs while the other has stiff ARDS lungs. If they were both being ventilated on pressure control mode at the same pressure, the healthy lungs would receive a higher tidal volume than the patient with ARDS because they are more compliant.

Michael: How would the ventilator be best set up in ARDS?

Dr. Hansen: For ARDS, there is little evidence to suggest one mode is superior to others.⁷ Our goal is to find a balance between maximizing gas exchange and minimizing the risk of ventilator-induced lung injury. This is referred to as a lung protective ventilation strategy.⁷ The injuries we are trying to prevent include volutrauma, which is over distension of the alveoli, barotrauma, which is pressure mediated damage, atelectrauma, which is the cyclical opening and closing of alveoli, and oxygen toxicity.⁴

Michael: Let's talk about volutrauma first. How do we set the ventilator to prevent that?

Dr. Hansen: Low tidal volumes help to minimize volutrauma. This is supported by the ARDS Network trial, which was a landmark study published in the New England Journal of Medicine in 2000.⁸ This study compared traditional tidal volumes of 12 mL/kg to a lower 6 mL/kg in adults with ARDS. They found lower tidal volumes to be superior, with a 22% reduction in mortality, more ventilator-free days, lower rates of secondary organ failure, and lower serum levels of inflammatory markers. PALICC recommends physiologic tidal volumes of 5-8 mL/kg for children with preserved respiratory compliance, and lower tidal volumes of 3-6 mL/kg for those with low compliance.⁷

Michael: What about barotrauma?

Dr. Hansen: Barotrauma is an important consideration because high pressures can lead to air leak and pneumothorax. To avoid this, PALICC suggests a maximum peak inspiratory pressure of 28 cm H₂O for most patients, and a slightly higher range of 29-32 cm H₂O for children with increased chest wall elastance.⁷

Michael: What about preventing atelectrauma?

Dr. Hansen: Reducing the risk of atelectrauma requires optimizing PEEP.¹ PEEP helps to stent alveoli open at the end of expiration, which is when they are most prone to collapse. In stiff
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lungs this helps prevent repeated opening and closing of alveoli, which would promote sheer stress and be detrimental to gas exchange. PALICC recommends moderately elevated PEEP, defined as 10-15 cm H₂O.⁷ This is supported by a pediatric study that found PEEP lower than recommended by the ARDS Network is associated with higher mortality.⁹ However, because ARDS is a highly heterogeneous condition with regions of atelectasis, edema, and over distension, it can be difficult to determine the optimal PEEP for an individual patient.

Michael: Are there any ways to optimize PEEP for a particular patient?

Dr. Hansen: One suggested method is to perform recruitment maneuvers in small incremental and decremental steps.⁷ This involves starting at a low PEEP and moving up and down slowly until the best achievable compliance and oxygen saturation is reached. A novel imaging modality known as electrical impedance tomography can help optimize recruitment maneuvers.¹⁰ Electrical impedance tomography involves a band placed around the patient's chest that provides real-time images of regional lung volumes without radiation. This allows clinicians to visualize the PEEP value that optimizes recruitment. Hemodynamics must also be monitored during these maneuvers, as increasing PEEP decreases venous return and preload, which can diminish cardiac output.¹

Michael: My last question about ventilation, how is oxygen toxicity minimized?

Dr. Hansen: Prolonged exposure to elevated FiO₂ promotes formation of reactive oxygen species. These molecules oxidize lipids, DNA, and protein, as well as promoting apoptosis.¹¹ These risks can be minimized by an approach called permissive hypoxemia, where the patient is allowed to be slightly hypoxemic.⁷ PALICC recommends titrating SpO₂ to 92-97% for patients on PEEP less than 10, and SpO₂ 88-92% for patients on PEEP 10 or higher. A similar strategy, called permissive hypercapnia, is used to limit the risks of over ventilation. pH is titrated to 7.15-7.30 by lowering minute ventilation, allowing lower tidal volumes and pressures to be used.

Michael: To summarize, a lung protective ventilation strategy is preferred for ARDS. This involves low tidal volumes, limiting peak inspiratory pressure, moderate to high PEEP, and permissive hypoxemia and hypercapnia. Besides mechanical ventilation, are there any other therapies to consider?

Dr. Hansen: Exogenous surfactant has been studied as it could theoretically improve atelectasis, however it does not have a mortality benefit.¹² Inhaled nitrous oxide, which vasodilates capillaries and promotes alveolar perfusion, has been shown to transiently improve oxygenation and thus may have a role for bridging severely hypoxemic patients to extracorporeal membrane oxygenation.¹² Placing patients in the prone position, or face down, is another approach being used in severe ARDS.^{13,14}

Michael: Could you tell us how the prone position helps?

Dr. Hansen: The prone position has been shown to improve oxygenation in pediatric ARDS, likely by recruiting dorsal alveoli and reducing V/Q mismatch.¹² When supine, ventral alveoli are better ventilated than dorsal alveoli. This means that V/Q values are higher in ventral regions compared to dorsal regions due to gravitational effects. Ventral alveoli can also expand more easily as the anterior chest wall is more compliant. This puts pressure on the dorsal units below. In addition, the weight of the heart compresses lung tissue when supine, especially the left lower lobe. Conversely, when prone, dorsal alveoli experience less compression from ventral alveoli and the heart, possibly allowing recruitment of atelectasis and more homogenous lung. Developed by Dr. Michael Prodanuk, Dr. Tanya Holt, and Dr. Gregory Hansen for PedsCases.com. August 4th, 2018.

inflation. Oxygenation often improves as dorsal recruitment outweighs any ventral collapse. The prone position is generally safe, however clinicians need to be careful of accidental extubation. PALICC suggests that the prone position can be considered for severe ARDS but notes that it has not been shown to improve mortality or speed recovery.¹²

Dr. Holt: Let's apply our new knowledge of ARDS management to our case patient. Following intubation and initial fluid resuscitation, our patient was placed on a volume-controlled mode with low tidal volume and moderate PEEP. These settings were chosen to minimize the risk of volutrauma and to recruit atelectasis. Because he required an FiO_2 of 0.55 to maintain oxygenation at those settings, we performed electrical impedance tomography to evaluate regional lung inflation. We incrementally escalated PEEP while monitoring the lung inflation in real-time and determined that his optimal lung inflation was at a PEEP of 14 cmH_2O . Within two hours of these recruitment maneuvers, his FiO_2 was able to be weaned to 0.45. However, if these maneuvers had not been successful, prone ventilation would be our next option to improve V/Q matching. To address his underlying condition, likely a secondary bacterial pneumonia following a viral upper respiratory tract infection, he was placed on broad-spectrum IV antibiotics.

MORTALITY

Michael: Clearly ARDS is a serious condition as most children need admission to the PICU. What is the mortality of this syndrome?

Dr. Holt: A 2017 systematic review and meta-analysis determined that the overall mortality of pediatric ARDS is roughly 24%.¹⁵ Sadly, this means that approximately 1 in 4 children will die. However, this review showed that mortality is improving over time, possibly due to earlier recognition and improvements in ventilation strategy. Predictors of mortality include degree of hypoxemia, need for mechanical ventilation, immunosuppression, and failure of an organ in addition to the lungs.¹ Most deaths were attributed to sepsis or multi-organ dysfunction rather than respiratory failure alone.

To return again to our patient, he was mechanically ventilated for 4 days before being weaned from the ventilator and stayed in the PICU another 2 days. He was then transferred to the ward for continued antibiotic therapy and was discharged home after 12 days in hospital.

KEY LEARNING POINTS

Michael: That brings us to the end of our podcast. Let's summarize the key points we discussed:

1. Acute respiratory distress syndrome is a life-threatening lung condition characterized by pulmonary edema, reduced respiratory compliance, and hypoxemic respiratory failure. In children it is diagnosed clinically using the PALICC definition.
2. The etiologies of ARDS are either direct insults, where there is damage to the alveolar epithelium, or indirect insults, where there is damage to the capillary endothelium.
3. The pathophysiology of ARDS involves disruption of the alveolar-capillary barrier, accumulation of fluid in the alveoli, atelectasis, and heterogeneous V/Q mismatch.
4. The management of ARDS is supportive and involves lung protective ventilation strategies and treating the underlying condition.
5. The mortality of ARDS is high, however it is improving with medical advancements.

Thank you for listening to our podcast on pediatric ARDS. We hope you learned something useful and will stay tuned for future PedsCases podcasts.

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