Respiratory Distress Management in Pediatric Critically Ill Patients: A Focus on the Use of ECMO

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Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- Describe the pathophysiology and risk factors of respiratory distress in pediatric ICU patients
- Formulate clinical therapeutic recommendations for the management of respiratory distress in pediatric patients
- Evaluate the role of extracorporeal membrane oxygenation (ECMO) in the management of pediatric patients with respiratory distress
- Identify possible issues for pharmacists in dosing other medications while patients are on ECMO
- Describe adverse effects and monitoring parameters used for pediatric patients on ECMO

Definition

- Acute Respiratory failure
  - Inability of lungs to maintain adequate oxygen and carbon dioxide homeostasis
  - Acute hypoxemia (SaO2 < 90%, PaO2 < 60 mmHg)
  - Acute hypercarbia, hypercapnia (PaCO2 > 55 mmHg)
  - pH < 7.35

Airway Differences

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>Large</td>
<td>Normal</td>
</tr>
<tr>
<td>Epiglottis Shape</td>
<td>Floppy, U-shaped</td>
<td>Firm, Flatter</td>
</tr>
<tr>
<td>Epiglottis Level</td>
<td>Level of C3 – C4</td>
<td>Level of C5 – C6</td>
</tr>
<tr>
<td>Trachea</td>
<td>Smaller, shorter</td>
<td>Wider, longer</td>
</tr>
<tr>
<td>Larynx Shape</td>
<td>Funnel shaped</td>
<td>Column</td>
</tr>
<tr>
<td>Larynx Position</td>
<td>Angles posteriorly away from glottis</td>
<td>Straight up and down</td>
</tr>
<tr>
<td>Narrowest Point</td>
<td>Sub-glottic region</td>
<td>At level of Vocal cords</td>
</tr>
<tr>
<td>Lung Volume</td>
<td>250 mL at birth</td>
<td>6000 mL as adult</td>
</tr>
</tbody>
</table>

Pediatric Respiratory System

- Poor accessory muscle development
- Less rigid thoracic cage
- Horizontal ribs, primarily diaphragm breathers
- Increased metabolic rate, increased O2 consumption

Pediatric Respiratory System

- respiratory reserve + \( \uparrow \) \( \text{O}_2 \) demand \( \Rightarrow \) respiratory failure risk

Common Causes

- Croup
- Aspiration
- Asthma
- Bronchiolitis
- Bronchopulmonary dysplasia (BPD)
- Pneumonia
- Sepsis
- Near Drowning

Patient Case

- TE is a 2 yo 15 kg F with previous history of 3 reactive airway exacerbations in the last 4 months who presents with worsening cough, increased work of breathing and wheezing. On PE – RR is 48 breaths/min with moderate retractions, SpO\(_2\) 88%.

- What is most likely cause of TE’s respiratory distress?
  - Acute asthma exacerbation
  - Pneumonia
  - Croup

Asthma

- Definitions
  - Asthma
    - Chronic, inflammatory disorder of airways mediated by mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells
  - Asthma exacerbations
    - Acute or subacute episodes of progressively worsening SOB, cough, wheezing, and chest tightness
  - Status asthmaticus (SA)
    - Life threatening form of asthma unresponsive to initial standard therapy that leads to respiratory failure

Asthma Pathophysiology

- Inflammation
- Airway Hyperresponsiveness
- Airway Obstruction
- Clinical Symptoms
Risk Factors:
Asthma-Related Death

- Previous severe exacerbation
- Intubation or ICU admission for asthma
- ≥2 hospitalizations or >3 ED visits in past year
- Use of >2 canisters of SABA per month
- Difficulty perceiving airway obstruction or severity of worsening asthma
- Low socioeconomic status or inner-city residence
- Comorbidities
  - Cardiovascular disease or other chronic lung disease

SABA: Short-acting beta agonist

Patient Case

- TE is a 2 yo 15 kg F with previous history of 3 reactive airway exacerbations in the last 4 months who presents to the ED with worsening cough, increased work of breathing and wheezing. On PE – RR is 48 breaths/min with moderate retractions, SpO₂ 88%
- What medications are needed?

Treatment Goals

- Correct hypoxemia
- Reverse airflow obstruction
- Decrease airway edema
- Restore adequate pulmonary functions
- Reduce likelihood of relapse

SA Treatment in the PICU

Patient Case

- TE continued to have wheezing and increased work of breathing after receiving albuterol 2.5 mg and ipratropium 0.5 mg q20 min x 3 doses with methylprednisolone 30 mg (2 mg/kg). She was admitted to the general pediatrics floor for further management.
Community-Acquired Pneumonia (CAP)

- **Definition**
  - Presence of signs and symptoms of pneumonia in a previously healthy child due to an infection acquired outside of the hospital

- **IDSA guideline scope**
  - 3 months – 18 years of age

- **Exclusions**
  - Immunocompromised
  - Mechanical ventilation
  - Chronic lung disease (e.g. cystic fibrosis)

**Risk Factors**

- Not fully immunized
- Underlying medication conditions
  - Sickle cell disease
  - Asthma
  - BPD
  - Cystic fibrosis
  - Immunodeficiency syndromes

**Common Pathogens**

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacteria</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks - 3 months</td>
<td>Chlamydia trachomatis, S. pneumoniae, Haemophilus influenzae</td>
<td>Respiratory syncytial virus (RSV), Parainfluenza, Human metapneumovirus</td>
</tr>
<tr>
<td>4 months - 4 years</td>
<td>S. pneumoniae, H. influenzae, M. pneumoniae</td>
<td>RSV, Parainfluenza, Human metapneumovirus, Influenza</td>
</tr>
<tr>
<td>5 years - Adolescence</td>
<td>S. pneumoniae, M. pneumoniae, Ch. pneumoniae</td>
<td>Ch. pneumoniae</td>
</tr>
</tbody>
</table>

**Site-of-Care Management**

**Hospitalization Criteria**

- Moderate to Severe CAP
- Respiratory distress
- SpO₂ < 90%

- Infants < 3-6 months with suspected bacterial CAP
- Suspected or documented CAP caused by virulent pathogen (e.g. CA-MRSA)
- Concern regarding monitoring or compliance at home

- PICU Criteria
  - Invasive mechanical ventilation
  - Noninvasive positive pressure ventilation (e.g. CPAP or BiPAP)
  - Impending respiratory failure
  - Sustained tachycardia, hypotension, or need pharmacologic support for BP or perfusion
  - SpO₂ < 92% or inspired O₂ > 0.50
  - Altered mental status

**Inpatient Empiric Therapy**

- **Fully Immunized**
  - Ampicillin IV 200-400 mg/kg/day, divided q6h
  - Penicillin G IV 200,000-250,000 units/kg/day, divided q4-6h
  - Alternatives: Ceftriaxone IV 50-100 mg/kg/day, divided q12-24h
  - Cefotaxime IV 150 mg/kg/day, divided q8h
  - Azithromycin IV 10 mg/kg/day, once daily on day 1
  - 5 mg/kg/day, once daily on days 2-5
  - Alternatives: Doxycycline IV 2-4 mg/kg/day, divided q12h
  - Erythromycin IV 20 mg/kg/day, divided q6h
  - Levofloxacin IV 500 mg/day, divided q12h

- **Not Fully Immunized**
  - Ceftriaxone IV 50-100 mg/kg/day, divided q12-24h
  - Cefotaxime IV 150 mg/kg/day, divided q8h
  - Alternatives: Levofloxacin IV 500 mg/day, divided q12h

**Length of therapy**

- Typical duration is 10 days
- Follow up for improvement in 48-72h

**Minimizing resistance**

- Limit exposure to antibiotics
- Limit spectrum
- Proper dose
- Shortest effective duration
**CAP Prevention**

- Immunizations
  - *Streptococcus Pneumoniae*
  - *Haemophilus influenzae*
  - Pertussis
  - Influenza annually (>6 months)
  - Parents and caregivers of infants <6 months should be immunized for influenza and pertussis

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**Patient Case**

- On evening of admission TE found in respiratory distress. Mom yelled for help and Pediatric Code Blue was called. BVM ventilation initiated. On PE - Severe retractions, spontaneous respirations, minimal air entry
  - Continuous albuterol 10 mg/hr and magnesium sulfate 750 mg IV over 20 min
- Upon arrival to PICU
  - BiPAP, continuous albuterol 20mg/hr, ipratropium 0.5 mg Q4h, methylprednisolone 1.5 mg IV Q6h, magnesium sulfate infusion 50mg/kg/hr x 5 hrs

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**Patient Case**

- TE had acute oxygen desaturation into 20’s with placement of NG tube, required BVM ventilation.
  - Continuous albuterol 20 mg/hr, terbutaline load 2 mcg/kg and infusion 0.08 mcg/kg/min, magnesium sulfate infusion 50 mg/kg/hr x 5 hours
  - Episode of acute oxygen desaturation into 60’s with minimal air movement.
    - Intubated and placed on mechanical ventilation
    - Terbutaline titrated

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**Patient Case**

- Continued episodes of acute desaturation with optimal ventilation settings
  - Aminophylline load 5.7 mg/kg, infusion 1.01 mg/kg/hr
- TE placed on ECMO for continued support

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**Extracorporeal membrane oxygenation (ECMO)**

- Modified cardiopulmonary bypass circuit
- Provides cardiac support, blood oxygenation and carbon dioxide removal
- Allows for support for a prolonged period of time (days to weeks)

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**History of ECMO**

- First report of ECMO use in adult with post-traumatic respiratory failure
  - Bartlett et al. and O’Rourke et al. showed improved outcomes in newborns and children with respiratory failure
- ECMO Life Support Organization (ELSO) established
- Randomized clinical trial compared ECMO to conventional ventilator therapy for ARDS failed to show improved outcomes
- 1972 1979 1980s 1989
### Extracorporeal Life Support Organization Registry Report 2012

**ECMO Indications**
- Lung or cardiac disease that is:
  - Acute
  - Life-threatening
  - Reversible
  - Unresponsive to conventional therapy
- Chronic respiratory failure as bridge to transplant
- Cardiopulmonary support for organ donation after circulatory determination of death

**ECMO Contraindications**
- Irreversible respiratory or cardiac failure
- Mechanical ventilation ≥10 days?
- Contraindication to anticoagulation
- Malignancy
- Incurable disease
- <2 kg and <34 weeks post-menstrual age
- Multi-organ failure
- Severe or irreversible brain injury

**Is ECMO of Proven Benefit for Respiratory Failure?**
- Neonatal respiratory failure
  - Persistent pulmonary hypertension, meconium aspiration, congenital diaphragmatic hernia
  - UK randomized trial of neonatal ECMO (Lancet, 1996)
    - ECMO: 32% (30/93) neonatal deaths
    - Conventional Therapy: 59% (54/92) neonatal deaths
    - Relative risk 0.55 (95% CI 0.39-0.77; p = 0.0005)
    - Proven benefit in regionalized setting

- Pediatric respiratory failure
  - No good prospective study
  - Retrospective data: benefit in higher risk (not moribund) patients with respiratory failure
  - Green et al
    - Multi-center, retrospective cohort analysis
    - 331 patients, 2 weeks to 18 years of age
    - ECMO decreased mortality from 47.2% to 26.4% (p<0.01)

**Is ECMO of Proven Benefit for Respiratory Failure?**

- ECMO vs. non-ECMO Patients on Function of Mortality Risk Predicted by Oxygenation Index and PIM3 Score
  - ECMO Patients: 9%
  - Non-ECMO Patients: 19%
  - P < 0.05
Survival After ECMO

<table>
<thead>
<tr>
<th>ECMO Indication</th>
<th>Number of ECMO Uses</th>
<th>Survival to Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal (&lt;30 days)</td>
<td>Respiratory</td>
<td>27,728</td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>5,810</td>
</tr>
<tr>
<td></td>
<td>ECMR</td>
<td>1,112</td>
</tr>
<tr>
<td>Pediatric (30 days-16 yo)</td>
<td>Respiratory</td>
<td>6,569</td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>7,314</td>
</tr>
<tr>
<td></td>
<td>ECMR</td>
<td>2,370</td>
</tr>
<tr>
<td>Adults (&gt;16 yo)</td>
<td>Respiratory</td>
<td>7,008</td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>5,603</td>
</tr>
<tr>
<td></td>
<td>ECMR</td>
<td>1,657</td>
</tr>
</tbody>
</table>

Predictors of Survival

- Younger age (<10 yo)
- Ventilator days pre-ECMO (<14 days)
- Lower PIP, lower A-a gradient
- No difference in survival if >2 weeks on ECMO

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Types of ECMO

- Based upon site of cannula insertion
  - Venoarterial (VA)
    - Most commonly used form
    - Removal of venous blood from the right internal jugular vein
    - Returned to body through cannula in right common carotid artery
    - Required for cardiac support
    - Appropriate for respiratory support
  - Venovenous (VV)
    - Blood is withdrawn from and returned to the right atrium via the right internal jugular vein
    - No hemodynamic support
    - Preferred for respiratory
      - Uses only one major artery
      - Avoids potential systemic embolization
      - Maintains normal pulsatile blood flow

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Extracorporeal Life Support Organization, January 2015


ECMO Circuit

Medication Use During ECMO
- Standard medications used during ECMO
  - Heparin – Prevention of clots in the circuit
  - Antibiotics – Prophylaxis & treatment of infection
  - Electrolyte supplementation
  - Sedatives & Analgesics
  - Anticonvulsants
- Clinical studies of medication PK/PD in ECMO
  - Limitations:
    - Small sample sizes
    - Differences in ECMO techniques & equipment
    - Complexity of patient population with widely divergent medical conditions

Changes During ECMO
- Factors affecting medication dosing in ECMO
  - Physiologic
    - Increased extracellular fluid (ECF)
    - Change in renal function
  - Pharmacokinetic
    - Increased volume of distribution (Vd)
    - Prolonged elimination
    - Alterations in drug delivery
      - Administration into the circuit

Physiologic Alterations
- Increased ECF
  - Patient’s blood volume + exogenous blood for priming the ECMO circuit
  - Priming the circuit
    - Requires 300-400 mL of exogenous blood products
- Decrease in renal function
  - More of a function of severe illness
  - Renal damage due to circulating vasoactive substances caused by ECMO

Pharmacokinetic Alterations
- Increased volume of distribution
  - Priming the circuit
- Slower drug clearance
  - More of a function of severe illness, not ECMO itself
  - Concomitant renal dysfunction
    - Hemofiltration or hemodialysis
- Pharmacokinetic alterations return to baseline after decannulation

Alterations in Drug Delivery
- Medication interactions with ECMO circuit
  - Inactivation
    - Half-life of medication in relation to site of administration
      - Eg. Adenosine
  - Adsorption - Binding of some medications to membrane oxygenator
    - Time since last circuit change
      - Eg. Fentanyl, Insulin
    - Sequestration
      - Shorter administration time acceptable for some medications
      - Dilution during passage through circuit
        - Eg. Vancomycin
Drug Factors

- **Hydrophilicity**
  - Increased volume of distribution
  - Clearance neutral
  - Dosage adjustment
  - Increased loading dose

- **Lipophilicity**
  - Volume of distribution is unchanged
  - Increased circuit sequestration
  - Clearance neutral
  - Dosage adjustment
  - Increased loading dose
  - Increased frequency


Inactivation

- **Medications with short half-lives**
  - Administered into the circuit
    - Activity can be lost before it reaches the patient
    - Examples:
      - Adenosine
      - Vasopressors – Epinephrine, norepinephrine
    - Should not be administered to the circuit
    - Administer as close to patient as possible
  - Effects on pharmacokinetics
    - Increased clearance
    - Decreased bioavailability


Adsorption

- **Actual loss of drug in the circuit**
  - Pre- and post-oxygenator concentrations
  - Significant binding by medication
    - Lipophilic medications
  - Factors affecting adsorption
    - Type of circuit
      - Polypropylene hollow fiber membrane oxygenator
      - Silicone membrane with hollow fiber oxygenator
    - Age of circuit
      - "Old" circuits
        - Less medication binding
        - Saturated binding sites
  - Pharmacokinetic effects
    - Increased volume of distribution
    - Decreased peak concentration


Sequestration

- **Injection sites**
  - Pre-reservoir & reservoir injections
  - Incomplete mixing
  - Delayed drug delivery to patient
  - Post-reservoir injection is preferred

- **Flow rates**
  - Less than 250 mL/min
  - Results in pooling of the drug
  - Pharmacokinetic effects
    - Increased volume of distribution
    - Decreased peak concentration


Summary

- Medication dosing in ECMO is affected by the following factors:
  - Physiologic alterations
    - Increased extracellular fluid
    - Change in renal function
  - Pharmacokinetic alterations
    - Larger volume of distribution
    - Slower clearance
  - Administration issues
    - Delay in medication delivery
    - Loss of medication in circuit
  - Increased medication doses

Adverse Effects

- **Thrombosis**
- **Bleeding**
  - Cannulation site
  - Intracranial hemorrhage
  - Gastrointestinal
  - Mucous membranes
  - Uterine
  - Thrombocytopenia
  - Heparin Induced Thrombocytopenia (HIT)

[Sources: Buck ML. Clin Pharmacokinet 2003; 42 (5): 403-417]
**Thrombosis**

- Thrombosis in the ECMO circuit
  - Every circuit will have some small clots
    - Located: site of connectors, infusion lines, pre-pump bladder or membrane lung
    - Size: ≤5 mm – observation
    - Size: >5 mm – require removing section or circuit change
  - Require careful examination with flashlight
    - Seen as very dark non-moving areas on the surfaces
- Platelet/fibrin thrombi
  - Appear as white areas on the circuit at connectors or stagnant areas

**Etiology:**
- Periods of low flow
- Inadequate anticoagulation
- 20% result in circuit change

**Management of Bleeding**

- Packed Red Blood Cell (PRBC) transfusion
- Fresh Frozen Plasma
- Cryoprecipitate
  - Fibrinogen levels <100-150 mg/dL
- Platelet transfusion
  - 10 mL/kg to maintain platelets > 100,000 mcg/L
- Antifibrinolytic Therapy
  - Aminocaproic acid or Tranexamic acid
- Recombinant Activated Factor VII (rVIIa)
  - Dose: 40-90 mcg/kg
- Prothrombin Complex Concentrates
  - Dose: 25-50 international units/kg

**Thrombocytopenia**

- Definition: Platelet count less than 150,000 mcg/L
- Common in patients on ECMO
- Causes:
  - Underlying disease
  - Medications
  - Blood surface exposure

- Platelet count will be consistently less than 10,000 mcg/L
- Must stop heparin and switch to different anticoagulant
- Direct thrombin inhibitors
  - Argatroban – Usual 1st line
  - Hirudin

**Anticoagulation in ECMO**

- Continuous contact between circulating blood and its cellular components with the nonbiologic surface of ECMO circuit
  - Massive inflammatory & clotting response
    - Results in hypercoagulant state
    - Increased risk of thromboses
    - Anti-thrombotic therapy
      - Prevention of thromboses
      - Unfractionated heparin (UFH)
      - Most widely used agent
Coagulation System in Children

- **Adults vs. children**
  - Coagulation system for neonates, infants, & children
  - Contains all components for clotting but different concentrations
    - Factors VIII, IX, X, XI, XII, prekallikrein, and high molecular weight kininogen
    - Newborns: 50% of adult levels
    - Platelets: Newborns: Hyporeactive compared to adults
    - Inhibitors of clotting: Protein C & S, Antithrombin III
      - Newborns: 50% of adult levels
      - Newborn coagulation system overall matures over 6 months to adult levels and function

Anticoagulation Monitoring

- **Heparin Monitoring**
  - Several whole blood & plasma based test to assess coagulation in vitro
    - Activated Clotting Time (ACT)
    - Activated Partial Thromboplastin Time (APTT)
    - Antifactor Xa Assay
    - Thromboelastography (TEG)
  - All of the tests are not standardized
  - **Anti thrombin III (ATIII)**
  - **Platelets**

Activated Clotting Time (ACT)

- Basic test measuring clotting of whole blood
- Performed at bedside by exposing sample to one of 2 activators
- Used for decades
- Advantages
  - Point-of-care test that can be performed at bedside
  - The only routine point-of-care test for anticoagulation
- Disadvantages
  - Inconsistency in measurements
  - Reliability in neonate population
  - Variation between machines

Antifactor Xa Assay

- Measure of UFH effect
  - Based on the ability of UFH to catalyze the inhibition of factor Xa by antithrombin
- Outside of ECMO, gold standard for monitoring
- UFH
  - Low molecular weight heparin
    - Becoming gold standard for management of UFH therapy in ECMO at many centers
  - Measurements are performed daily
  - Usual goal: 0.3-0.7 IU/mL
    - Some centers use higher goal of 0.7-1.1 IU/mL
  - Poor correlation between ACT ranges and antifactor Xa levels
    - Children and adults undergoing cardiopulmonary bypass for cardiac surgery

Thromboelastography (TEG)

- Whole blood point of care test of the viscoelastic properties of clot formation
  - Measures integrity of coagulation cascade
  - From time of fibrin formation to clot lysis
  - Includes contribution of platelets
  - Provides information relating to multiple phases of coagulation in whole blood
  - Very relevant to ECMO patients as they often have more than one reason for coagulation abnormalities (e.g., fibrinolysis and platelet dysfunction)

Anticoagulation Management

- Anticoagulation at initiation of ECMO
  - UFH bolus 50-100 units/kg IV to the patient
    - Administered 3 minutes prior to cannulation
  - UFH drip initiated at 7.5-20 units/kg/hr
    - Infused over ACT > 300 seconds
    - Adults: Lower dose range
    - Neonates & pediatrics: Higher dose range
  - Routine anticoagulation during ECMO
    - Standard goal ACT:
      - 180-220 seconds
    - Variable from center to center & type of monitoring equipment being used
    - Usual UFH infusion rates: 20-50 units/kg/hr

UFH = Unfractionated Heparin
ACT = Activated Clotting Time
Antithrombin III (ATIII)

- Neonates and infants
  - Developmentally low AT activity & antigen levels

- Optimal AT activity for patients receiving UFH for anticoagulation in ECMO
  - Unknown

- Acquired AT deficiency
  - Escalating UFH requirements
    - UFH doses >35-40 units/kg/hr
    - Low AT concentrations in plasma
  - Clotting can still occur despite high doses of heparin

- Subtherapeutic anticoagulation
  - AT activity < 30 to 60%
  - Evidence of reduced UFH effect clinically
  - Low ACT or anti-Xa levels
  - Most centers target levels >50% to >100%

AT = Antithrombin
UFH = Unfractionated Heparin
ACT = Activated Clotting Time

Summary

- Thrombosis and bleeding are adverse effects that need to be monitored and addressed during ECMO therapy
- There are several different tests available to monitor anticoagulation in ECMO
  - All have advantages and disadvantages
  - Multiple tests will be used concomitantly
- Monitoring and replacement of antithrombin when anticoagulation is not adequate

AT = Antithrombin
UFH = Unfractionated Heparin
ACT = Activated Clotting Time