Evidenced-Based Decision Making in Selected Pediatric and Neonatal Critical Care Cases

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Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives 1-3

1. Select a first-line opioid and sedative infusion strategy for a patient in the neonatal intensive care unit (NICU) or the pediatric intensive care unit (PICU).

2. Given a patient case, develop a sedation and analgesia infusion regimen to prevent opioid tolerance and delirium in the NICU or PICU.

3. Given a patient case, determine the most appropriate inotrope or vasopressor for a patient with fluid-refractory shock.
Learning Objectives 4-5

4. Given a patient case, design a corticosteroid regimen for a patient with septic shock with adrenal insufficiency.

5. Given a patient case, determine the role of inhaled nitric oxide to treat a patient with a pulmonary hypertension crisis in the PICU.
History of Present Illness

- AC is a 13 month-old female with lethargy & respiratory distress
- Past medical history:
  - Prematurity (32 week GA)—3 month NICU stay
  - Trisomy 21
  - Bronchopulmonary dysplasia
  - Obstructive sleep apnea
  - Ventricular septal defect (unrepaired)
  - Adrenal insufficiency (hydrocortisone discontinued at 10 months of age)

GA = Gestational age
Review of Last 3 Days

- ↑ work of breathing x 3 days
- Seen by pulmonologist & given prednisolone orally x 7 days & amoxicillin orally x 10 days
- Last evening AC had ↑ work of breathing & lethargy
- Home O₂ ↑ to 2 L/min
- Mom drove A.C. to Emergency Department
## Current Medications

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Drug/Strength/Regimen</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2017</td>
<td>Albuterol 90 mcg MDI—2 puffs every 4 hr as needed</td>
<td>Wheezing</td>
</tr>
<tr>
<td>1/2018</td>
<td>Fluticasone 88 mcg MDI every 12 hr</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>12/2018</td>
<td>Amoxicillin orally—dose unknown</td>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>12/2018</td>
<td>Prednisolone orally—dose unknown</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
</tbody>
</table>

**Immunizations:** Status unknown

**Allergies:** NKDA

**Other:** 1 L/min O₂ by nasal cannula at home
<table>
<thead>
<tr>
<th>Data</th>
<th>Exam Finding/Objective Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>• Tachypneic</td>
</tr>
<tr>
<td></td>
<td>• Subcostal retractions with moderate intercostal retractions</td>
</tr>
<tr>
<td></td>
<td>• Diffuse crackles, rhonchi, &amp; wheezing present</td>
</tr>
<tr>
<td>Cardiology</td>
<td>• Tachycardic with poor perfusion</td>
</tr>
<tr>
<td></td>
<td>• Capillary refill 4-5 seconds</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cool hands &amp; feet</td>
</tr>
<tr>
<td>Vital signs</td>
<td>• Weight: 13.5 kg; height: 80 cm</td>
</tr>
<tr>
<td></td>
<td>• Temperature: 39.2 °C</td>
</tr>
<tr>
<td></td>
<td>• Heart rate: 160 beats per min</td>
</tr>
<tr>
<td></td>
<td>• Respiratory rate: 45 breaths per min</td>
</tr>
<tr>
<td></td>
<td>• Blood pressure: 71/43 mm Hg</td>
</tr>
<tr>
<td></td>
<td>• O2 saturation: 86%</td>
</tr>
</tbody>
</table>
Other Objective Findings

- Chest X-ray: Right middle lobe pneumonia with pleural effusion
- Cultures:
  - Nasal pharyngeal wash: positive for influenza A
  - Blood & urine cultures: pending
- Laboratory data:
  - Complete metabolic panel & complete blood count: pending
  - Procalcitonin: pending
Question 1:

Which of the following fluid boluses would you recommend for AC to ↓ mortality, acute kidney injury (AKI), & number of vasoactive infusion days?

A. 0.9% Sodium chloride  
B. 0.45% Sodium chloride  
C. Lactated Ringer’s (LR)  
D. 25% Albumin
Shock

• Inadequate perfusion to meet demand

• Stages:
  - Compensated
  - Hypotensive
  - Cardiac Arrest

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Systolic Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Infants</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Children (1-10 years)</td>
<td>&lt; 70 + (age in years x 2)</td>
</tr>
<tr>
<td>Children &gt; 10 years</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

• Sepsis-3 Task Force: life-threatening organ dysfunction caused by a dysregulated host response to infection:
  - Not designed for or validated in children
  - Adapted by Schlapbach et al using SOFA and PELOD-2

SIRS = systemic inflammatory response syndrome
CV = cardiovascular
SOFA = sequential organ failure assessment
PELOD = pediatric logistic organ dysfunction

## Warm vs. Cold Septic Shock

<table>
<thead>
<tr>
<th>Warm Shock</th>
<th>Cold Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents and adults</td>
<td>Young children</td>
</tr>
<tr>
<td>↓afterload (SVR) and ↑ cardiac output (CO)</td>
<td>↑SVR and ↓CO</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Pink extremities</td>
<td>Mottled, cool extremities</td>
</tr>
<tr>
<td>Bounding pulses</td>
<td>Weak pulses</td>
</tr>
<tr>
<td>Flash capillary refill</td>
<td>Capillary refill ≥ 3 sec</td>
</tr>
</tbody>
</table>

SVR = Systemic vascular resistance

<table>
<thead>
<tr>
<th>Steps</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fluid resuscitation</td>
<td>20 mL/kg 0.9% Normal Saline (NS) or LR boluses up to 60 mL/kg</td>
</tr>
<tr>
<td></td>
<td>Correct laboratory abnormalities (hypoglycemia and hypocalcemia)</td>
</tr>
<tr>
<td></td>
<td>Begin antibiotics</td>
</tr>
<tr>
<td>2. Fluid-refractory shock</td>
<td>Titrate norepinephrine (NE) from 0.05 mcg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Start dopamine ≥ 10 mcg/kg/min if NE not available</td>
</tr>
<tr>
<td>3. Adrenal insufficiency</td>
<td>Consider Hydrocortisone</td>
</tr>
<tr>
<td>4. Catecholamine &amp; steroid-resistant shock</td>
<td>Euvolemic: Add vasopressin 0.05 – 2 milliunits/kg/min</td>
</tr>
<tr>
<td></td>
<td>Low cardiac index: Add epinephrine 0.01 – 0.05 mcg/kg/min,</td>
</tr>
<tr>
<td></td>
<td>dobutamine 2.5 – 15 mcg/kg/min, or levosimendan</td>
</tr>
<tr>
<td>5. Refractory shock</td>
<td>Extracorporeal Membrane Oxygenation (ECMO)</td>
</tr>
</tbody>
</table>

ACCCM = American College of Critical Care Medicine

## ACCCM Cold Shock Algorithm

<table>
<thead>
<tr>
<th>Steps</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fluid resuscitation</td>
<td>20mL/kg NS or LR boluses up to 60 mL/kg</td>
</tr>
<tr>
<td></td>
<td>Correct electrolytes (hypoglycemia and hypocalcemia)</td>
</tr>
<tr>
<td></td>
<td>Begin antibiotics</td>
</tr>
<tr>
<td>2. Fluid refractory shock</td>
<td>Titrate epinephrine (epi) 0.05-0.3 mcg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Start dopamine 5-9 mcg/kg/min if epi not available</td>
</tr>
<tr>
<td>3. Adrenal insufficiency</td>
<td>Consider Hydrocortisone</td>
</tr>
<tr>
<td>4. Catecholamine &amp; steroid resistant shock</td>
<td>Normotensive: Add milrinone 0.25 mcg/kg/min.</td>
</tr>
<tr>
<td></td>
<td>Low cardiac index: consider levosimendan</td>
</tr>
<tr>
<td></td>
<td>Hypotensive: Add norepinephrine 0.05 mcg/kg/min.</td>
</tr>
<tr>
<td></td>
<td>Low cardiac index: dobutamine, milrinone, or levosimendan</td>
</tr>
<tr>
<td>5. Refractory shock</td>
<td>Extracorporeal Membrane Oxygenation (ECMO)</td>
</tr>
</tbody>
</table>

ACCCM = American College of Critical Care Medicine

Fluid Resuscitation

- Push 20 mL/kg isotonic saline boluses and reassess after each bolus up to 60 mL/kg until improved perfusion

Which type of fluid?  How much volume?  What timeframe?

Type of Fluid

• Crystalloids:
  - Fluid of choice
  - NS most commonly prescribed

• Albumin:
  - Recommended after administration of substantial amounts of crystalloids
  - Potential mortality benefit in septic shock

• Hydroxyethyl starches:
  - Not recommended
  - ↑ mortality and kidney injury


NS = normal saline
Choice of Crystalloid

• NS can cause hyperchloremia:
  - Altered renal blood flow = ↑ kidney injury
  - Pro-inflammatory
  - ↑ mortality:
    ▪ Hyperchloremia @ 72 hours in adults
    ▪ Cl > 110 mmol/L during first 7 days in pediatrics

• Balanced crystalloids:
  - LR and Plasmalyte
  - Use for 72 hours resuscitation ↓ mortality, AKI, & number of vasoactive infusion days

<table>
<thead>
<tr>
<th>Solution</th>
<th>Sodium (mEq/L)</th>
<th>Chloride (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>154</td>
<td>154</td>
</tr>
<tr>
<td>LR</td>
<td>130</td>
<td>109</td>
</tr>
<tr>
<td>Plasmalyte</td>
<td>140</td>
<td>98</td>
</tr>
</tbody>
</table>

Volume of Fluid

• Limited data to support fluid boluses vs. vasopressors
• Overall goal after risk of septic shock identified:
  - Adults: 30 mL/kg within 3 hours then guided by hemodynamic status
  - Pediatrics: 20-60 mL/kg within 15 minutes
• Conservative fluid strategies:
  - Cardiogenic shock or congenital heart disease
  - Severe anemia (dilutes hemoglobin)
  - Low-risk PICU patients: high cumulative % positive fluid balance ↑ mortality
  - Resource-limited settings: FEAST trial showed fluid boluses ↑ mortality

Timeframe of Fluid Administration

- Initial bolus of 20 mL/kg bolus IV push as rapid as possible (5-10 minutes)
- Study comparing boluses over 15-20 min vs. 5-10 min in pediatric patients
  - ↓ risk of intubation and % fluid overload
  - Limited cardiovascular and organ perfusion data
  - Study sopped early due to high risk of mechanical ventilation and/or impaired oxygenation in control group

Question 2:

Following fluid resuscitation, which of the following inotropes or vasopressors should be initiated for cold shock?

A. Dopamine  
B. Epinephrine  
C. Milrinone  
D. Norepinephrine
Initial Resuscitation of Septic Shock

**Current State**
- Capillary refill 4-5 seconds
- BP 71/43 mm Hg
- Cool hands & feet
- Lethargy

**Goals within 15 minutes**
- Capillary refill ≤ 2 seconds
- Normal BP for age
- Warm extremities
- Normal mental status

# Fluid-Refractory Shock

<table>
<thead>
<tr>
<th></th>
<th>Cold Shock</th>
<th>Warm Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td>Epinephrine 0.05-0.3 mcg/kg/min</td>
<td>Norepinephrine ≥ 0.05 mcg/kg/min</td>
</tr>
<tr>
<td><strong>Alternate</strong></td>
<td>Dopamine 5-9 mcg/kg/min</td>
<td>Dopamine ≥ 10 mcg/kg/min</td>
</tr>
</tbody>
</table>

Dopamine vs. Epinephrine

- 2009-2013
- Prospective, double-blind placebo-controlled trial:
  - Dopamine 5 mcg/kg/min
  - Epinephrine 0.1 mcg/kg/min
- 120 patients (1 months to 15 years) with fluid-refractory shock
- Subsequent dose escalation every 20 minutes x 3
- Children receiving dopamine had:
  - ↑ death at 28 days (OR 6.51; p = 0.037)
  - Longer resuscitation (33.6 hr vs. 16.1 hr; p = 0.024)
  - ↑ healthcare-associated infection (28.5% vs. 2.3%, p=0.001)

Question 3:

Following initiation of epinephrine, A.C. still does not respond to epinephrine. Which of the following IV hydrocortisone dosages should be initiated (current weight = 13.5 kg)?

A. 50 mg every 6 hr
B. 75 mg every 8 hr
C. 18 mg every 8 hr
D. 14 mg every 6 hr
Corticosteroid Effects

• Mineralocorticoid effect in the renal system from sodium retention

• Cardiovascular:
  - ↑ inotropy
  - ↑ blood pressure
    ▪ Increased atrial natriuretic peptide and angiotensin synthesis
    ▪ Decreased prostaglandin synthesis
    ▪ Increased sensitivity to catecholamines

• Immune regulation:
  - ↓ circulating T-cells, eosinophils, & monocytes
  - Impaired neutrophil migration
  - ↓ pro-inflammatory cytokine production

Adrenal Insufficiency (AI)

- Stress/sepsis
  - ↑ free cortisol
  - ↓ corticosteroid binding proteins & receptor sensitivity
- ACTH stimulation test not recommended in septic shock
- 30-52% pediatric patients have Critical Illness-Related Corticosteroid Insufficiency
  - Delta total cortisol < 9 mcg/dL or random total cortisol < 10 mcg/dL
  - Steroids recommended in septic shock not responsive to moderate/high-dose vasopressors
- Age-related considerations:
  - Cortisol low at birth, ↑ by 1 month of age
  - No diurnal variation until 4-6 months of age

Hydrocortisone

- Steroid of choice in septic shock
- 2\textsuperscript{nd} highest relative mineralocorticoid activity among steroids
- Adults:
  - “Low dose” 50 mg every 6 hr or 200 mg/day
  - Fluid- and vasopressor-refractory shock
  - CORTICUS trial showed no benefit in mortality reduction
- Pediatrics:
  - In catecholamine-resistant shock (epinephrine or norepinephrine)
  - If risk for absolute AI
  - Dose?

Hydrocortisone in Pediatric SIRS/Sepsis

<table>
<thead>
<tr>
<th>Patients</th>
<th><strong>Hebbar et al 2011</strong></th>
<th><strong>Menon et al 2015</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 78 PICU patients with SIRS</td>
<td>• 364 PICU patients with shock</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing</th>
<th><strong>Hebbar et al 2011</strong></th>
<th><strong>Menon et al 2015</strong></th>
</tr>
</thead>
</table>
|                | • Hydrocortisone 100 mg/m\(^2\) x 1, then 25 mg/m\(^2\) IV every 6 hr  
• + fludrocortisone 50-100 mcg per physician discretion (63-68% of patients) | • Hydrocortisone 1 mg/kg q6h  
• Cumulative dose 23.1 mg/kg = ~5.7 days of therapy |

<table>
<thead>
<tr>
<th>Outcomes</th>
<th><strong>Hebbar et al 2011</strong></th>
<th><strong>Menon et al 2015</strong></th>
</tr>
</thead>
</table>
|                | • ↓ duration and rate of dopamine & norepinephrine  
• 92% of patients with AI responded | • ↑ duration of vasopressors  
• ↑ positive cultures in septic patients |

Levosimendan

- Ca\(^{2+}\) sensitizer and ATP-dependent K+ channel opener
- Decreased mortality in adults:
  - All settings: heart failure, post-surgery, sepsis
  - 2017 systematic review in patients with septic shock saw no impact
- Reduces biomarkers of myocardial injury compared with dopamine

<table>
<thead>
<tr>
<th></th>
<th>Standard Care</th>
<th>Levosimendan</th>
<th>Risk Ratio 0.74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality All settings</td>
<td>22.4% (3236/1457)</td>
<td>17.6% (333/1893)</td>
<td>95% CI = 0.62-0.89</td>
</tr>
<tr>
<td>Mortality In sepsis</td>
<td>61% (74/121)</td>
<td>47% (59/125)</td>
<td>95% CI = 0.63-0.98</td>
</tr>
</tbody>
</table>

## PICU Days 1-5

<table>
<thead>
<tr>
<th>PICU Day(s)</th>
<th>Course</th>
</tr>
</thead>
</table>
| 1-4        | • Intubated & placed on mechanical ventilator  
• Received 60 mL/kg IV LR, epinephrine, hydrocortisone  
• Initiated on vancomycin 20 mg/kg/dose IV every 6 hr & ceftriaxone 100 mg/kg/dose IV every 24 h  
• Initiated on fentanyl 1 mcg/kg/h & lorazepam 0.1 mg/kg/dose IV every 2-4 hr as needed for agitation |
| 5          | • Developed several episodes of oxygen desaturation to 70s requiring prolonged bagging  
• Echocardiogram suggestive of pulmonary hypertension  
• Initiated on 20 mL/kg IV Lactated Ringers’ & epinephrine restarted  
• ↑ Positive end expiratory pressure (PEEP) from 8 to 10 mm Hg  
• Fentanyl ↑ 3 mcg/kg/hr |
Question 4:

The PICU team wishes to add inhaled nitric oxide. What is the role of nitric oxide for pulmonary hypertension outside of the NICU?

A. Standard of care for treatment of pulmonary hypertension crises
B. Reduces mPAP in hypoxic respiratory failure and post-CHD surgery
C. Decreased mortality associated with post-op pulmonary hypertension
D. All of the above

mPAP = Mean pulmonary artery pressure
CHD = Congenital heart disease
Pulmonary Hypertension Crisis (PHC)

• **Physiology:**
  - ↑ in pulmonary artery pressure (PAP)
  - ↑ in pulmonary vascular resistance (PVR)

• **Incidence and mortality:**
  - Postoperative PHC has decreased from 31% to 6.8%
  - PHC overall mortality ranges from 20% to 50%, with 20% a more recent estimate

• **Goals of therapy:**
  - Pulmonary vasodilation
  - Augment / maintain right ventricle (RV) function and cardiac output (CO)
  - Avoid systemic hypotension and hypoxia

<table>
<thead>
<tr>
<th>Etiology of PHC</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Pain           | • Opioid infusions  
• Pre-emptive use of as needed opioids prior to interventions (prevents stress response) |
| Anxiety/Agitation | • Consider as needed sedatives prior to interventions  
• Sedative infusions (benzodiazepines or dexmedetomidine) |
| Hypoxia        | • ↑ supplemental oxygen  
• Optimize mechanical ventilation (maintain adequate lung volumes & gas exchange) |
| Acidosis       | • Hyperventilation  
• Sodium bicarbonate as needed ± infusion |
Nitric Oxide (NO)

- “Standard” therapy for PHC
- Endothelium-derived relaxing factor in its gaseous form that relaxes pulmonary vascular smooth muscle
- Inactivated by hemoglobin - delivery by inhalation
- Dose of 2 to 80 parts per million (ppm)
- Concerns / disadvantages:
  - Side effects
  - Administration
  - Cost: $85 - $150 per hour; approximately $2000 - $3600 per day

iNO: History of Evidence

• Early 1990s – the beginning:
  - Animal data and case reports, small case series
  - Role in pediatric patients with PH, some with exposure to cardiopulmonary bypass (CPB) or associated with CHD
  - Varying degree of efficacy reported
    ▪ Variability in dosing strategies / administration techniques
  - Concluded that iNO appeared to reduce PVR and PAP, with minimal systemic effects or toxicity with short-term exposure
    ▪ Encouraged larger, randomized, double-blind investigations
  - Reliable and safe administration possible

## iNO History of Evidence Cont’d

<table>
<thead>
<tr>
<th>Patients</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 CHD surgery</td>
<td>iNO 80 ppm around CPB</td>
<td>mPAP ↓ 11% pre- and 23% post-CPB</td>
</tr>
<tr>
<td>17 hypoxic respiratory failure</td>
<td>iNO 20 – 40 ppm for 30 minutes</td>
<td>mPAP ↓ 26%</td>
</tr>
<tr>
<td>36 CHD surgery</td>
<td>iNO 80 ppm vs. placebo for 20 minutes post CPB</td>
<td>mPAP ↓ 19%</td>
</tr>
<tr>
<td>124 CHD surgery</td>
<td>iNO 10 ppm vs. placebo until extubated</td>
<td>Fewer PHCs in iNO group</td>
</tr>
<tr>
<td>38 CHD surgery</td>
<td>iNO 20 ppm vs. conventional therapy for 60 minutes post CPB</td>
<td>No benefit from iNO in occurrence of PHCs</td>
</tr>
</tbody>
</table>


CHD = Congenital heart disease  
mPAP = Mean pulmonary artery pressure  
CPB = Cardiopulmonary bypass
Mortality Benefit with iNO

- What about mortality?
- Observational study over 10 years in 64 patients who underwent surgical palliation of a CHD (AV-canal) and experienced severe postoperative PH
- Interventions

<table>
<thead>
<tr>
<th>Years 1 - 8</th>
<th>Years 9 - 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% Oxygen</td>
<td>100% Oxygen</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Metabolic acidosis correction</td>
<td>Metabolic acidosis correction</td>
</tr>
<tr>
<td>Muscle paralysis</td>
<td>iNO 25 ± 8.6 ppm</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
</tr>
<tr>
<td>Alprostadil (as needed)</td>
<td></td>
</tr>
</tbody>
</table>

- iNO significantly decreased mortality when compared with previous standard of care: 24%; 95% CI, 7 to 41% versus 56%; 95% CI 37 to 75%; p = 0.02

iNO Summary

• Surely there is some guidance available, right?
• Cochrane review of 4 studies published in 2014 (3 presented)
• Concluded that iNO conferred no advantage over conventional therapy in:
  - Mortality
  - PHC
  - Change in mPAP, arterial pressure, HR, or oxygenation
• Authors report difficulty in drawing valid conclusions due to the small numbers subjects, low event rates, and variability in iNO administration

Question 5:

The PICU team wishes to initiate an additional agent with nitric oxide to manage AC's PHCs. Which of the following is most appropriate?

A. Inhaled sildenafil
B. Oral sildenafil
C. IV epoprostenol
D. Oral bosentan
## Alternative First-Line Options

<table>
<thead>
<tr>
<th>Route</th>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenylate cyclase stimulators</td>
<td>• Iloprost</td>
</tr>
<tr>
<td></td>
<td>“prostacyclins”</td>
<td>• Epoprostenol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treprostinil</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Nitric oxide donors</td>
<td>• Nitroglycerin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nitroprusside</td>
</tr>
<tr>
<td></td>
<td>Phosphodiesterase inhibitors</td>
<td>• Milrinone</td>
</tr>
<tr>
<td>IV</td>
<td>Phosphodiesterase inhibitors</td>
<td>• Milrinone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sildenafil</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin agonist</td>
<td>• Alprostadil</td>
</tr>
</tbody>
</table>
Inhaled Prostacyclin

- Iloprost – most studied
- Epoprostenol
- Treprostinil

- Review article published in 2012 detailed the findings of 28 studies investigating the role of iloprost in the acute management of PH in children
  - 195 children received iloprost perioperatively for cardiac surgery, vasoreactivity testing, and/or persistent pulmonary hypertension of the newborn (PPHN)
- Results of review suggest that inhaled iloprost may have a diverse role in the treatment of acute PH, conferring benefits similar to iNO

## Perioperative Inhaled Prostacyclin

<table>
<thead>
<tr>
<th>N</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>• iNO at 20 ppm for 10 minutes</td>
<td>Pulmonary to systemic vascular resistance ratio (Rp/Rs) decreased significantly with iNO and Iloprost alone; no benefit with concomitant administration</td>
</tr>
<tr>
<td></td>
<td>• Baseline therapy for 10 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Iloprost 25 ng/kg/min for 10 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Iloprost + iNO at 20 ppm for 10 minutes</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>• Iloprost 50 ng/kg/min for 10 minutes</td>
<td>Significant reduction in mPAP (mmHg) and increase in O₂ saturation (%) noted at conclusion of Iloprost treatment</td>
</tr>
<tr>
<td></td>
<td>• Increased (stepwise, due to lack of response) to a maximum of 200 ng/kg/min for 10 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Administered every 30 minutes for up to 5 doses</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>• Iloprost 0.5 mcg/kg every 2 hours vs. iNO 20 ppm (n=7) for at least 72 hours</td>
<td>No difference in PHC occurrence, mPAP, Rp/Rs, CO, PVR or duration of mechanical ventilation between Iloprost and iNO</td>
</tr>
</tbody>
</table>

Inhaled Prostacyclin: Transition

- Transition from iNO to iloprost in conjunction with standard postop care
- Protocol developed and tested by Vorhies et al. in 2014
  - Iloprost
    ▪ Initial weight-based dose administered over 10-15 min
    ▪ Second dose 1 hour later
    ▪ Subsequent doses every 2 hours
  - iNO wean by protocol for hemodynamics
  - If unable to wean iNO, baseline dose of iNO resumed and iloprost dose increased per protocol

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>1.25</td>
</tr>
<tr>
<td>5-10</td>
<td>2.5</td>
</tr>
<tr>
<td>10-15</td>
<td>3.75</td>
</tr>
<tr>
<td>15-20</td>
<td>5</td>
</tr>
<tr>
<td>20-25</td>
<td>6.25</td>
</tr>
<tr>
<td>25-50</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;50</td>
<td>10</td>
</tr>
</tbody>
</table>

Inhaled Prostacyclin: Transition

- 7 patients completed study and showed no significant difference in mPAP, SpO₂, PaO₂, CVP, pH, HR, or occurrence of adverse events between iNO and iloprost therapy
- Safe, effective, and affordable alternative to iNO
  - Median iloprost cost $533 ($213 - $1317) vs. $9504 for iNO

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>1.25</td>
</tr>
<tr>
<td>5-10</td>
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<tr>
<td>10-15</td>
<td>3.75</td>
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<tr>
<td>15-20</td>
<td>5</td>
</tr>
<tr>
<td>20-25</td>
<td>6.25</td>
</tr>
<tr>
<td>25-50</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;50</td>
<td>10</td>
</tr>
</tbody>
</table>
Inhaled Milrinone

Singh et al. in 2010 investigated inhaled milrinone and inhaled nitroglycerin as alternatives to iNO in 35 children with acyanotic CHD and PH

- Inhaled milrinone 50 mcg/mL (18 patients)
- Inhaled nitroglycerin 50 mcg/mL (17 patients)
- Therapy administered for 10 minutes and then hemodynamics measured and compared with baseline (on 100% oxygen)
- Inhaled milrinone, nitroglycerin, and 100% oxygen caused significant reductions in PAP and PVR
- Inhaled milrinone more efficacious in lowering PAP than 100% oxygen and nitroglycerin
Inhaled Milrinone vs Iloprost

- What about comparison to a prostacyclin, such as iloprost?
- Recent study in 36 ADULT patients retrospectively evaluating the use of inhaled milrinone versus inhaled iloprost in patients with PH following CPB
  - Inhaled milrinone 50 mcg/kg
  - Inhaled iloprost 20 mcg
    - Both administered over 15 minutes
- Hemodynamics assessed at baseline, after study drug administration, and then 40 and 60 minutes after start of drug administration
  - Significant reduction in mPAP and PVR noted in both treatment groups; more prominent reduction was noted with iloprost

Inhaled PDE Inhibitors: Sildenafil

- Theoretically would be a potent and selective pulmonary vasodilator when inhaled
- Animal models (lamb and pig)
  - Showed significant reductions (dose dependent) in mPAP; greater when administered with low-dose iNO
  - Prevented post-CPB PH, improved oxygenation, and reduced endothelial dysfunction

Intravenous Sildenafil

- Schulze-Neick et al. reported in 2003 on the effects of intravenous sildenafil in 12 pediatric patients with CHD and PH post-op
  - FIO₂ was increased to 0.65 and then the following were administered:
    ▪ iNO at 20 ppm x 10 minutes
    ▪ Oxygen only x 10 minutes
    ▪ IV sildenafil at 0.025, 0.1, and 0.33 mg/kg over 10 to 15 minutes
    ▪ iNO at 20 ppm added back for 10 minutes
  - Hemodynamics measured after each intervention
    ▪ Pulmonary vascular resistance index (PVRI) significantly decreased with hyperoxia, no benefit from addition of iNO or sildenafil
    ▪ mPAP significantly decreased with sildenafil, similar to iNO
    ▪ Physiologic dead-space ventilation (Vd/Vt) remained unchanged
    ▪ Arterial pO₂ decreased significantly, but no clinical hypoxemia occurred

Intravenous Sildenafil Cont’d

- Double-blind, multicenter, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy and safety of IV sildenafil for the management of postop PH in patients with CHD (N=17)
  - Randomized to low-, medium-, or high-dose sildenafil (n = 4 each) or placebo (n = 5)
  - Administered as a bolus dose, then a continuous infusion for 24-72 hours
  - After 30 min, additional PH therapies could be added per study protocol

**Intravenous Sildenafil Cont’d**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of therapy</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Mechanical ventilation duration</td>
<td>Sildenafil &lt; placebo</td>
</tr>
<tr>
<td>Post-op length of stay</td>
<td>ICU: sildenafil &lt; placebo</td>
</tr>
<tr>
<td></td>
<td>Hospital: No significant difference between groups</td>
</tr>
<tr>
<td>Hemodynamics (PAP, CVP)</td>
<td>Sildenafil &lt; placebo</td>
</tr>
</tbody>
</table>

# Additional Therapies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agents or Therapies</th>
</tr>
</thead>
</table>
| Need to limit iNO exposure & ↓ rebound with iNO discontinuation            | • Dipyridamole, IV  
• Sildenafil, oral  
• IV prostacyclins  
• Endothelin receptor antagonists (ETRA), oral  
• L-arginine/L-citrulline, IV |
| Need to augment cardiac output                                              | • Milrinone, IV  
• Levosimendan, IV  
• Nesiritide, IV  
• Isoproterenol, IV |
| Need to treat PHC associated hypotension                                    | • Vasopressin, IV |
| Salvage                                                                     | • ECMO or Ventricular assist device  
• Atrial septostomy  
• Lung transplant |
Oral Sildenafil

- Used to prevent rebound from iNO discontinuation / aid in weaning
- Single dose of oral sildenafil 0.4 mg/kg given 1 hour prior to (repeated attempt at) discontinuation of iNO compared with placebo (N= 29, including 15 sildenafil, 14 placebo)
  - N patients receiving sildenafil experienced rebound, but sildenafil did not significantly reduce PAP pressure
  - Sildenafil reduced duration of mechanical ventilation
- Oral sildenafil 0.25 mg/kg given 4 times daily initiated in patients who previously failed iNO discontinuation, when iNO dose was 5 ppm (N=15)
  - Sildenafil dose increased as tolerated to 1 mg/kg
  - iNO therapy successfully discontinued in all sildenafil-treated patients

Oral Sildenafil Cont’d

• Use to avoid postop need for iNO & ↓ postop PVR
• Study in 24 children undergoing cardiac surgery showed no PVR benefit compared with placebo from a single oral sildenafil dose of 0.5 mg/kg given the day prior to surgery
  - Associated with a negative impact on ventricular function and oxygenation
• Study in 38 children undergoing cardiac surgery
  - 15 received enteral sildenafil 0.35 mg/kg every 4 hours for 1 week before AND 1 week after surgery
  - 23 received sildenafil 0.35 mg/kg every 4 hours for 1 week after surgery only
  - Patients treated with sildenafil pre- and postoperatively had significantly lower mPAP compared with patients treated only postoperatively; preop treatment also resulted in shorter CPB times, mechanical ventilation times, and length of stay in the ICU and hospital

Intravenous Prostacyclins

- Less appealing for PHC treatment than inhaled options
  - Continuous infusion
  - Concerns for high cardiac output failure
  - Paradoxical embolization
  - Line-associated sepsis
  - Reserve for patients with persistent / chronic severe PH
ETRAs

- Data limited to case reports of role in PH associated with CHD – additional study data needed to determine whether (short term given safety profile of the drugs) pretreatment with ETRA will influence morbidity and mortality in patients at high risk for PHC

<table>
<thead>
<tr>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Teratogenicity</td>
</tr>
<tr>
<td>Fluid retention</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Testicular atrophy/infertility</td>
</tr>
</tbody>
</table>
AHA & ATS Guidelines

- Avoid PHCs by avoiding hypoxia, acidosis, and agitation
- Opiates, sedatives, and muscle relaxers indicated to decrease postop stressors
- iNO or inhaled prostacyclin should be used in addition to conventional therapy to treat PHCs
- Sildenafil should be used to prevent rebound / assist in weaning of iNO
- Inotropes/vasopressors should be used to treat systemic hypotension to decrease risk of RV ischemia

- Class I, Level of Evidence B = Procedure / treatment SHOULD be performed / administered; evidence from a single randomized trial or nonrandomized studies

## PICU Days 5-9

<table>
<thead>
<tr>
<th>PICU Day(s)</th>
<th>Course</th>
</tr>
</thead>
</table>
| 6-9         | • Initiated on iNO 20 ppm  
• Paralyzed with vecuronium infusion  
• Fentanyl ↑ 5 mcg/kg/hr  
• Vecuronium infusion discontinued on PICU day 9 |
| 10          | • State Behavioral Scale (SBS) scores ↑ to +1 to +2  
• Thrashing of arms & attempts to remove endotracheal tube noted |
Question 6:

The PICU team wishes to add a sedative infusion to AC’s fentanyl infusion. Which of the following sedatives infusions should be added next?

A. Dexmedetomidine  
B. Midazolam
Sedation & Analgesia Overview

- ACCCM guidelines for adults recommend **analgosedation**
- Pediatric guidelines expected from ACCCM in 2019
- Pain scores:
  - **Faces, Legs, Arms, Cry, Consolability** (FLACC) scale
  - **Multidimensional Assessment of Pain Scale** (MAPS), revised

ACCCM = American College of Critical Care Medicine

Sedation & Analgesia Overview

- Scales for assessment:

<table>
<thead>
<tr>
<th>Scale</th>
<th>Recommended Age Range/Groups</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn State Children’s Sedation Algorithm</td>
<td>&lt; 18 years of age</td>
<td>• Not validated&lt;br&gt;• Used to assess paralyzed patients&lt;br&gt;• Used to assess pain</td>
</tr>
<tr>
<td>SBS</td>
<td>6 weeks to 6 years of age</td>
<td>• Validated</td>
</tr>
<tr>
<td>COMFORT Behavioral Scale</td>
<td>&lt; 18 years of age</td>
<td>• Validated&lt;br&gt;• Used to assess pain</td>
</tr>
</tbody>
</table>

ACCCM = American College of Critical Care Medicine

## Comparing First-Line Opioids

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Morphine</th>
<th>Remifentanil</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
<td>N-dealkylation CYP3A4/5 substrate</td>
<td>Glucuronidation</td>
<td>Blood &amp; tissue esterases</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td><strong>Metabolite</strong></td>
<td>None</td>
<td>6- and 3-glucuronide metabolites</td>
<td>None</td>
<td>6-hydroxy and 3-glucuronide metabolites</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine (inactive metabolites) Feces (~9%)</td>
<td>Urine (as M3G, higher in neonates) Feces (7-10%)</td>
<td>Urine (90%)</td>
<td>Urine (as glucuronide conjugates) Feces (1%)</td>
</tr>
</tbody>
</table>

M3G = Morphine 3-glucuronide

Fentanyl Adverse Events

• Chest wall rigidity:
  - Older reports with doses ≥ 25 mcg/kg
  - Recent report with 1.5-2.7 mcg/kg

• Tolerance:
  - ↑ tolerance with semi-synthetic opioids
  - Incidence in children ranges from 16-78% of children depending on the definition utilized

### Fentanyl Tolerance Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 419)</th>
<th>Postoperative (n = 210)</th>
<th>Medical (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>p</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td><strong>Baseline opioid dose</strong></td>
<td>0.96 (0.95, 0.98)</td>
<td>&lt; 0.001</td>
<td>0.96 (0.94, 0.98)</td>
</tr>
<tr>
<td>(1 mcg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphine vs fentanyl</strong></td>
<td>0.48 (0.25, 0.92)</td>
<td>0.03</td>
<td>0.27 (0.08, 0.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Opioid infusion &gt; 7 days</strong></td>
<td>7.85 (4.32, 14.3)</td>
<td>0.03</td>
<td>5.86 (2.10, 16.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior PICU admission</strong></td>
<td>0.37 (0.15, 0.89)</td>
<td>0.03</td>
<td>Not selected for analysis</td>
</tr>
<tr>
<td><strong>Females (vs males)</strong></td>
<td>1.10 (0.61, 1.96)</td>
<td>0.75</td>
<td>2.79 (0.99, 7.87)</td>
</tr>
</tbody>
</table>

Hydromorphone

- Paucity of studies evaluating hydromorphone infusions in children
  - Pharmacokinetic profile not defined
  - One study in 92 children, 0.024-0.14 mg/kg/hr
- Tolerance probably less likely than with fentanyl but not confirmed by clinical studies

Morphine

- Lower degree of tolerance than fentanyl
- Not associated with chest wall rigidity
- Has established dosing & PK data
- Preferred for selected patients:
  - Hypertension (↑ histamine release)
  - ECMO

### Comparing First-Line Opioids: Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>• Low risk of hemodynamic effects</td>
<td>• Tolerance (↑)</td>
</tr>
<tr>
<td></td>
<td>• Short half-life</td>
<td>• Binds with oxygenator in ECMO pump</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>• Long half-life</td>
<td>• Limited dosing info for continuous infusion</td>
</tr>
<tr>
<td></td>
<td>• Less risk of tolerance than fentanyl</td>
<td>• Medication safety concerns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ histamine release than morphine</td>
</tr>
<tr>
<td>Morphine</td>
<td>• Long half-life</td>
<td>• Less histamine release than morphine</td>
</tr>
<tr>
<td></td>
<td>• Less lipophilic</td>
<td>• Renally eliminated &amp; hepatically metabolized</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>• Extremely short half-life</td>
<td>• Very high risk of tolerance</td>
</tr>
<tr>
<td></td>
<td>• May aid in neurologic assessment</td>
<td>• Risk of dosing errors</td>
</tr>
</tbody>
</table>

## Selection of Sedatives

<table>
<thead>
<tr>
<th>First-line options</th>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benzodiazepines</td>
<td>• Lorazepam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Midazolam</td>
</tr>
<tr>
<td></td>
<td>Alpha-2 Agonists</td>
<td>• Clonidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dexmedetomidine</td>
</tr>
<tr>
<td>Alternative sedatives</td>
<td>Miscellaneous</td>
<td>• Ketamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Propofol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pentobarbital</td>
</tr>
</tbody>
</table>

Benzodiazepines

- 92% received benzodiazepines in 2013 study by Anand
- Provide anticonvulsant & anxiolytic/amnestic effects
- Comparison of Agents:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>• Long half-life (10.5-40.2 hr)</td>
<td>• Risk of propylene glycol toxicity (metabolic acidosis, seizures, renal failure)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>• Fast onset (1-5 min)</td>
<td>• Accumulates in renal &amp; hepatic dysfunction (metabolized by CYP 3A4)</td>
</tr>
<tr>
<td></td>
<td>• Short half-life (2.9-12.0 hr)</td>
<td></td>
</tr>
</tbody>
</table>

- Downsides:
  - Respiratory depression
  - Drug withdrawal (approx. 24% with midazolam)
  - ↑ risk of opioid tolerance when used concomitantly

Dexmedetomidine

- 36.1% in usual care & intervention arms in RESTORE study received dexmedetomidine
- No negative effects on respiratory drive
- Analgesic effects:

<table>
<thead>
<tr>
<th>Variable [Median (IQR) or Number (%)]</th>
<th>Dexmed Initiated as Primary Sedative (n=138)</th>
<th>Dexmed Not Initiated (n=628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative opioid exposure (mg/kg)</td>
<td>12.4 (4.9-38.6)</td>
<td>13.3 (3.9-36.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inadequate number (%) pain management</td>
<td>22 (16)</td>
<td>64 (10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Dexmedetomidine Disadvantages

- **Potential ↓ efficacy:**

<table>
<thead>
<tr>
<th>Variable [Median (IQR) or Number (%)]</th>
<th>Dexmed Initiated as Primary Sedative (n=138)</th>
<th>Dexmed Not Initiated (n=628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine exposure (mg/kg)</td>
<td>13.1 (4.1-33.7)</td>
<td>9.3 (2.8-26.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of sedative agents received</td>
<td>4 (3-5)</td>
<td>2 (2-3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Dexmedetomidine Disadvantages

- Drug withdrawal symptoms: 5-35%
- Cost for 10-kg patient:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose</th>
<th>Product Concentration</th>
<th>Cost Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>0.5 mcg/kg/hr</td>
<td>200 mcg/2 mL</td>
<td>$57.96</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1 mg/kg/hr</td>
<td>5 mg/5 mL</td>
<td>$7.50</td>
</tr>
</tbody>
</table>

Question 7:

AC is initiated on dexmedetomidine 0.5 mcg/kg/hr. She continues to have agitation & an SBS score of +1. Her Cornell Assessment of Pediatric Delirium (CAPD) score is 15. What would you recommend next?

A. Add diphenhydramine 1 mg/kg/dose IV every 6 hr
B. Add haloperidol 0.05 mg/kg/dose IV every 8 hr
C. ↑ dexmedetomidine to 1 mcg/kg/hr
D. Add risperidone 0.1 mg/kg/dose orally daily at 2100
### Etiologies for Increased Opioid Use

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Pain</th>
<th>Hyperalgesia</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease progression</td>
<td>↑ afferent neuron activity</td>
<td>Receptor desensitization</td>
</tr>
<tr>
<td></td>
<td>Neuropathic pain</td>
<td>Upregulation of dynorphin &amp; glutamate activity (NMDA receptor)</td>
<td>Activation of cAMP (↑ NMDA activity)</td>
</tr>
<tr>
<td></td>
<td>↑ metabolism &amp; excretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pain</th>
<th>Hyperalgesia</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑ Opioid dose</td>
<td>Taper opioid dose</td>
<td>Add dexmedetomidine</td>
</tr>
<tr>
<td></td>
<td>Treat neuropathic pain</td>
<td>Add NMDA antagonist</td>
<td>Switch opioids</td>
</tr>
<tr>
<td></td>
<td>Add non-opioid</td>
<td>Use long-acting opioid</td>
<td>Add methadone</td>
</tr>
<tr>
<td></td>
<td>Add adjuvant agents</td>
<td>Rotate opioids</td>
<td>Add ketamine</td>
</tr>
</tbody>
</table>

- Add non-opioid
- Add adjuvant agents
- Taper opioid dose
- Add NMDA antagonist
- Use long-acting opioid
- Rotate opioids
- Add non-opioid
- Add adjuvant agents
- Add dexmedetomidine
- Switch opioids
- Add methadone
- Add ketamine
- Add gabapentin

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Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Dexmedetomidine

- **Rationale**: Activate K+ channel through same G-stimulatory proteins as opioids to ↓ pain & potentially tolerance
- **Limited supporting data**:

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes from Dexmedetomidine</th>
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</table>
| Tobias et al. 2004. Prospective RCT (n=20) Dexmedetomidine vs. midazolam | • ↓ morphine use  
• ↑ time with adequate sedation |
| Grant et al. 2016. Prospective RCT (n= 2,449) Dexmedetomidine vs. usual care | • More rapid achievement of sedation target  
• ↑ time within sedation target  
• ↓ opioid use |

- **Adverse events**: Withdrawal & bradycardia

Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Opioid Rotation

• **Rationale:** Use agents with different receptor activity
• **Tolerance profile:** fentanyl >morphine/hydromorphone
• **Rotation in pediatric oncology:**
  - 22/162 children (14%) underwent 30 opioid rotations
  - Excessive ADEs with or without adequate analgesia were main reason in 26/30 rotations
  - 10% ADEs NOT resolved with rotation
• **Limited data in PICU setting**

Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Methadone

- **Rationale**: Long-acting opioid & partial NMDA antagonist
- Murine model with reversal of morphine tolerance
  - Morphine 10 mg/kg IV twice daily +/- methadone 2.5 mg/kg IV twice daily
  - Findings:
    - Methadone reversed morphine tolerance
    - Promoted mu-opioid receptor endocytosis
    - ↓ adenylate cyclase and NMDA alteration
- **Adverse reactions**:
  - Usual opioid ADEs
  - Bradycardia & QTc prolongation

Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Ketamine

- **Rationale:** Analgesic properties & NMDA antagonist
- Recent consensus guidelines suggest low-to-moderate evidence
- Low-dose infusion in pediatric oncology:
  - 8/11 (73%) children had ↓ opioid requirements (28-100%)
  - Dosing: 0.1-0.2 mg/kg/hr
- Limited data in critically-ill children
- Adverse events:
  - Hallucinations & emergence delirium
  - ↑ heart rate & blood pressure

Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Gabapentin

- **Rationale:** GABA analog
- **Pro- & anti-inflammatory cytokines involved in morphine tolerance**
  - Hyperalgesia symptoms are similar to neuropathic pain
  - Neuropathic pain results in ↓ morphine efficacy and ↑ tolerance
- **Gabapentin affects inflammatory pathway:**
  - Activates IL-10, an anti-inflammatory cytokine
  - Inhibits release of TNF-α and IL-1β resulting in anti-hyperalgesic effect
- **Adverse events & other issues:**
  - Sedation
  - Wide inter-patient variability in dosing requirements (15-60 mg/kg/day divided every 8 hr)

Johnson PN. Advanced Pediatric Therapeutics, 1st ed. 2015;433-59.
Delirium in the PICU

• Multicenter prevalence study: 23.3% (IQR 20-35.4%)

• Single-center study:
  - 78% developed delirium within 3 days
  - ↑ PICU length of stay, OR 2.3, 95% CI: 2.1-2.5
  - ↑ Mortality: OR 4.39, 95% CI:1.96-9.99

## Delirium in the PICU

**Risk factors:**

<table>
<thead>
<tr>
<th>Age &lt; 2 years</th>
<th>High severity of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Restraints</td>
<td>Low albumin</td>
</tr>
</tbody>
</table>
| Mechanical ventilation | Medications:  
  - Anticholinergic agents (diphenhydramine)  
  - Benzodiazepines  
  - Opioids  
  - Vasopressors |
| Preexisting medical conditions | |

Delirium Treatment Algorithm

**Step 1: Underlying disease:**
- Assess infection
- Address hypoxemia
- Optimize pain control
- Correct metabolic abnormalities

**Step 2: Iatrogenic factors:**
- ↓ sedation
- Recognize & treat drug withdrawal
- Avoid restraints
- Review medications

**Step 3: Environmental Modification:**
- Early mobilization
- Cognitive stimulation
- Clustered care
- Sleep hygiene (limited evidence with melatonin)

**Step 4: Pharmacologic:**
- Analgesic & sedative regimens
- Antipsychotics

Analgesia & Sedation Regimens for Delirium

- Utilize opioid first then sedatives (analgesedation)
- Avoid benzodiazepine infusions:
  - ↑ delirium rates (OR 4.4, 95% CI: 1.7-11.1)
  - Each 1 log increase in dosage associated with 43% ↑ in delirium
- Dexmedetomidine regimens may ↓ delirium:
  - Possible neuroprotective effects in animal studies
  - 2 studies in adults found ↓ delirium vs benzodiazepines
  - 1 small study in adolescents status-post scoliosis surgery found ↓ risk of delirium vs benzodiazepines

Antipsychotics

- Agents: for treatment **NOT** prevention of delirium

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations</th>
</tr>
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</table>
| Haloperidol                  | • Adult trial found no significant difference in delirium duration vs placebo for prevention  
                               | • Limited data in children with PICU delirium                                            
                               | • ADEs: ↑ extrapyramidal effects & hypotension (IV use)                                    |
| Atypical antipsychotics      | • Data reported for risperidone, quetiapine, & olanzapine                                  
                               | • ADE profile worse with olanzapine & risperidone: ↑olanzapine—↑ risk of dyslipidemia & risperidone—↑ extrapyramidal effects   
                               | • Study in adults noted significant ↓ delirium with quetiapine                             
                               | • Recent safety data with quetiapine in children                                           |

- Summary: atypical antipsychotics preferred over haloperidol for treatment of delirium in children

KEY TAKEAWAYS

1) KEY TAKEAWAY—SEPTIC SHOCK
To treat septic shock, provide judicious fluid resuscitation. Use epinephrine for cold shock and norepinephrine for warm shock. Consider hydrocortisone for suspected adrenal insufficiency.

2) KEY TAKEAWAY—PULMONARY HYPERTENSION
To treat pulmonary hypertension, address pain/anxiety/agitation, hypoxia, and acidosis first, then use iNO or inhaled prostacyclin with mechanical ventilation. Alternatively, use sildenafil to wean iNO.

3) KEY TAKEAWAY—SEDATION/ANALGESIA/DELIRIUM
To treat agitation/pain/delirium, use analgesics first. Avoid benzodiazepine infusions. Consider use of adjunctive agents or opioid rotations