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Clinical Meeting & Exhibition

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 O_2 ↑ to 2 L/min
- Mom drove A.C. to Emergency Department

Current Medications

Start Date	Drug/Strength/Regimen	Indication
1/2017	Albuterol 90 mcg MDI—2 puffs every 4 hr as needed	Wheezing
1/2018	Fluticasone 88 mcg MDI every 12 hr	Bronchopulmonary dysplasia
12/2018	Amoxicillin orally—dose unknown	Upper respiratory infection
12/2018	Prednisolone orally—dose unknown	Bronchopulmonary dysplasia
Immunizations: Status unknown		
Allergies: NKDA		
Other: 1 L/min O_2 by nasal cannula at home		

Physical Exam

Data	Exam Finding/Objective Data
Respiratory	• Tachypneic • Subcostal retractions with moderate intercostal retractions • Diffuse crackles, rhonchi, & wheezing present
Cardiology	• Tachycardic with poor perfusion • Capillary refill 4-5 seconds
Extremities	Cool hands & feet
Vital signs	• Weight: 13.5 kg; height: 80 cm • Temperature: 39.2 ˚C • Heart rate: 160 beats per min • Respiratory rate: 45 breaths per min • Blood pressure: 71/43 mm Hg • O2 saturation: 86%

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

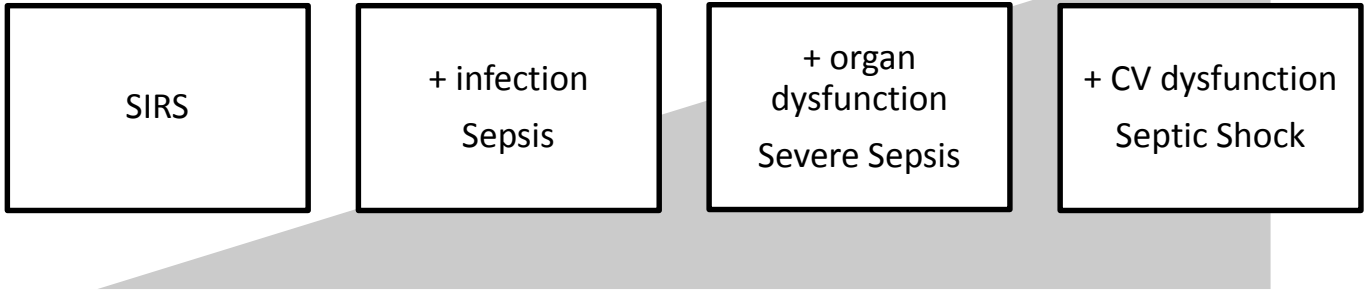
Shock

- Inadequate perfusion to meet demand
- Stages:
  - Compensated
  - Hypotensive
  - Cardiac Arrest

Age Group	Systolic Blood Pressure (mm Hg)
Neonates	< 60
Infants	< 70
Children (1-10 years)	< 70 + (age in years x 2)
Children > 10 years	< 90

de Caen AR. *Circulation*. 2015; 132 (18 Suppl 2): S526.
Samson RA. Pediatric Advanced Life Support: Provider Manual. American Heart Association; 2016.

Septic Shock



- 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

Goldstein B, et al. *Pediatr Crit Care Med.* 2005;6:2-8.
Schlapbach LJ, et al. *Intensive Care Med.* 2018;44:179-88.
Weiss SL, et al. *Intensive Care Med.* 2018;44:392-4.

Warm vs. Cold Septic Shock

Warm Shock	Cold Shock
Adolescents and adults	Young children
↓afterload (SVR) and ↑ cardiac output (CO) Vasodilation	↑SVR and ↓CO Vasoconstriction
Pink extremities	Mottled, cool extremities
Bounding pulses	Weak pulses
Flash capillary refill	Capillary refill ≥ 3 sec

de Caen AR. Circulation. 2015; 132 (18 Suppl 2): S526.
Samson RA. Pediatric Advanced Life Support: Provider Manual. American Heart Association; 2016.

SVR = Systemic vascular resistance

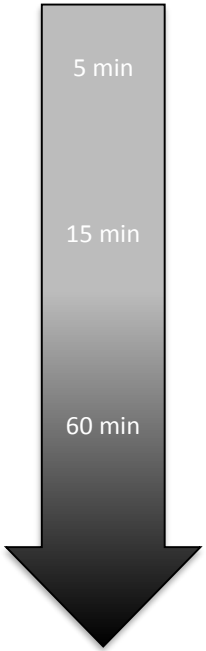
ACCCM Warm Shock Algorithm

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

ACCCM = American College of Critical Care Medicine

Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

ACCCM Cold Shock Algorithm



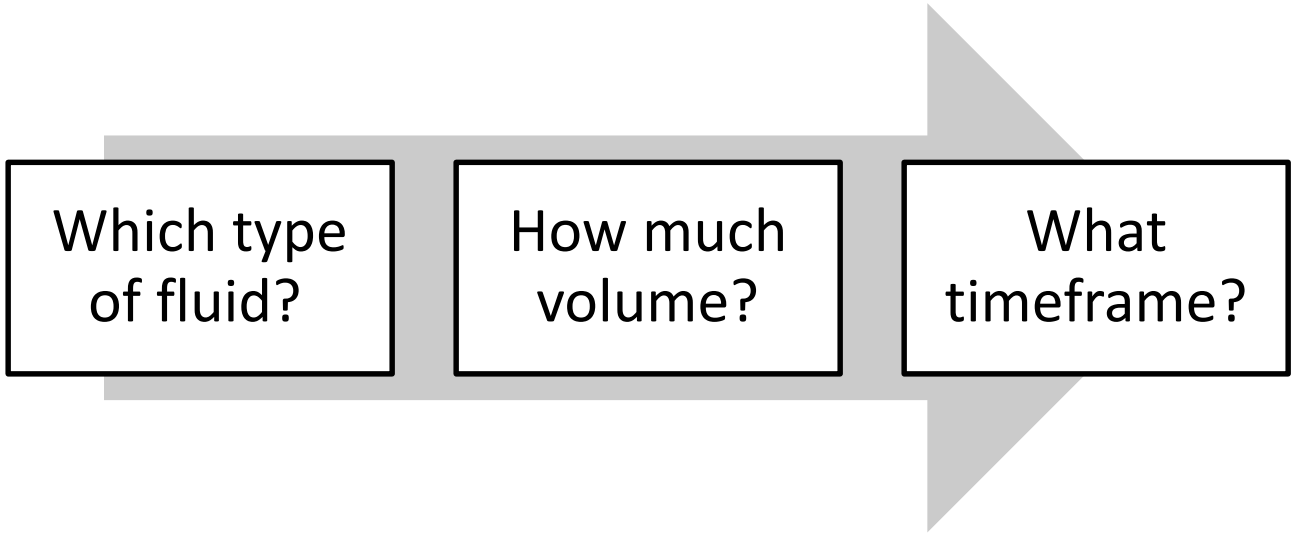
Steps	Intervention
1. Fluid resuscitation	20mL/kg NS or LR boluses up to 60 mL/kg
	Correct electrolytes (hypoglycemia and hypocalcemia)
	Begin antibiotics
2. Fluid refractory shock	Titrate epinephrine (epi) 0.05-0.3 mcg/kg/min
	Start dopamine 5-9 mcg/kg/min if epi not available
3. Adrenal insufficiency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

ACCCM = American College of Critical Care Medicine

Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

Fluid Resuscitation

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



Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

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

Rhodes A, et al. *Crit Care Med.* 2017;45:486-552.
Chang R, et al. *Shock.* 2016;46:17-26.

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

Solution	Sodium (mEq/L)	Chloride (mmol/L)
NS	154	154
LR	130	109
Plasmalyte	140	98

Emrath ET, et al. Crit Care Med. 2017;45:1177-83.
Stenson EK, et al. Pediatr Crit Care Med. 2018;19:155-60.
Chang R, et al. Shock. 2016;46:17-26.

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

Rhodes A, et al. *Crit Care Med.* 2017;45:486-552.
Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.
Maitland K, et al. *N Engl J Med.* 2011;364:2483-95.
Abulebda K, et al. *Crit Care Med.* 2014;42:397-403.
Gelbart B, et al. *Pediatric Crit Care Med.* 2015;16:e297-307.

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

Rhodes A, et al. *Crit Care Med.* 2017;45:486-552.
Sankar J, et al. *Pediatr Crit Care Med.* 2017;18:e435-45.
Russel MJ, et al. *Pediatr Crit Care Med.* 2018;19:369-71.
Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

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

Rhodes A, et al. *Crit Care Med.* 2017;45:486-552.
Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

Fluid-Refractory Shock

	Cold Shock	Warm Shock
First Line	Epinephrine 0.05-0.3 mcg/kg/min	Norepinephrine ≥ 0.05 mcg/kg/min
Alternate	Dopamine 5-9 mcg/kg/min	Dopamine ≥ 10 mcg/kg/min

Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.

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)

Ventura AMC, et al. *Crit Care Med.* 2015;43:2292-302.

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

Shenker Y, et al. *Am J Respir Crti Care Med.* 2001;163(7):1520-3.
Cooper MS, et al. *N Engl J Med.* 2003;348(8):727-34.

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

Cooper MS, et al. *N Engl J Med.* 2003;348(8):727-34.
Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.
Annane D, et al. *Crit Care Med.* 2017;45:2078-88.

Hydrocortisone

- Steroid of choice in septic shock
- 2nd 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?

Rhodes A, et al. *Crit Care Med.* 2017;45:486-552.
Davis AL, et al. *Pediatr Crit Care Med.* 2017;18:884-90.
Sprung CL, et al. *N Engl J Med.* 2008;358:111-4.

Hydrocortisone in Pediatric SIRS/Sepsis

	Hebbar et al 2011	Menon et al 2015
Patients	• 78 PICU patients with SIRS	• 364 PICU patients with shock
Dosing	• 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
Outcomes	• ↓duration and rate of dopamine & norepinephrine • 92% of patients with AI responded	• ↑ duration of vasopressors • ↑ positive cultures in septic patients

Menon K, et al. *Shock.* 2015;44:402-409.
Hebbar KB, et al. *Crit Care Med.* 2011;39:1145-9.

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

	Standard Care	**Levosimendan**	
Mortality All settings	22.4% (3236/1457)	17.6% (333/1893)	Risk Ratio 0.74 95% CI = 0.62-0.89
Mortality In sepsis	61% (74/121)	47% (59/125)	Risk Ratio 0.79 95% CI = 0.63-0.98

Pollesello P, et al. *Int J Cardiol.* 2016;209:77-83.
Meng JB, et al. *Med Sci Monit.* 2016;22:1486-96.

PICU Days 1-5

PICU Day(s)	Course
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

Abman SH, et al. *Circulation.* 2015; 132: 2037-99.

Initial PHC Therapy

Etiology of PHC	Treatment
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

Abman SH, et al. *Circulation.* 2015; 132: 2037-99.

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

Abman SH, et al. *Circulation.* 2015; 132: 2037-99.
Limsuwan A, et al. *Int J Cardiol.* 2008; 129: 333-8.
Vorhies EE, et al. *Pediatr Cardiol.* 2014; 35: 1337-43.
Wessel DL, et al. *Crit Care Med.* 1994; 22: 930-8.

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 = Inhaled nitric oxide
PH = Pulmonary hypertension

Roberts JD. *Crit Care Med.* 1993; 21(9 Suppl): S374-S6.
Roberts JD, et al. *Circulation.* 1993; 87: 447-53.
Wessel DL. *Crit Care Med.* 1993; 21: S344-45.

iNO History of Evidence Cont'd

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

Abman SH, et al. *J Pediatr.* 1994; 124: 881-8.
Russell IAM, et al. *Anesth Analg.* 1998; 87: 46-51.
Miller OI, et al. *Lancet.* 2000; 356: 1464-9.
Day RW, et al. *Ann Thorac Surg.* 2000; 69: 1907-13.

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

Years 1 - 8	Years 9 - 10
100% Oxygen	100% Oxygen
Fentanyl	Fentanyl
Metabolic acidosis correction	Metabolic acidosis correction
Muscle paralysis	iNO 25 ± 8.6 ppm
Isoproterenol	
Alprostadil (as needed)	

- 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

Journois D, et al. *Chest.* 2005; 128: 3537-44.

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

Bizzarro M et al. *Cochrane Database Syst Rev.* 2014; (7):CD005055.

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

Route	Class	Examples
Inhaled	Adenylate cyclase stimulators "prostacyclins"	• Iloprost • Epoprostenol • Treprostinil
	Nitric oxide donors	• Nitroglycerin • Nitroprusside
	Phosphodiesterase inhibitors	• Milrinone
IV	Phosphodiesterase inhibitors	• Milrinone • Sildenafil
	Prostaglandin agonist	• Alprostadil

Thunberg CA, et al. *Ann Card Anaesth.* 2015; 18: 394-402.
Brunner N, et al. *Pulm Circ.* 2014; 4: 10-24.
Schulze-Neick I, et al. *Euro Resp Rev.* 2010; 19: 331-9.

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

Mulligan C, et al. *Pediatr Crit Care Med.* 2012; 13: 472-80.

Perioperative Inhaled Prostacyclin

N	Intervention	Outcome
5	• iNO at 20 ppm for 10 minutes • Baseline therapy for 10 minutes • Iloprost 25 ng/kg/min for 10 minutes • Iloprost + iNO at 20 ppm for 10 minutes	Pulmonary to systemic vascular resistance ratio (Rp/Rs) decreased significantly with iNO and Iloprost alone; no benefit with concomitant administration
8	• Iloprost 50 ng/kg/min for 10 minutes • Increased (stepwise, due to lack of response) to a maximum of 200 ng/kg/min for 10 minutes • Administered every 30 minutes for up to 5 doses	Significant reduction in mPAP (mmHg) and increase in O_2 saturation (%) noted at conclusion of Iloprost treatment
8	• Iloprost 0.5 mcg/kg every 2 hours vs. iNO 20 ppm (n=7) for at least 72 hours	No difference in PHC occurrence, mPAP, Rp/Rs, CO, PVR or duration of mechanical ventilation between Iloprost and iNO

Rimensberger PC, et al. *Circulation.* 2001; 103: 544-8.
Limsuwan A, et al. *Int J Cardiol.* 2008; 129: 333-8.
Loukanov T, et al. *Clin Res Cardiol.* 2011; 100: 595-602.

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

Weight (kg)	Starting dose (mcg)
<5	1.25
5-10	2.5
10-15	3.75
15-20	5
20-25	6.25
25-50	7.5
>50	10

Vorhies EE, et al. *Pediatr Cardiol.* 2014; 35: 1337-43.

Inhaled Prostacyclin: Transition

- 7 patients completed study and showed no significant difference in mPAP, SpO_2, PaO_2, 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

Weight (kg)	Starting dose (mcg)
<5	1.25
5-10	2.5
10-15	3.75
15-20	5
20-25	6.25
25-50	7.5
>50	10

Vorhies EE, et al. *Pediatr Cardiol.* 2014; 35: 1337-43.

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

Singh R, et al. *J Cardiothorac Vasc Anesth.* 2010; 24: 797-801.

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

Theodoraki K, et al. *Heart Vessels.* 2017; 32: 1488-97.

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

Thunberg CA, et al. *Ann Card Anaesth.* 2015; 18: 394-402.

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
  - FIO_2 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 pO_2 decreased significantly, but no clinical hypoxemia occurred

Schulze-Neick I, et al. *Circulation.* 2003; 108(Suppl 1):II-167-73.

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

Fraisse A, et al. *Intensive Care Med.* 2011; 37: 502-9.

Intravenous Sildenafil Cont'd

Endpoint	Result
Addition of therapy	No significant difference between groups
Mechanical ventilation duration	Sildenafil < placebo
Post-op length of stay	ICU: sildenafil < placebo Hospital: No significant difference between groups
Hemodynamics (PAP, CVP)	Sildenafil < placebo

Fraisse A, et al. *Intensive Care Med.* 2011; 37: 502-9.

Additional Therapies

Indication	Agents or Therapies
Need to limit iNO exposure & ↓ rebound with iNO discontinuation	• Dipyridamole, IV • Sildenafil, oral • IV prostacylins • 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

Namachivayam P, et al. *Am J Respir Crit Care Med.* 2006; 174: 1042-7.
Humpl T, et al. *Cardiol Young.* 2011; 21: 187-93.

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

Vassalos A, et al. *Anaesthesia.* 2011; 66: 472-80.
Palma G, et al. *Tex Heart Inst J.* 2011; 38: 238-42.

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

Brunner N, et al. *Pulm Circ.* 2014; 4: 10-24.

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

Adverse Effects	
Hepatotoxicity	Anemia
Teratogenicity	Fluid retention
Peripheral edema	Testicular atrophy/infertility

Brunner N, et al. *Pulm Circ.* 2014; 4: 10-24.

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

AHA = American Heart Association
ATS = American Thoracic Society

Abman SH, et al. *Circulation.* 2015; 132: 2037-99.

PICU Days 5-9

PICU Day(s)	Course
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:
  - **F**aces, **L**egs, **A**rms, **C**ry, **C**onsolability (FLACC) scale
  - **M**ultidimensional **A**ssessment of **P**ain **S**cale (MAPS), revised

Johnson PN, et al. *AACN Adv Crit Care.* 2012; 23:415-34.
Barr J, et al. *Crit Care Med.* 2013; 41:263-306.
Playfor S, et al. *Intensive Care Med.* 2006:32:1125-36.

ACCCM = American College of Critical Care Medicine

Sedation & Analgesia Overview

- Scales for assessment:

Scale	Recommended Age Range/Groups	Characteristics
Penn State Children's Sedation Algorithm	< 18 years of age	• Not validated • Used to assess paralyzed patients • Used to assess pain
SBS	6 weeks to 6 years of age	• Validated
COMFORT Behavioral Scale	< 18 years of age	• Validated • Used to assess pain

Johnson PN, et al. *AACN Adv Crit Care.* 2012; 23:415-34.
Barr J, et al. *Crit Care Med.* 2013; 41:263-306.
Playfor S, et al. *Intensive Care Med.* 2006:32:1125-36.

ACCCM = American College of Critical Care Medicine

Comparing First-Line Opioids

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

M3G = Morphine 3-glucoronide

Taketomo CK, ed. Pediatric & Neonatal Dosage Handbook, 24th ed. 2017.

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

Anand KJS, et.al. *Pediatrics.* 2010;125:e1208-25.
Fahnenstich H, et al. *Crit Care Med.* 2000;28:836-39.
Dewhirst E, et al. *Pediatr Emerg Care.* 2012;28:465-8.
Anand KJS, et.al. *Pediatr Crit Care Med.* 2013;14:27-36.
Ibach BW, et al. *J Pediatr Intensive Care.* 2017;6:83-90.

Fentanyl Tolerance Analysis

Variable	All Patients (n = 419)		Postoperative (n = 210)		Medical (n = 209)	
	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Baseline opioid dose (1 mcg/kg)	0.96 (0.95, 0.98)	< 0.001	0.96 (0.94, 0.98)	0.001	0.97 (0.95, 0.99)	0.004
Morphine vs fentanyl	0.48 (0.25, 0.92)	0.03	0.27 (0.08, 0.88)	0.003	0.60 (0.27, 1.33)	0.21
Opioid infusion ≥ 7 days	7.85 (4.32, 14.3)	0.03	5.86 (2.10, 16.3)	< 0.001	7.06 (3.33, 15.0)	< 0.001
Prior PICU admission	0.37 (0.15, 0.89)	0.03	Not selected for analysis	-	Not selected for analysis	-
Females (vs males)	1.10 (0.61, 1.96)	0.75	2.79 (0.99, 7.87)	0.052	0.68 (0.33, 1.40)	0.29

Anand KJS, et.al. *Pediatr Crit Care Med.* 2013;14:27-36.

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

Anand KJS, et.al. *Pediatrics.* 2010;125:e1208-25.
Johnson PN, et al. *AACN Advanced Critical Care.* 2012;23:415-34.
Reiter PD, et al. *J Opioid Manag.* 2012;8:99-104.

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

Anand KJS, et.al. *Pediatrics.* 2010;125:e1208-25.
Johnson PN, et al. *AACN Advanced Critical Care.* 2012;23:415-34.

Comparing First-Line Opioids: Summary

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

Johnson PN, et al. *AACN Adv Crit Care.* 2012; 23:415-34.
Taketomo CK, ed. Pediatric & Neonatal Dosage Handbook, 24th ed. 2017.
Anand KJS, et al. *Pediatrics.* 2010; 125:e1208-25.

Selection of Sedatives

First-line options	Class	Agents
	Benzodiazepines	• Lorazepam • Midazolam
	Alpha-2 Agonists	• ~~*Clonidine*~~ • Dexmedetomidine
Alternative sedatives	Miscellaneous	• Ketamine • Propofol • Pentobarbital

Taketomo CK, ed. Pediatric & Neonatal Dosage Handbook, 24th ed. 2017.
Capino AC, et al. *Pharmacotherapy.* 2016;36:1290-9.

Benzodiazepines

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

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

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

Anand KJS, et.al. *Pediatr Crit Care Med.* 2013;14:27-36.
Johnson PN, et al. *AACN Advanced Critical Care.* 2012;23:415-34.
Dominguez KD, et.al. *Ann Pharmacother.* 2006;40:1035-9.

Dexmedetomidine

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

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

Curley MA, et al. *JAMA.* 2015;313:379-89.
Grant MJC, et al. *Pediatr Crit Care Med.* 2016;17:1131-41.

Dexmedetomidine Disadvantages

- Potential ↓ efficacy:

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

Grant MJC, et al. *Pediatr Crit Care Med.* 2016;17:1131-41.
Whalen LD, et al. *Pediatr Crit Care Med.* 2014;15:706-14.
Haenecour AS, et al. *J Pediatr Pharmacol Ther.* 2017;22:453-60.
Shutes BL, et al. *Pediatric Crit Care Med.* 2018;19:287-97.
Schickli MA, et al. *Ann Pharmacother.* 2017;51:27-32.

Dexmedetomidine Disadvantages

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

Agent	Initial Dose	Product Concentration	Cost Per Day
Dexmedetomidine	0.5 mcg/kg/hr	200 mcg/2 mL	$57.96
Midazolam	0.1 mg/kg/hr	5 mg/5 mL	$7.50

Grant MJC, et al. *Pediatr Crit Care Med.* 2016;17:1131-41.
Whalen LD, et al. *Pediatr Crit Care Med.* 2014;15:706-14.
Haenecour AS, et al. *J Pediatr Pharmacol Ther.* 2017;22:453-60.
Shutes BL, et al. *Pediatric Crit Care Med.* 2018;19:287-97.
Schickli MA, et al. *Ann Pharmacother.* 2017;51:27-32.

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

	Pain	Hyperalgesia	Tolerance
Mechanisms	• Disease progression • Neuropathic pain • ↑ metabolism & excretion	• ↑ afferent neuron activity • Upregulation of dynorphin & glutamate activity (NMDA receptor)	• Receptor desensitization • Activation of cAMP (↑ NMDA activity)
Treatment	- ↑ Opioid dose - Treat neuropathic pain - 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

Anand KJS, et.al. *Pediatrics.* 2010;125:e1208-25.
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:

Study	Outcomes from Dexmedetomidine
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.
Grant MJC, et al. *Pediatr Crit Care Med.* 2016;17:1131-41.
Tobias JD, et al. *South Med J.* 2004;97:451-5.

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.
Fine PG, et al. *J Pain Symptom Manage.* 2009;38:418-25.
Drake R, et al. *J Palliat Med.* 2004;7:419-22.

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.
Posa L, et al. *Int J Neuropsychopharmacol.* 2016;19:1-11.

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.
Finkel JC, et al. *J Pain.* 2007;8:515-21.
Schwenk ES, et al. *Reg Anesth Pain Med.* 2018;43:456-66.
Golding CL, et al. *Ann Pharmacother.* 2016;50:234-41.

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.
Przewlocki R, et al. *Curr Pharm Des.* 2005;11:3013-25.
Bao YH, et al. *J Mol Neurosci.* 2014;54:137-46.
Sacha GL, et al. *J Pediatr Pharmacol Ther.* 2017;22:207-11.

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

Traube C, et al. *Crit Care Med.* 2017;45:584-90.
Traube C, et al. *Crit Care Med.* 2017;45:891-98.
Patel AK, et al. *Pediatr Clin North Am.* 2017;64:1117-32.

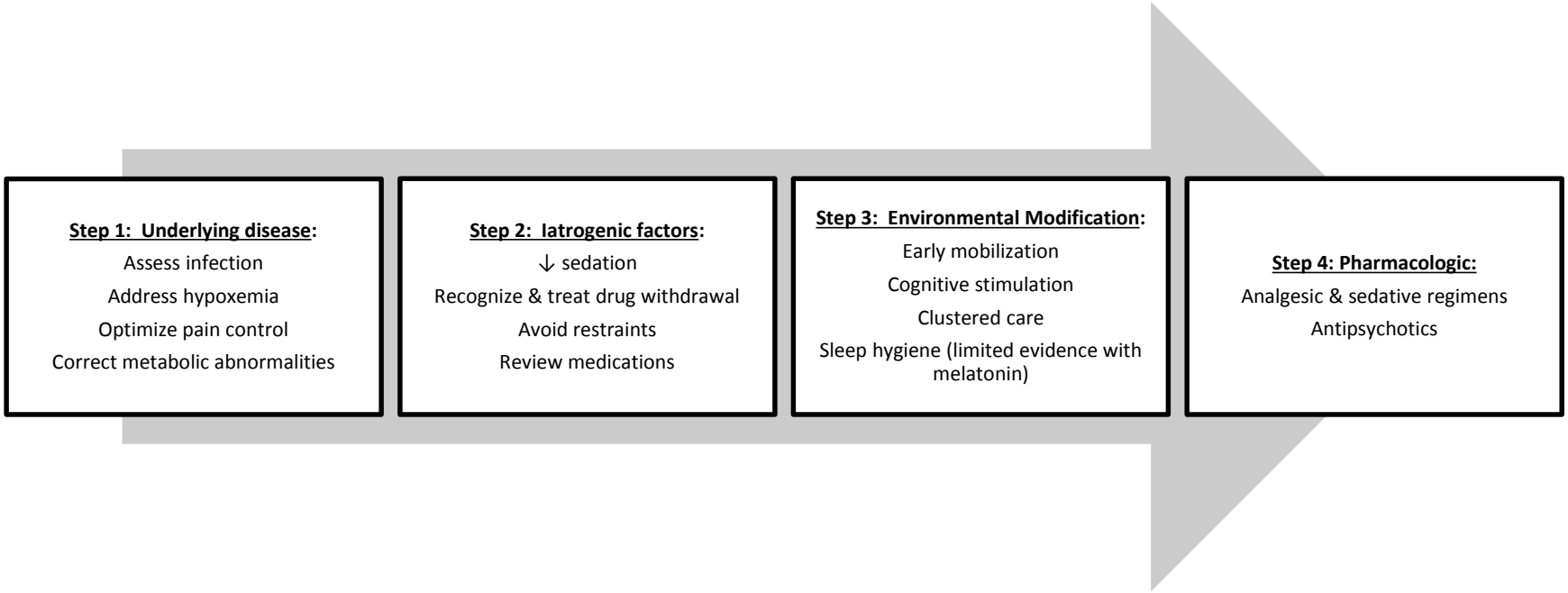
Delirium in the PICU

- Risk factors:

Age < 2 years	High severity of illness
Developmental delay	Immobilization
Restraints	Low albumin
Mechanical ventilation	Medications: • Anticholinergic agents (diphenhydramine) • Benzodiazepines • Opioids • Vasopressors
Preexisting medical conditions	

Traube C, et al. *Crit Care Med.* 2017;45:584-90.
Traube C, et al. *Crit Care Med.* 2017;45:891-98.
Patel AK, et al. *Pediatr Clin North Am.* 2017;64:1117-32.

Delirium Treatment Algorithm



Traube C, et al. *Crit Care Med.* 2017;45:891-98.
Traube C, et al. *J Pediatr Intensive Care.* 2013;2:121-6.
Joyce C, et al. *J Child Adolesc Psychopharmacol.* 2015;25:666-70.

Analgesia & Sedation Regimens for Delirium

- Utilize opioid first then sedatives (analgosedation)
- 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

Barr J, et al. *Crit Care Med.* 2013;41:278-80.
Mody K, et al. *Crit Care Med.* 2018;46:1486-91.
Pandharipande PP, et al. *Crit Care.* 2010;14:R38.
Riker RR, et al. *JAMA.* 2009;301:489-99.
Aydogan MS, et al. *Paediatr Anaesth.* 2013;23:446-52.

Antipsychotics

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

Agent	Considerations
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

Slooff VD, et al. *Intensive Care Med.* 2014;40:1602-3.
Ratcliff SL, et al. *J Burn Care Rehabil.* 2004;25:472-8.
Joyce C, et al. *J Child Adolesc Psychopharmacol.* 2015;25:666-70.
Delvin JW, et al. *Crit Care Med.* 2010;38:419-27.

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