PHARMACY VISION 20/20

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

Clinical Conundrums in Critically Ill Pediatric Patients

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DISCLOSURE

Christy Smith has no conflicts of interest to disclose.

Learning Objectives

- Discuss sedation management in the pediatric intensive care unit (PICU).
- Examine the data surrounding IV fluid use in critically ill pediatric patients.
- Explore pharmacotherapy options for management of pediatric sepsis beyond the guidelines.

Session Outline

- Sedation in the PICU
- IV fluid management
- Adjuvant therapies in sepsis

SEDATION IN THE PICU

Question

What medications should be used for sedation in critically ill children?

ICU Liberation Initiative

"The Society of Critical Care Medicine's ICU liberation initiative aims to liberate patients from the harmful effects of **pain**, **agitation/sedation**, **delirium**, **immobility**, and **sleep disruption** in the intensive care unit."

ICU Liberation Bundle

A	• Assess, prevent, and manage pain
B	• Both spontaneous awakening trials and spontaneous breathing trials
C	• Choice of analgesia and sedation
D	• Delirium: assess, prevent, and manage
E	• Early mobility and exercise
F	• Family engagement and empowerment

www.sccm.org/ICULiberation

C Choice of analgesia and sedation

- Use an assessment-driven, protocol-based, stepwise approach for pain and sedation management
  - Includes regular pain and sedation assessment using validated tools
  - Provides clear guidance on medication choice and dosing
  - Makes **treating pain a priority** over providing sedatives
    - Use of **analgesia-first** or **analgesia-based sedation** to reach sedative goal

www.sccm.org/ICULiberation

Devlin JW, et al. *Crit Care Med* 2018.

C CHOICE OF ANALGESIA AND SEDATION

- Maintain light levels of sedation
  - RASS goal of -2 to +1

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

www.sccm.org/ICULiberation
Devlin JW, et al. *Crit Care Med* 2018.
Sessler CN, et al. *Am J Respir Crit Care Med* 2002.

C CHOICE OF ANALGESIA AND SEDATION

- Use of nonbenzodiazepines over benzodiazepines for sedation

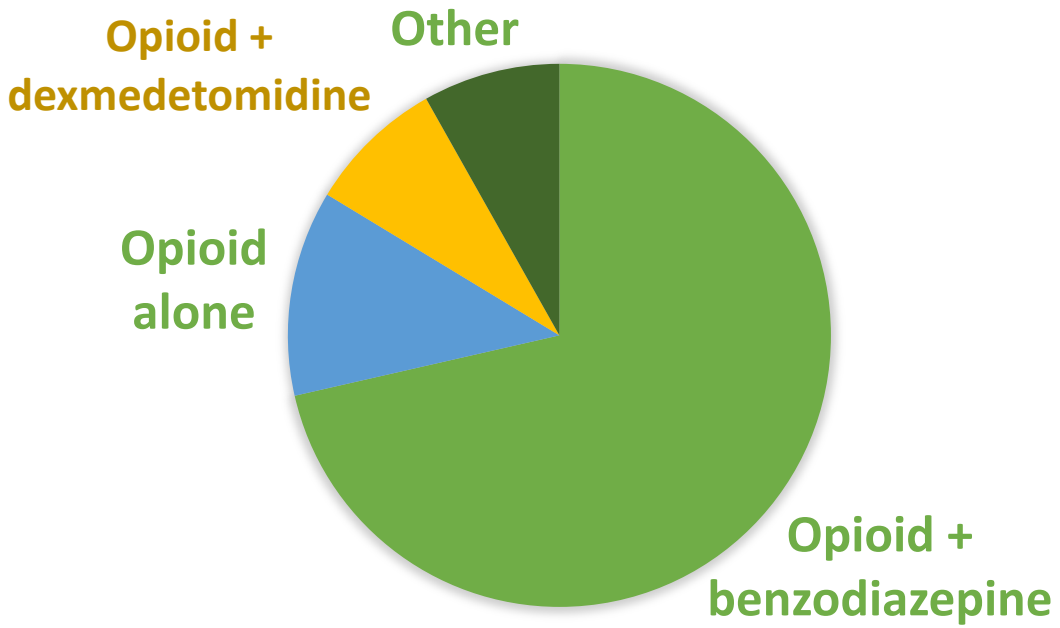
www.sccm.org/ICULiberation

Devlin JW, et al. *Crit Care Med* 2018.

Sedation Use in the PICU

- Survey of 341 pediatric intensivists worldwide
  - 27% written sedation protocols in place

SEDATION REGIMENS USED



Opioid choice

66% fentanyl
28% morphine

93% as continuous infusion

Benzodiazepine choice

86% midazolam
12% lorazepam

80% as continuous infusion

Kudchadkar SR, et al. *Crit Care Med.* 2014.

BENZODIAZEPINES AND NEUROTOXICITY-

Developmental neurotoxicity of sedatives and anesthetics: A concern for neonatal and pediatric critical care medicine?

- Widespread brain cell death observed after midazolam, diazepam, clonazepam, ketamine, propofol, phenobarbital, pentobarbital, and chloral hydrate
- Benzodiazepines and ketamine found to increase apoptotic brain cell death
- Dose-response and exposure time relationship exists for neurologic events
- High vulnerability from ~20 to 40 weeks' gestational age

Loepke AW. *Pediatr Crit Care Med* 2010.

BENZODIAZEPINES AND NEUROLOGIC EVENTS-

Intravenous midazolam infusion for sedation in infants in the neonatal intensive care unit

- No difference in mortality
- No difference in ventilator days, pneumothorax, or supplemental oxygen use
- Increased NICU LOS with midazolam
- Higher incidence of adverse neurological events (death, grade III or IV intraventricular hemorrhage, or periventricular leukomalacia)

Ng E, et al. *Cochrane Database Syst Rev* 2017.

BENZODIAZEPINES AND DELIRIUM-

Risk factors for the development of postoperative delirium in pediatric intensive care patients

Objective	To determine and quantify risk factors for postoperative pediatric delirium
Study design	Single-center, prospective cohort study
Patient population	93 children admitted to the PICU after major elective surgery
Outcome	Association between potential risk factors and delirium development

Meyburg J, et al. *Pediatr Crit Care Med* 2018.

Risk factors for the development of postoperative delirium in pediatric intensive care patients

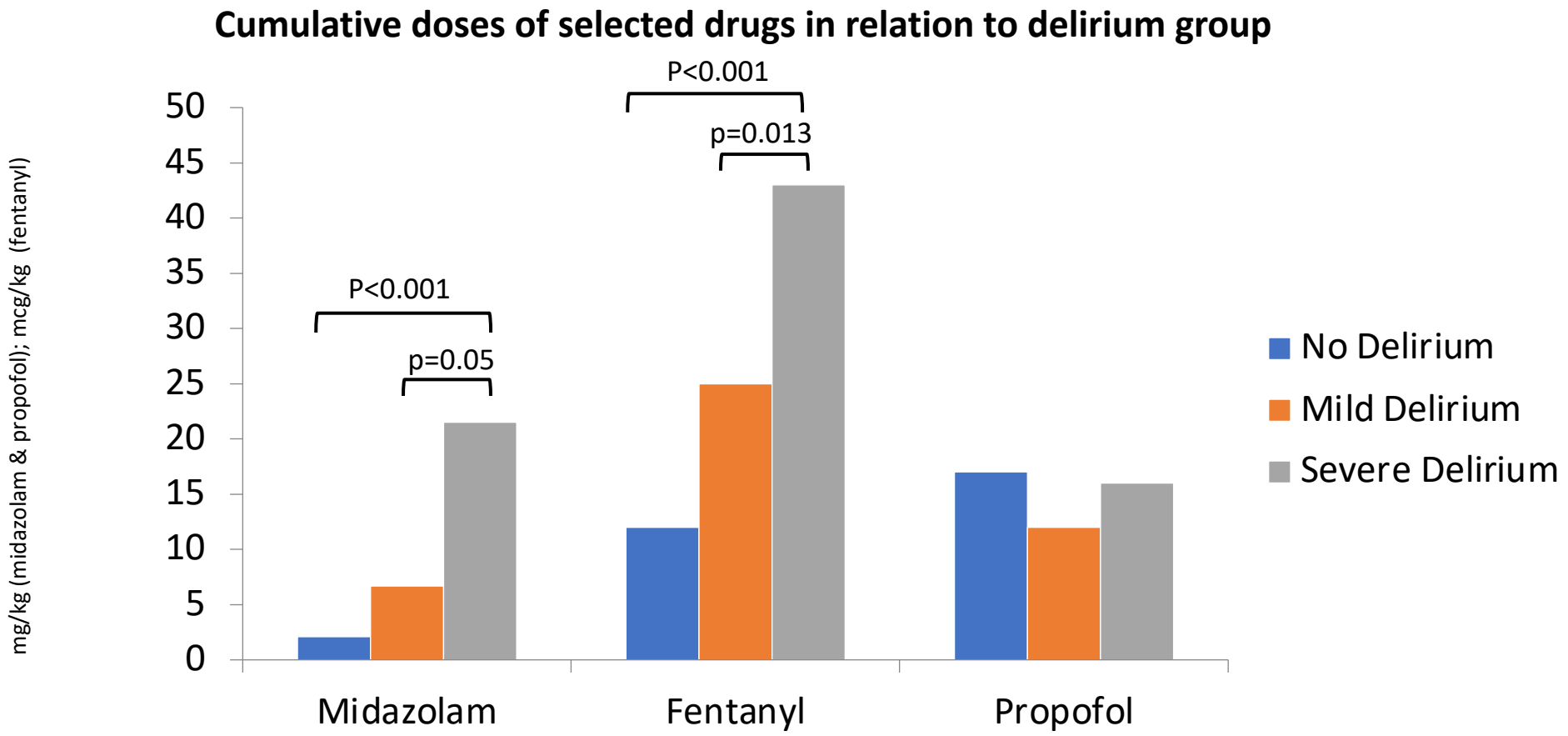
- 66% of patients experienced delirium (CAPD >9)
- 33% of patients had delirium that lasted several days
- 85% of patients <1 year of age had some degree of delirium

Cumulative doses of select drugs in relation to delirium group

Drug (mg/kg)	No Delirium, Mean ± SD	Mild Delirium, Mean ± SD	Severe Delirium, Mean ± SD	p-Value
Midazolam	2.1±3.4	6.7±11.4	21.5±28.5	< 0.001
Phenobarbital	1.1±3.3	4.7±8.7	20.4±27.7	< 0.001
Chloral hydrate	26±49	92±107	200±127	< 0.001
Fentanyl	0.012±0.016	0.025±0.022	0.043±0.032	< 0.001
Propofol	17±20	12±24	16±5	NS
Ketamine	1.1±4.1	1.6±4.9	15.0±54.9	NS
Etomidate	0.10±0.45	0.06±0.10	0.20±0.48	NS
Morphine	0.08±0.20	0.30±0.56	0.68±1.62	NS

Meyburg J, et al. *Pediatr Crit Care Med* 2018.

Risk factors for the development of postoperative delirium in pediatric intensive care patients



Meyburg J, et al. *Pediatr Crit Care Med* 2018.

Benzodiazepines and development of delirium in critically ill children: estimating the causal effect

Objective	To determine the temporal relationship of benzodiazepines and delirium development and to evaluate the association between dosage of benzodiazepines and subsequent delirium
Study design	Retrospective observational study
Patient population	580 pediatric patients admitted to the PICU
Primary outcome	Development of delirium after benzodiazepine exposure, controlling for time-varying covariates such as MV and opioids
Secondary outcome	Association of benzodiazepine dose and delirium development

Mody K, et al. *Pediatr Crit Care Med* 2018.

Benzodiazepines and development of delirium in critically ill children: estimating the causal effect

- Delirium diagnosis was made on 21% of included days
- Hypoactive delirium most common (52%), followed by mixed (39%), and hyperactive (8%)

Predictors of delirium in study cohort

Risk factor day prior	Multivariable mixed effects model OR (95% CI)
Delirious	**8.16 (5.67, 11.74)**
Benzodiazepine	**2.01 (1.39, 2.93)**
Opioids	1.09 (0.75, 1.59)
Mechanical ventilation	**3.92 (2.59, 5.92)**

Mody K, et al. *Pediatr Crit Care Med* 2018.

Benzodiazepines and development of delirium in critically ill children: estimating the causal effect

After controlling for mechanical ventilation and opioid exposure, benzodiazepine exposure **quadrupled** risk of subsequent delirium development

With every one-log increase in benzodiazepine dosage administered, there was a **43% increase** in risk for delirium development

Mody K, et al. *Pediatr Crit Care Med* 2018.

PROPOFOL-

Is propofol a friend or a foe of the pediatric intensivist? Description of propofol use in a PICU

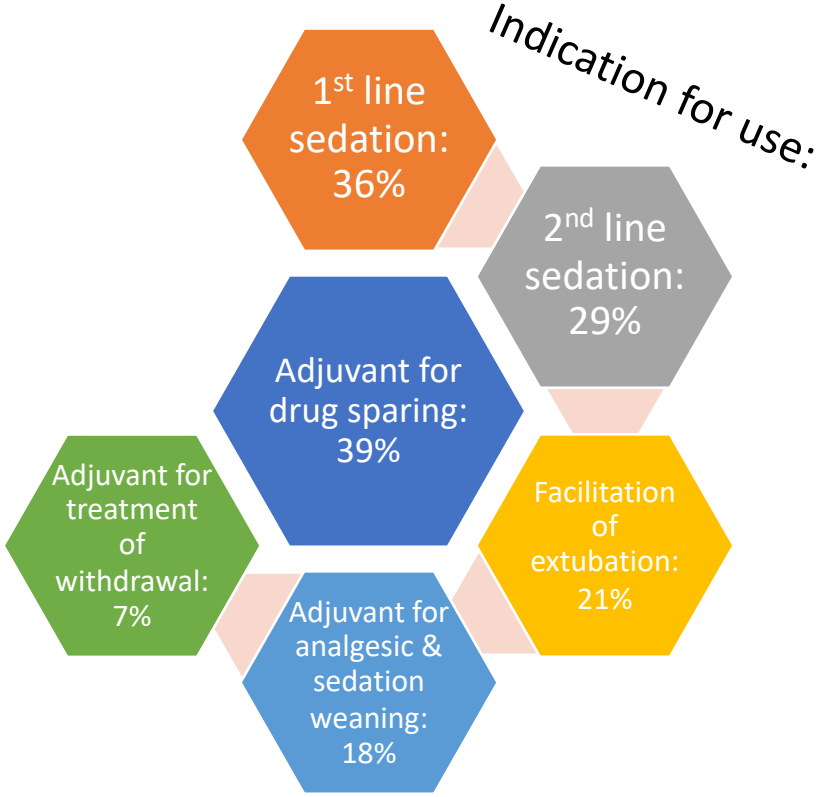
- Average infusion rate: 45 mcg/kg/hr (IQR 32 to 60 mcg/kg/hr)
- Average infusion duration: 10.3 hours (range 0.3 to 41.3 hours)
- No incidence of propofol-related infusion syndrome (PRIS)
- Lipemia: 4 patients (1.9%); mild metabolic acidosis: 4 patients (1.9%)

Koriyama H, et al. *Pediatr Crit Care Med* 2014.

DEXMEDETOMIDINE-

Dexmedetomidine for prolonged sedation in the PICU: a systematic review and meta-analysis

- Dosing
  - Min and max infusion range: 0.1-0.5 mcg to 0.3-2.5 mcg/kg/hr
  - Mean/median infusion duration range: 25 to 540 hours
- Use
  - Used with opioids: 88%, used with benzodiazepines: 58%, monotherapy: 11%
- Safety
  - Bradycardia: 2.6%, hypotension: 6.1%
  - Withdrawal: 0-27%, rebound effects: 0-24%



Daverio M, et al. *Pediatr Crit Care Med* 2020.

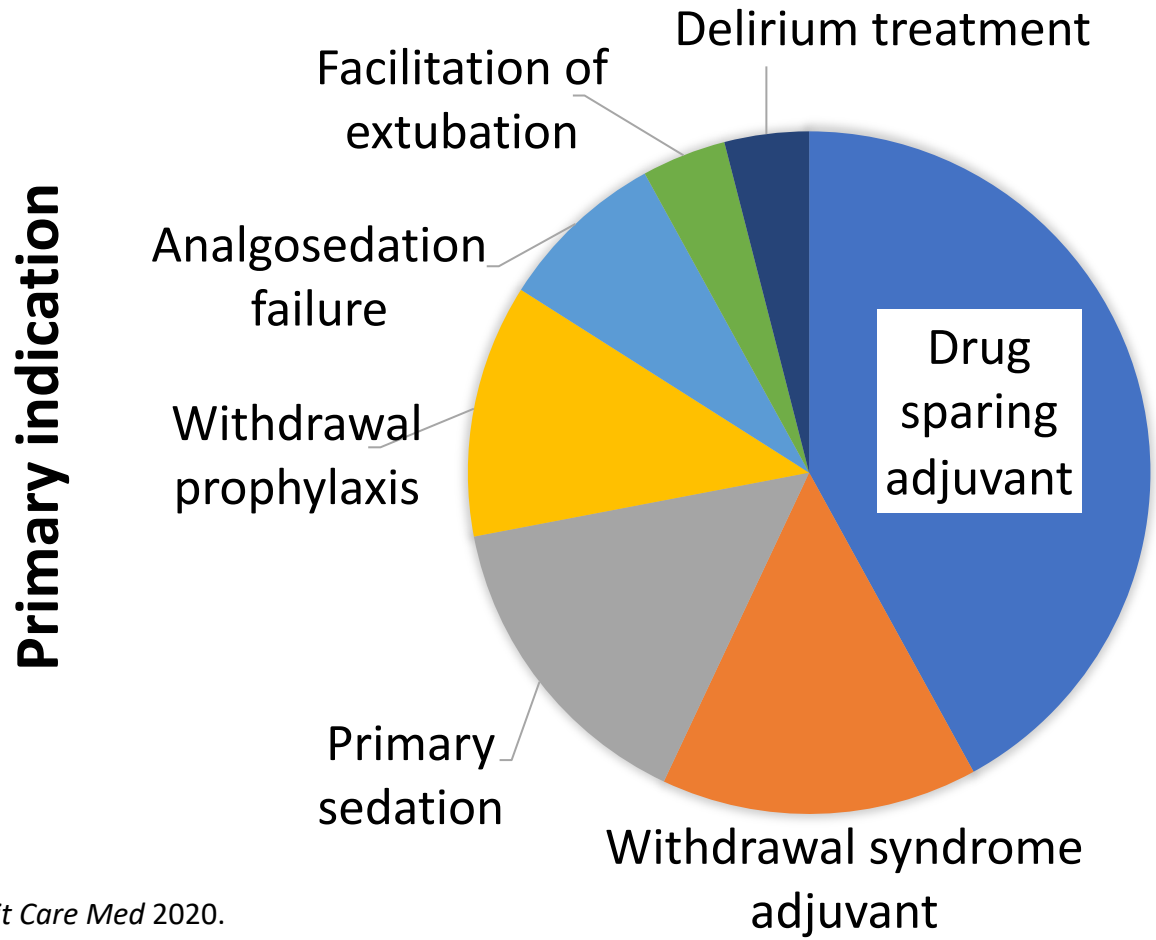
Efficacy and safety of dexmedetomidine for prolonged sedation in the PICU: a prospective multicenter study

Objective	To evaluate dexmedetomidine efficacy and safety when used for prolonged sedation in critically ill patients
Study design	Multi-center, observational prospective study
Patient population	163 patients <18 years of age who received dexmedetomidine for ≥24 hours in the PICU
Primary outcome	Reduction of clinical score (CBS or WAT-1) at 24 hours of dexmedetomidine infusion
Secondary outcomes	Reduction of CAPD at 24 hours of dexmedetomidine infusion Dose reduction of concomitant analgosedation drugs Reduction in prevalence of withdrawal syndrome and delirium Successful extubation
Safety outcomes	Presence of bradycardia, hypotension, hypertension Presence of withdrawal within 24 hours of discontinuation

Sperotto, et al. *Pediatr Crit Care Med* 2020.

Efficacy and safety of dexmedetomidine for prolonged sedation in the PICU: a prospective multicenter study

- <u>Use</u>
  - With opioid: 80%
  - With benzodiazepine: 61%
  - Monotherapy: 14%
- <u>Dosing</u>
  - Median min and max dose: 0.4 and 0.8 mcg/kg/hr
  - Median duration: 108 hours
  - 85% weaned off over a median of 36 hours



Sperotto, et al. *Pediatr Crit Care Med* 2020.

Efficacy and safety of dexmedetomidine for prolonged sedation in the PICU: a prospective multicenter study

Median point **reduction** after 24 hours of dexmedetomidine-

CBS: 5 points (p<0.001)
WAT-1: 2 points (p<0.001)
CAPD: 8 points (p=0.027)

Doses of concomitant benzodiazepines, opioids, propofol, and ketamine **significantly decreased**

Withdrawal syndrome **decreased from 19 to 2%** after dexmedetomidine initiation (p<0.001)

Sperotto, et al. *Pediatr Crit Care Med* 2020.

Efficacy and safety of dexmedetomidine for prolonged sedation in the PICU: a prospective multicenter study

Adverse Events	Total (n = 163)	Not Requiring Intervention (n = 47)	Requiring Intervention (n = 14)
Bradycardia, n (%)	45 (27)	37 (23)	8 (5)
Hypotension	18 (11)	10 (6)	8 (5)
Hypertension	3 (2)	2 (1)	1 (1)
Withdrawal	0	0	0

Use of **loading dose** (OR 4.8) and **doses >1.2 mcg/kg/hr** (OR 5.4) increase odds of hemodynamic changes

Before and after graph of CBS and WAT-1 Values

Sperotto, et al. *Pediatr Crit Care Med* 2020.

Clinical Effects of Sedative Agents-

	Sedation	Analgesia	Anxiolysis	Natural sleep promotion	Delirium reduction
Opioids	+	+++			
Dexmedetomidine	++	++	+	+	++
Benzodiazepines	+++		+		
Propofol	+++				

Joseph A. *J Emerg Crit Care Med* 2018.
Longrois D, et al. *Multidiscip Resp Med* 2014.

Adverse Effects of Sedative Agents-

	Respiratory depression	Hypotension	Bradycardia	Other
Opioids	+	+	+	
Dexmedetomidine		+	+	
Benzodiazepines	+	+		Lorazepam: propylene glycol toxicity
Propofol	+	+	+	↑TG → pancreatitis PRIS >67 mcg/kg/min, >48 hours

www.sccm.org/iculiberation
Devlin JW, et al. *Crit Care Med* 2010.

Cost of Sedative Agents-

20 kg patient

Agent	Rate	Daily Cost
Morphine	0.1 mg/kg/hr	$6
Fentanyl	1 mcg/kg/hr	$3
Hydromorphone	15 mcg/kg/hr	$4
Dexmedetomidine	1 mcg/kg/hr	$10
Propofol	50 mcg/kg/hr	$2
Midazolam	0.1 mg/kg/hr	$8

*Based on daily acquisition cost at Loma Linda University Children's Hospital as of June 15, 2020

Sedation with dexmedetomdine (vs. midazolam) associated with a median total cost savings of $9679 due to decreased ICU stay and MV costs

Dasta JF, et al. *Crit Care Med* 2010.

IN SUMMARY…

What we know

- Benzodiazepines are associated with neurotoxicity, poor neurologic outcomes, and delirium.
- Dexmedetomidine improves sedation scores, spares the use of opioids and sedatives, and attenuates withdrawal and delirium symptoms, with a small risk of adverse events.

What we do not know

- Can propofol at higher doses, longer durations, and as repeated infusions be used safely for sedation?
- Is the use of non-benzodiazepine sedation (i.e. dexmedetomidine) associated with improved mortality, PICU & hospital LOS, and long-term outcomes in pediatric ICU patients?
- What is the ideal sedative for use in the general PICU population, as well as other select patient populations (e.g. cardiac disease, neonates, etc.)?

IV Fluid Management

Question

What type of IV fluids should be provided for resuscitation and maintenance to critically ill children?

Phases of Fluid Therapy

Resuscitative Phase

Goal: restore adequate tissue perfusion and prevent or mitigate end-organ injury

Titration Phase

Goal: assess fluid losses

Maintenance Phase

Goal: achieve homeostatic balance between needs and losses

Convalescent Phase

Goal: maintain intrinsic fluid regulation

Feld GL, et al. *Pediatrics* 2018.
Hoste EA, et al. *Br J Anaesth.* 2014.

Composition of Commercially Available Crystalloid Solutions

Fluid	Glucose, g/dL	Sodium	Chloride	Potassium, mEq/L	Calcium	Magnesium	Buffer	Osmolarity,* mOsm/L
Human Plasma	0.07-0.11	135-145	95-105	3.5-5.3	4.4-5.2	1.6-2.4	23-30 bicarbonate	275-295
Hypotonic solutions								
D_5 0.2% NaCl	5	34	34	0	0	0	0	78
D_5 0.45% NaCl	5	77	77	0	0	0	0	154
Isotonic and/or near-isotonic solutions								
D_5 0.9% NaCl	5	154	154	0	0	0	0	308
D_5 lactated Ringer	5	130	109	4	3	0	28 lactate	273
PlasmaLyte	0	140	98	5	0	3	27 acetate 23 gluconate	294

*Osmolarity excludes the dextrose in the solution because dextrose is rapidly metabolized on infusion

Feld GL, et al. *Pediatrics* 2018.

Hyponatremia in Acute Illness

Non-osmotic states of AVP excess

Hemodynamic stimuli

- Volume depletion
- Hypotension
- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Adrenal insufficiency

Nonhemodynamic stimuli

- Pain and stress
- Nausea and vomiting
- Hypoxemia and hypercapnia
- Hypoglycemia
- Medications
- Perioperative state
- Inflammation
- Cancer
- Pulmonary disease
- CNS disease

Arginine vasopressin (AVP) excess can impair free-water excretion → increased risk of hyponatremia when hypotonic fluids are given

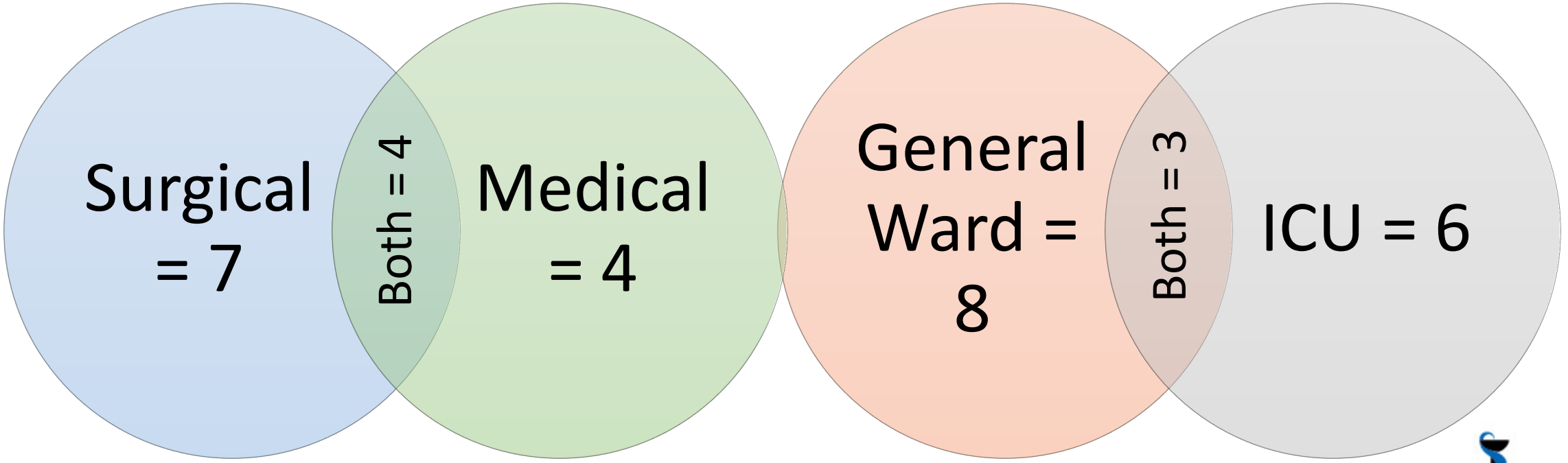
Feld GL, et al. *Pediatrics* 2018.
Moritz ML, et al. *N Engl J Med.* 2015.

American Academy of Pediatrics Clinical Practice Guideline: Maintenance Intravenous Fluids in Children

17 RCTs
2455 patients

Hypotonic vs. isotonic IV fluids

Included patient populations-



Feld GL, et al. *Pediatrics.* 2018.

Exclusions

Neurosurgical disorders
Congenital or acquired cardiac disease
Hepatic disease
Renal dysfunction
Cancer
Diabetes insipidus
Voluminous watery diarrhea
Severe burns
NICU patients
<28 days or >18 years old

Feld GL, et al. *Pediatrics* 2018.

Analysis of All Included RCTs-

Estimated **relative risk** of developing hyponatremia with isotonic fluids

= 0.46 (95% CI 0.37-0.57)

Feld GL, et al. *Pediatrics* 2018.

American Academy of Pediatrics Recommendation

Evidence quality: A
Strength: strong

Patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solution with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia.

Feld GL, et al. *Pediatrics* 2018.

Benefits

- More physiologic fluid
- Less hyponatremia

Risks

- Hypernatremia
- Fluid overload
- Hypertension
- Hyperchloremic metabolic acidosis
- Acute kidney injury

Feld GL, et al. *Pediatrics* 2018.

Composition of Commercially Available Crystalloid Solutions

Fluid	Glucose, g/dL	Sodium	Chloride	Potassium, mEq/L	Calcium	Magnesium	Buffer	Osmolarity,* mOsm/L
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*Osmolarity excludes the dextrose in the solution because dextrose is rapidly metabolized on infusion

Feld GL, et al. *Pediatrics* 2018.

HYPERCHLOREMIA OUTCOMES IN THE PICU

- In patients with septic shock-
  - **Minimum Cl ≥110 mmol/L** associated with ↑ risk of **complicated course** and **mortality**
  - **Mean Cl ≥110 mmol/L** associated with ↑ risk of **mortality**

- In patients requiring RRT-
  - Patients with **hyperchloremia** more likely to be **fluid overloaded** (p=0.04)
  - **Mortality**, **days intubated**, **time on RRT**, and **hospital LOS** all **significantly higher** in those with hyperchloremia
  - Hyperchloremia associated with **10.9 times greater odds of death**

Neyra JA, et al. *Crit Care Med.* 2015.
Stenson EK, et al. *Pediatr Crit Care Med.* 2018.
Yunos NM, et al. *Intensive Care Med.* 2015.
Barhight MF, et al. *Pediatr Nephrol.* 2018.

Isotonic Fluid Choice-

Effect of Balanced Crystalloids vs. Saline on Mortality Among Critically Ill Adults

Study	Individuals, n		Events, n (%)		OR (95% CI)
	Balanced	Saline	Balanced	Saline	
SPLIT	1152	1110	78 (7.6)	95 (8.6)	0.88 (0.65-1.19)
SALT	520	454	72 (13.8)	68 (15.0)	0.91 (0.64-1.30)
SALT-ED	6708	6639	94 (1.4)	102 (1.5)	0.89 (0.67-1.18)
SMART	7942	7860	818 (10.3)	875 (11.1)	0.90 (0.80-1.01)

Results favor the use of balanced fluids (not statistically significant).

Semler MW, et al. *Am J Respir Crit Care Med*. 2019.

Crystalloid fluid choice and clinical outcomes in pediatric sepsis: a matched retrospective cohort study

Objective	To test the hypothesis that resuscitation with balanced fluids is associated with improved outcomes compared with normal saline in pediatric sepsis	
Study design	Matched multicenter retrospective cohort study	
Comparison	NS vs. LR	
Patient population	12,529 pediatric patients with severe sepsis or septic shock	Only NS: 10,379 patients Any LR: 2117 patients
Primary outcome	All-cause 30-day hospital mortality	
Secondary outcomes	AKI, PICU LOS, hospital LOS	

Weiss SL, et al. *J Pediatr.* 2017.

Crystalloid fluid choice and clinical outcomes in pediatric sepsis: a matched retrospective cohort study

Primary Outcome-

No difference in mortality between the LR-any and LR-only vs. NS group (p=0.20)

No difference when matching stratified by volume and proportionate LR utilization

Secondary Outcomes-

No difference in AKI and PICU LOS

Greater hospital LOS in LR-any (p<0.001) and LR-only groups (p=0.01) vs. NS group

Weiss SL, et al. *J Pediatr.* 2017.

Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis

Objective	To evaluate outcomes in patients receiving balanced fluids (BF) for resuscitation in pediatric severe sepsis	
Study design	Matched multicenter retrospective cohort study	
Comparison	NS vs. BF	
Patient population	36,908 pediatric patients with severe sepsis	24h- Only NS: 30,166 pts; only BF: 2398 pts 72h- Only NS: 27,973 pts; only BF: 1,641 pts
Primary outcome	In-hospital mortality	
Secondary outcomes	AKI, use of CRRT, hospital LOS, PICU LOS, vasoactive infusion days	

Emrath ET, et al. *Crit Care Med.* 2017.

Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis

Propensity-matched outcomes for 24-hour fluid groups-

- Patients who received only balanced fluids had
  - **Longer hospital and PICU LOS** (22 vs. 18.6 days; 8.4 vs. 7.5 days, p<0.001)
  - **Lower mortality** (13.4 vs. 15.5%, p = 0.051)
  - No significant difference in vasoactive infusion days, AKI, or CRRT

Emrath ET, et al. *Crit Care Med.* 2017.

Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis

Propensity-matched outcomes for 72-hour fluid groups-

- Patients who received only balanced fluids had
  - **Longer hospital LOS** (21 vs. 18.1 days, p<0.001)
  - **Fewer vasoactive infusion days** (3 vs. 3.3 days, p < 0.001)
  - **Lower incidence of AKI** (16 vs. 19.2%, p = 0.028)
  - **Lower mortality** (12.5 vs. 15.9%, p=0.007)
  - No significant difference in PICU LOS or CRRT use

Emrath ET, et al. *Crit Care Med.* 2017.

In summary…

What we know

- Isotonic IVFs help decrease the risk of hyponatremia.
- Hyperchloremia is associated with poor renal outcomes, complicated course, and mortality.

What we do not know

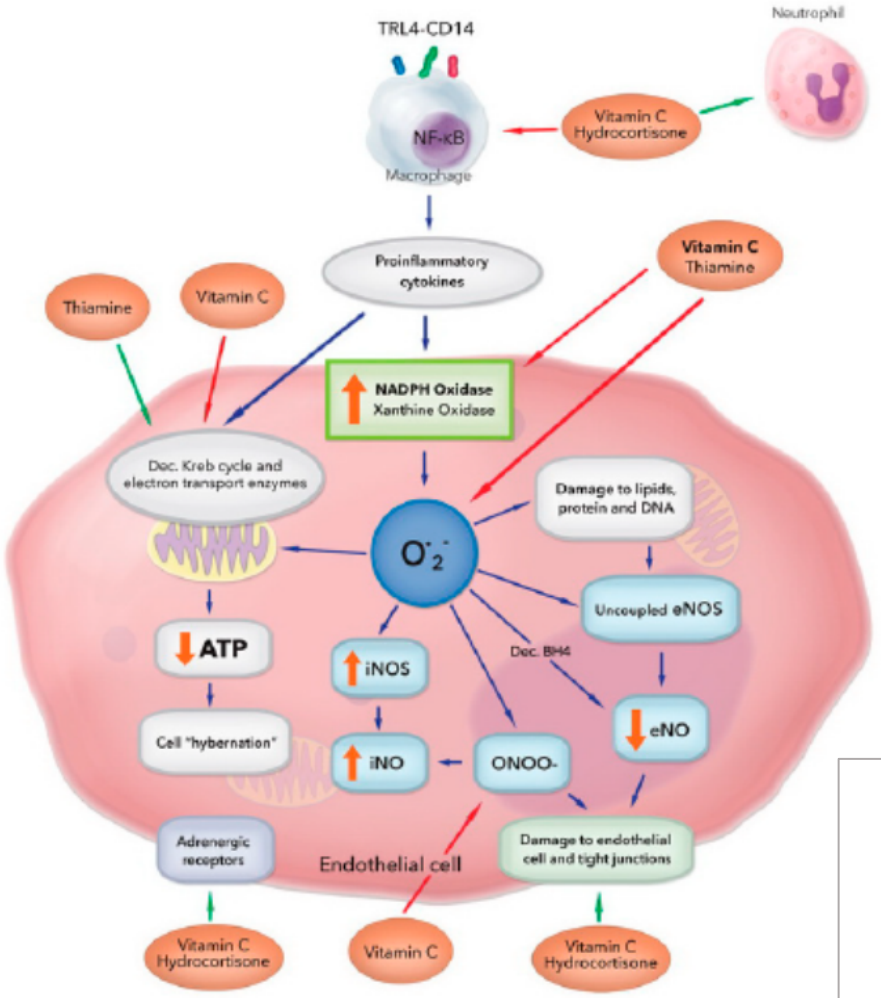
- Will increased use of 0.9% NaCl for maintenance IVFs increase the incidence of hyperchloremic metabolic acidosis?
- Are isotonic-balanced fluids for resuscitation associated with improved outcomes in pediatric ICU patients?
- What is the ideal IVF for use in select populations (i.e. cardiac disease, neonates, post-operative, burns)?

Adjuvant Therapies in Sepsis

Hydrocortisone
Ascorbic Acid
Thiamine

Role of Ascorbic acid, Thiamine, and Hydrocortisone in Sepsis

Ascorbic acid and thiamine restore and improve cellular ATP production



Ascorbic acid and hydrocortisone decrease the release of proinflammatory mediators

Ascorbic acid and thiamine are antioxidants that scavenge free radicals and protect from oxidative stress

Ascorbic acid and hydrocortisone increase adrenergic receptor function

Ascorbic acid and hydrocortisone restore endothelial tight junctions

Marik PE. *Nutrients* 2018.

HAT Therapy in Sepsis-

Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock

- Hospital mortality = **8.5% in treatment group** vs. **40.4% in control group** ($p < 0.001$)
- Propensity adjusted odds of mortality with HAT therapy was 0.13 ($p = 0.002$)
- SOFA scores decreased in all treated
- Vasopressors were weaned off a mean of 18.3 hours after starting treatment compared to 54.9 in the control group ($p < 0.001$)

Marik PE, et al. *Chest* 2017.

Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock

Hypothesis	Children receiving HAT therapy would have decreased mortality when compared with similar patients not receiving the treatment
Study design	Retrospective, propensity score-matched cohort study
Comparison	HAT therapy vs. no treatment HAT therapy vs. hydrocortisone only
Patient population	557 pediatric patients with septic shock 33 control patients 181 hydrocortisone-only 43 HAT therapy
Primary outcome	30-day mortality
Secondary outcomes	Vasoactive inotrope-free days, hospital free days, 90-day mortality

Wad EL, et al. *Am J Respir Crit Care Med.* 2020.

Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock

Matched patient outcomes	Controls (n=33)	Hydrocortisone-only therapy (n = 181)	HAT Therapy (n= 43)
Vasoactive inotrope-free days at 30 d, median (IQR)	25 (2-28)	27 (11-28)	26 (22-28)
Hospital-free days at 30 d, median (IQR)	2 (0-15)	0 (0-16)	0 (0-11)
Mortality at 30 d, n (%)	**12 (28)**	**13 (30)**	**4 (9)***
Mortality at 90 d, n (%)	**15 (35)**	**16 (37)**	**6 (14)***

*$p < 0.05$

Wad EL, et al. *Am J Respir Crit Care Med.* 2020.

Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock

30-day survival:

- **78 % untreated controls**
- **70% hydrocortisone-only**
- **91% HAT therapy**

Use of HAT therapy independently associated with a **30% decrease in risk of mortality** (HR 0.3, CI 0.1-0.9)

Wad EL, et al. *Am J Respir Crit Care Med.* 2020.

Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

We suggest **against using IV hydrocortisone** to treat children with septic shock if adequate fluid resuscitation and vasopressor therapy are used to restore hemodynamic stability.

We suggest that either **IV hydrocortisone or no hydrocortisone may be used** if adequate fluid resuscitation and vasopressor therapy are **not able to restore hemodynamic stability.**

We suggest **against the use of ascorbic acid** in the treatment of children with septic shock or other sepsis-associated organ dysfunction.

We suggest **against the use of thiamine** to treat children with sepsis-associated organ dysfunction.

Weiss, et al. *Pediatr Crit Care Med 2020.*

In summary…

What we know

What we do not know

- Are hydrocortisone, ascorbic acid, and thiamine, administered alone or together, associated with improved outcomes in pediatric patients with sepsis and septic shock?
- What is the optimal dose and duration of these medications, when used in patients with sepsis?

TEST QUESTIONS

1. Benzodiazepine use in children is associated with…
   a) Increased hospital length of stay
   b) Development of delirium
   c) Decreased opioid use
   d) Improved sleep quality

TEST QUESTIONS

2. Choose the correct statement. Isotonic fluids decrease the risk of…
   a) Hypernatremia.
   b) Acute kidney injury.
   c) Fluid overload.
   d) Hyponatremia.

TEST QUESTIONS

3. In the setting of sepsis, ascorbic acid
   a) Is an antioxidant that scavenges free radicals and protects from oxidative stress.
   b) Inhibits pro-inflammatory cytokines.
   c) Increases catecholamine synthesis.
   d) All of the above.

SEDATION REFERENCES

1. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines fro the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825-e873.
2. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale. *Am J Respir Crit Care Med* 2002;166:1338-1344.
3. Joseph A. Sedation of the trauma patient in the intensive care unit. *J Emerg Crit Care Med* 2018;2:8.
4. Longrois D, Conti G, Mantz J, et al. Sedation in non-invasive ventilation: do we know what to do (and why)? *Multidiscip Resp Med* 2014;9:56.
5. Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med* 2010;38(6):S231-243.
6. Dasta JF, Kane Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. *Crit Care Med* 2010;38(2):497-503.
7. Kawai Y, Rohlik GM, Neu LL, et al. D-escalation of care through pediatric intensive care unit liberation rounds and a daily checklist. *Pediatr Qual Saf* 2018;2(3):1-3.
8. Arteaga G, Kawai Y, Rowekamp D, et al. The pediatric ICU liberation project impact on patient outcomes: the Mayo experience. *Crit Care Med* 2018;46(1):628.
9. Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med* 2019;47(1):3-14.
10. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. *Crit Care Med* 2014;42(7):1592-1600.
11. Loepke AW. Developmental neurotoxicity of sedatives and anesthetics: A concern for neonatal and pediatric critical care medicine? *Pediatr Crit Care Med* 2010;11:217-226.
12. Meyburg J, Dill M, von Haken R, et al. Risk factors for the development of postoperative delirium in pediatric intensive care patients. *Pediatr Crit Care Med* 2018; 19(10):e514-521.
13. Mody K, Kaur S, Mauer EA, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal effect. *Pediatr Crit Care Med* 2018;14:1486-1491.
14. Koriyama H, Duff JP, Guerra GG, Chan AW. Is propofol a friend or foe of the pediatric intensivist? Description of propofol use in a PICU. *Pediatr Crit Care Med* 2014; 15:e66-e71.
15. Daverio M, Sperotto F, Zanetto L, et al. Dexmedetomidine for prolonged sedation in the PICU: a systematic review and meta-analysis. *Pediatr Crit Care Med* 2020; doi: 10.1097/PCC.0000000000002325.
16. Sperotto F, Mondardini MC, Dell'Oste C, et al. Efficacy and safety of dexmedetomidine for prolonged sedation in the PICU: a prospective multicenter study (PROSDEX). *Pediatr Crit Care Med* 2020; doi: 10.1097/PCC.0000000000002350

FLUID REFERENCES

1. Feld LG, Neuspiel DR, Foster BA, et al. Clinical practice guideline: maintenance intravenous fluids in children. *Pediatrics* 2018;142(6):e20183083.
2. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth.* 2014;113(5):740-747.
3. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2015;41(2):257-264.
4. Neyra JA, Canepa-Escaro F, Li, X, et al. Association of hyperchloremia with hospital mortality in critically ill septic patients. *Crit Care Med.* 2015;43(9):1938-1944.
5. Barhight MF, Lusk J, Brinton J, et al. Hyperchloremia is independently associated with mortality in critically ill children who ultimately require continuous renal replacement therapy. *Pediatr Neprhol.* 2018;33:1079-1085.
6. Stenson EK, Cvijanovich NZ, Anas N, et al. Hyperchloremia is associated with complicated course and mortality in pediatric patients with septic shock. *Pediatr Crit Care Med.* 2018;19(2)155-160.
7. Semler MW, Kellum JA. Balanced crystalloid solutions. *Am J Respir Crit Care Med.* 2019;199(8):952-960.
8. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit. *JAMA* 2015;314(16):1701-1710.
9. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit. The SALT randomized trial. *Am J Respir Crit Care Med.* 2017;195(10)1362-1372.
10. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med.* 2018;378:819-828.
11. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med.* 2018;278:829-839.
12. Weiss SL, Keele L, Balamuth F, et al. Crystalloid fluid choice and clinical outcomes in pediatric sepsis: a matched retrospective cohort study. *J Pediatr.* 2017;182:304-310.
13. Emrath ET, Fortenberry JD, Travers C, McCracken CE, Hebbar KB. Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis. *Crit Care Med.* 2017;45:1177-1183.

HAT Therapy References

1. Marik PE. Hydrocortisone, ascorbic acid and thiamine for the treatment of sepsis, focus on ascorbic acid. *Nutrients* 2018;10(11):1762.
2. Wald EL, Moran T, Badke CM, et al. Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock. *Am J Respir Crit Care Med* 2020; DOI: 10.1164/rccm.201908-1543LE.
3. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med* 2018; 46(9):1411-1420.
4. Putzu A, Daems A, Lopez-Delgado JC, et al. The effect of vitamin c on clinical outcome in critically ill patients: a systemic review with meta-analysis of randomized control trials. *Crit Care Med* 2019;47:774-783.
5. Miyamoto Y, Aso S, Iwagami M, et al. Association between IV thiamine and mortality in patients with septic shock: a nationwide observational study. *Crit Care Med* 2020; DOI: 10.1097/CCM.0000000000004394.
6. Weiss S, Blowey B, Keele L, et al. Matched retrospective cohort study of thiamine to treat persistent hyperlactatemia in pediatric septic shock. *Pediatr Crit Care Med* 2019; 20(9):e452-e456.
7. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock. *Chest* 2017;151(6):1229-1238.
8. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020; 21(2):e52-e106.

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