



PHARMACY
VISION
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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



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



CHOICE OF ANALGESIA AND SEDATION

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

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



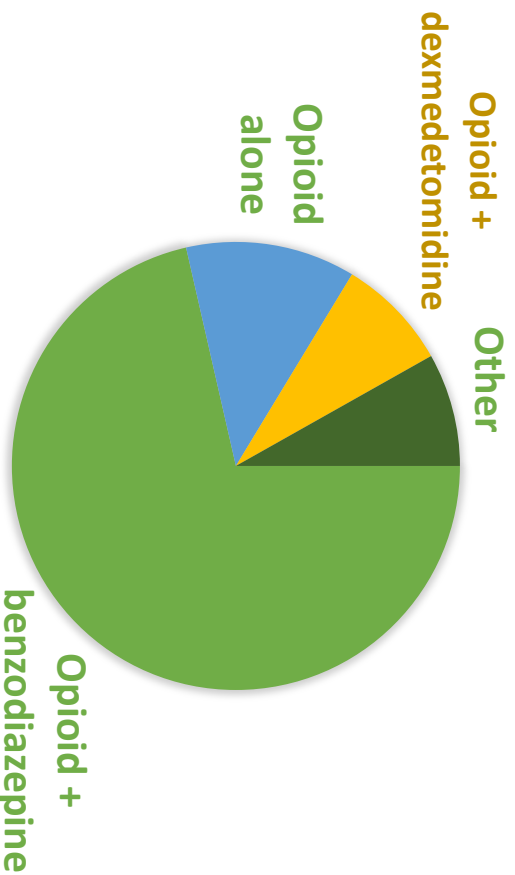
CHOICE OF ANALGESIA AND SEDATION

- Use of nonbenzodiazepines over benzodiazepines for sedation

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

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

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)

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

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

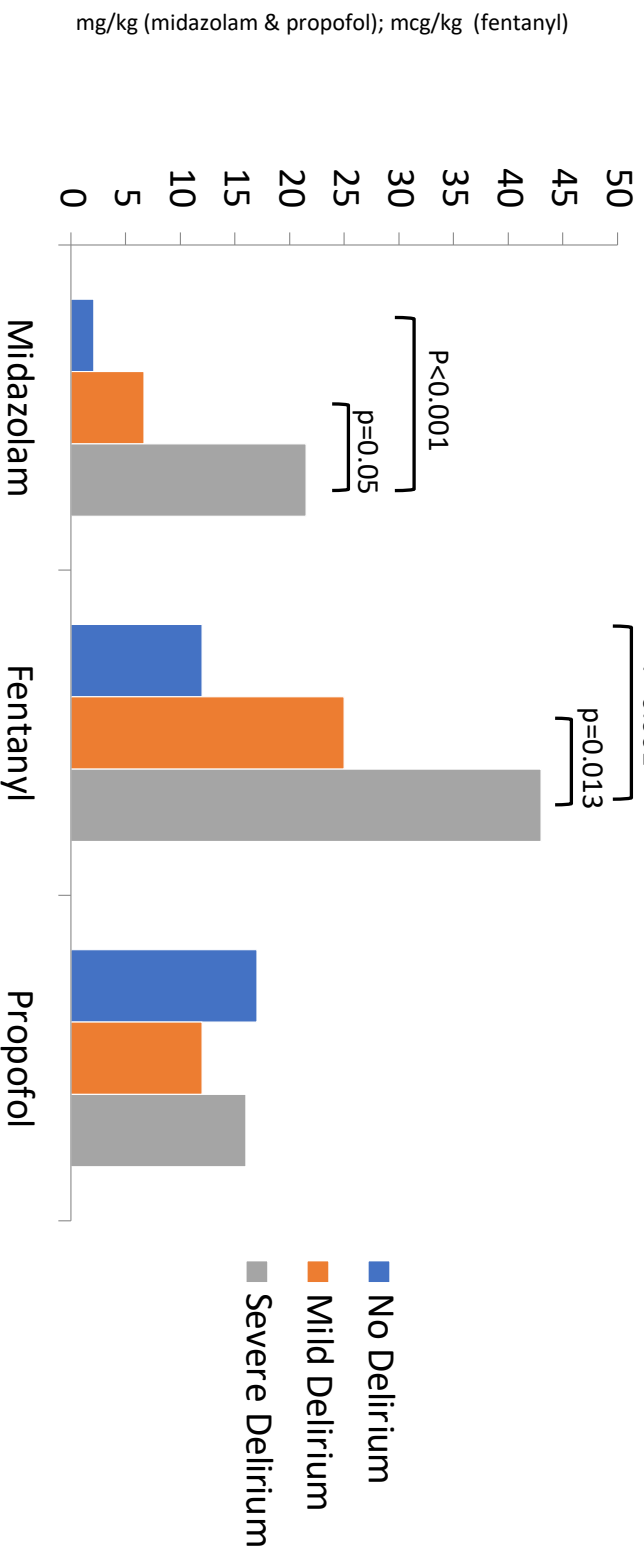
- 66% of patients experienced delirium (CAPD >9)
- 33% of patients had delirium that lasted several days
- 85% of patients <1 year of age had some degree of delirium

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

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

Cumulative doses of selected drugs in relation to delirium group



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

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)

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

PROPOFOL-

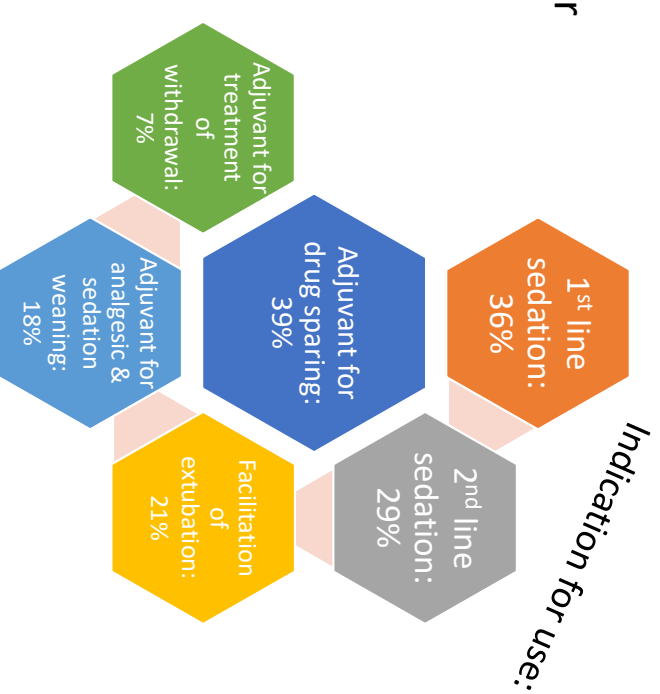
Is propofol a friend or a foe of the pediatric intensivist?
Description of propofol use in a PICU

- 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%)

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%



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 analgesedation drugs
Reduction in prevalence of withdrawal syndrome and delirium
Successful extubation

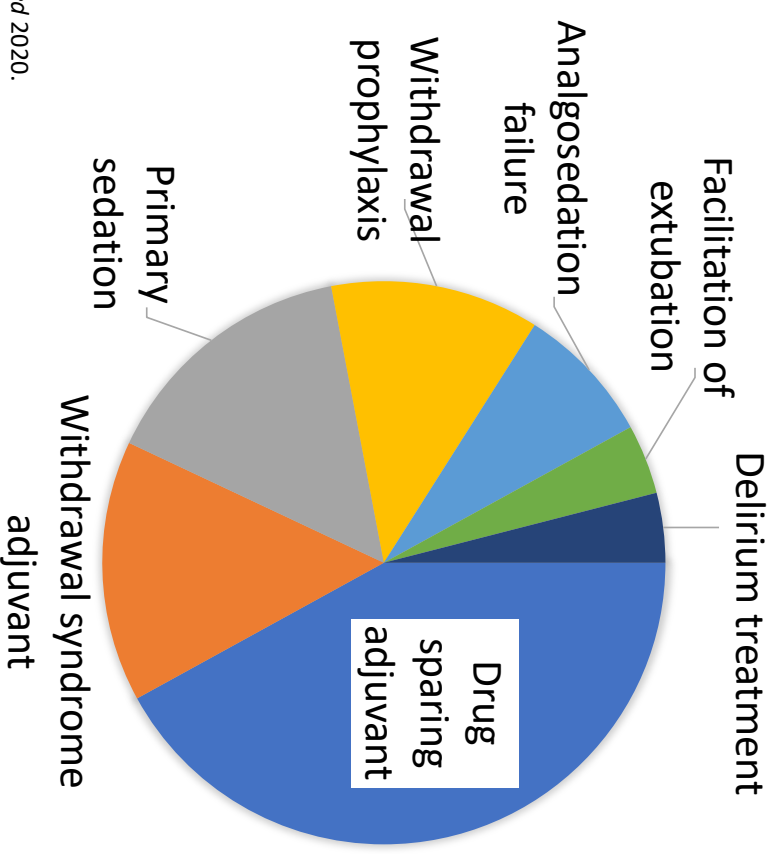
Safety outcomes

Presence of bradycardia, hypotension, hypertension
Presence of withdrawal within 24 hours of discontinuation

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

- Use
 - With opioid: 80%
 - With benzodiazepine: 61%
 - Monotherapy: 14%
- Dosing
 - 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

Primary indication



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)

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

CLINICAL EFFECTS OF SEDATIVE AGENTS-

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

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

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 dexmedetomidine (vs. midazolam) associated savings of \$9679 due to decreased ICU stay and MV costs

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

COMPOSITION OF COMMERCIALY 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

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

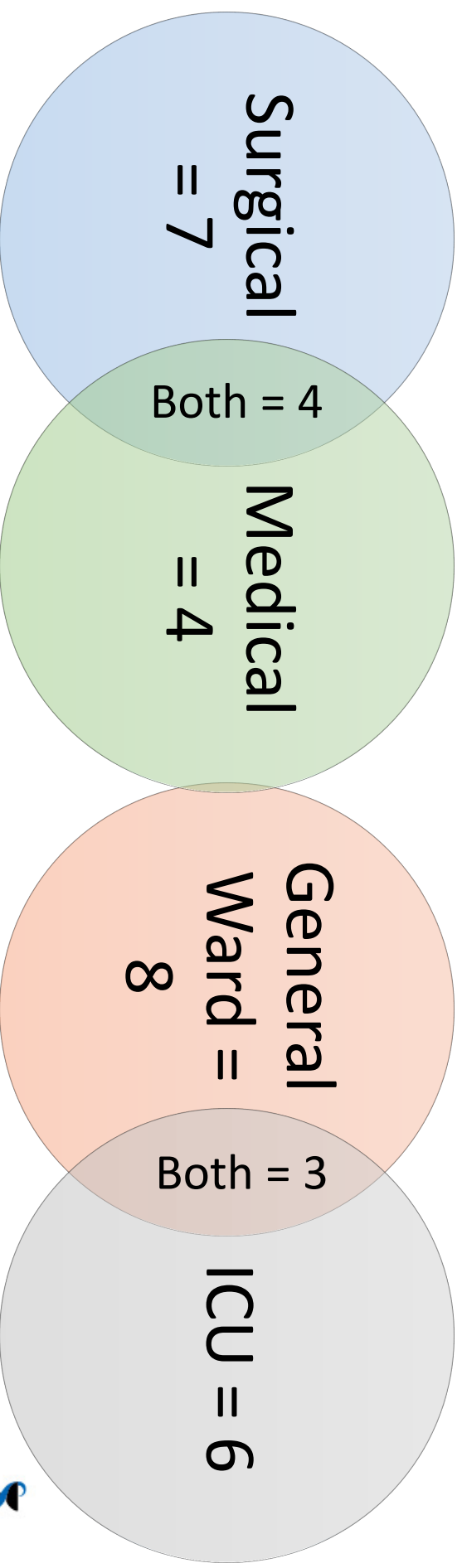
AMERICAN ACADEMY OF PEDIATRICS CLINICAL PRACTICE

GUIDELINE: MAINTENANCE INTRAVENOUS FLUIDS IN CHILDREN

17 RCTS
2455 patients

Hypotonic vs. isotonic IV fluids

Included patient populations-



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

ANALYSIS OF ALL INCLUDED RCTS-

Estimated **relative risk** of developing
hyponatremia with isotonic fluids
= **0.46** (95% CI 0.37-0.57)

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.



Benefits

- More physiologic fluid
- Less hyponatremia

Risks

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

COMPOSITION OF COMMERCIALY AVAILABLE CRYSTALLOID SOLUTIONS

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HYPERCHLOREMIA OUTCOMES IN THE PICU

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

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).

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	

Crystallloid 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

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 24h- Only NS: 30,166 pts; only BF: 2398 pts
severe sepsis 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

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

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

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

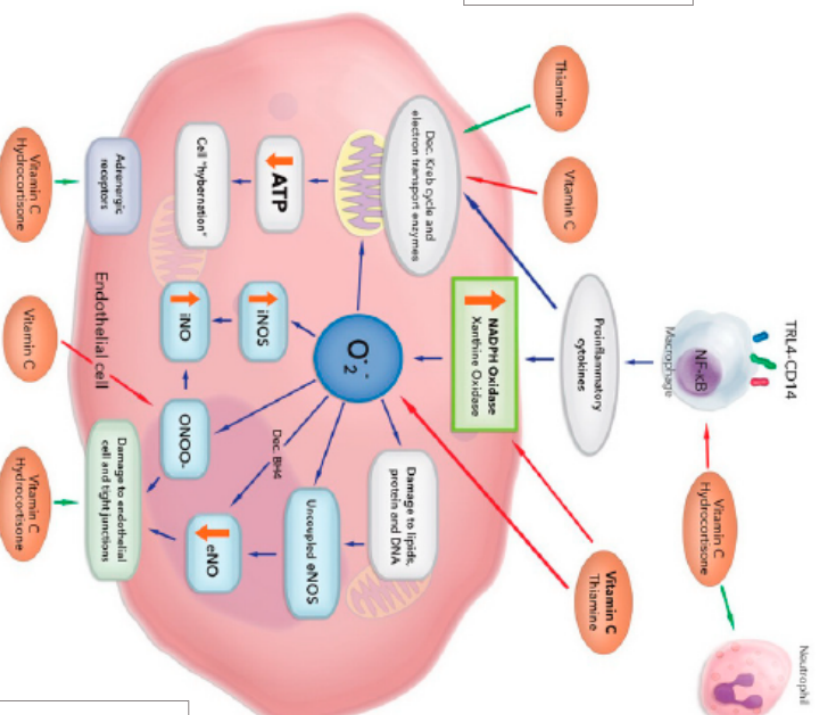
THIAMINE

ROLE OF ASCORBIC ACID, THIAMINE, AND HYDROCORTISONE IN

SEPSIS

Ascorbic acid and thiamine restore and improve cellular ATP production

Ascorbic acid and hydrocortisone increase adrenergic receptor function



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 restore endothelial tight junctions

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 ($p < 0.001$)

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

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

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)

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.

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.

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