Pediatric Pharmacy Advocacy Group

Why so salty?
IV fluids in the PICU

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Disclosures

- Pediatric Lexi-Comp, independent consultant

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Objectives

- Review AAP recommendations for intravenous fluids components in hospitalized children
- Debate the available evidence regarding hypotonic versus isotonic intravenous fluids, balanced versus non-balanced intravenous fluids
- Describe potential adverse effects of intravenous fluids in the critically ill population
- Design an intravenous fluid plan for a critically ill child

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Patient Case #1

18-month old, 12-kilogram, previously well child admitted to the PICU with acute hypoxic respiratory failure due to suspected viral bronchiolitis.

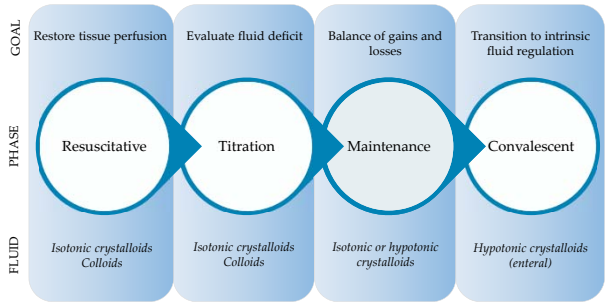
Labs:

138	3.7	16	115
108	24	0.26	

Which is the best choice for maintenance intravenous fluid (mIVF)?

a. D5W + 0.45% NaCl
b. D5W + 0.9% NaCl
c. D5W + LR
d. 0.9% NaCl

Phases of Fluid Therapy



Feld LG, et al. *Pediatrics*. 2018;142(6):e20183083

Rationale for Selection of Intravenous Fluid Products

Hypotonic IV Fluids

- Follows published electrolyte daily requirements for children
- Averts hyperchloremic metabolic acidosis
- Avoids acute hypernatremia

Isotonic IV Fluids

- Addresses inappropriate ADH secretion
- Avoids acute hyponatremia thus subsequent neurological sequelae

American Academy of Pediatrics Recommendation

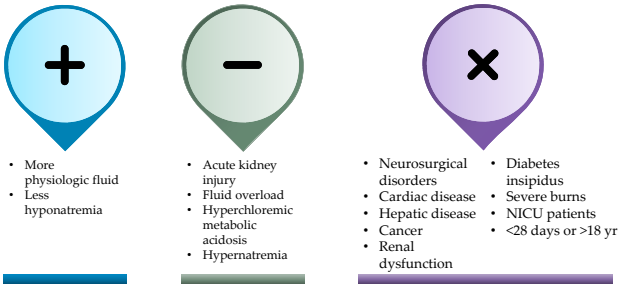
Patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia.

Evidence Quality: A

Recommendation Strength: Strong

Feld LG, et al. *Pediatrics*. 2018;142(6):e20183083

Benefits, Harm, and Exclusions



- More physiologic fluid
- Less hyponatremia

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

- Neurosurgical disorders
- Cardiac disease
- Hepatic disease
- Cancer
- Renal dysfunction
- Diabetes insipidus
- Severe burns
- NICU patients
- <28 days or >18 yr

Feld LG, et al. *Pediatrics*. 2018;142(6):e20183083

Pediatric Populations in Meta-Analyses

Studies	N	Age	Med/Surg	Setting
Brazel 1996	12	12 y – 18 y	Surg	PICU
Neville 2006	42	6 mo – 14 y	Med	Ward
Montanana 2008	122	29 d – 18 y	Surg	PICU
Yung 2009	61	30 d – 18 y	Both	PICU
Kannan 2010	114	3 mo – 12 y	Med	Ward
Neville 2010	124	6 mo – 15 y	Surg	Ward
Choong 2011	218	6 mo – 16 y	Surg	Mixed
Rey 2011	84	2 y – 10 y	Both	PICU
Saba 2011	37	3 mo – 18 y	Both	Ward
Coulthard 2012	79	4 y – 14 y	Surg	PICU

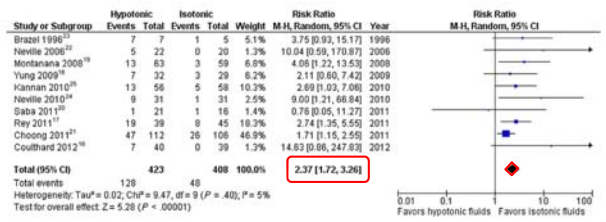
BY THE NUMBERS:

- ☑ Total patients = 893
- ☑ PICU patients = 358 (40%)
- ☑ Surgical ICU patients = 307 (85%)
- ☑ Excluded neonates, heart failure, renal insufficiency, shock
- ☑ Most studies 24 hours duration

Foster BA. *J Pediatr* 2014;165:163-9.
Wang J. *Pediatrics* 2014; 133:105-13.

Risk of Hyponatremia from mIVF in Children

Hyponatremia < 135 mmol/L



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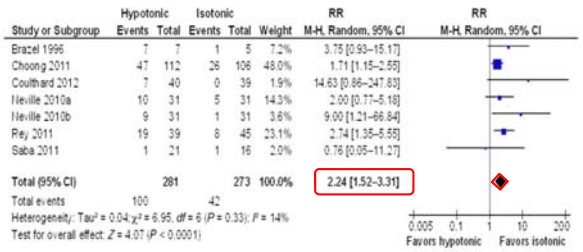

Wang J. *Pediatrics* 2014; 133:105-13.

Patient Case #2

18-month old, 12-kilogram, previously well child admitted to the PICU with acute hypoxic respiratory failure and septic shock.

Labs: $\begin{array}{l} 138 \mid 3.7 \mid 16 \\ 108 \mid 24 \mid 0.26 \end{array}$ 115

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b. LR

c. 0.9% NaCl

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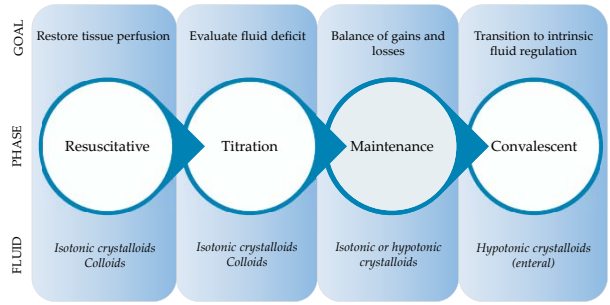

Feld LG, et al. *Pediatrics*. 2018;142(6):e20183083

What are "Balanced Fluids"?

Fluid	Sodium (mEq/L)	Chloride (mEq/L)	SID	Potassium (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Buffer (mEq/L)	Osmolarity (mOsm/L)	Osmolality (mOsm/kg)	pH (range)
Human Plasma	135-144	95-105	40	3.5-5.3	2.2-2.6	0.8-1.2	20-30 bicarbonate	308	288	7.35-7.45
Plasma-Lyte® 148*	140	98	42	5	--	3	27 acetate 23 gluconate	294	271	5.5 (4-8)
Plasma-Lyte® A*	140	98	42	5	--	3	27 acetate 23 gluconate	294	271	7.4 (6.5-8)
Normosol®-R*	140	98	42	5	--	3	27 acetate 23 gluconate	294		6.6 (4-8)
Normosol®-R pH 7.4*	140	98	42	5	--	3	27 acetate 23 gluconate	295		7.4 (6.5-7.6)
Lactated Ringers	130	109	21	4	2.7	0	28 lactate	273	254	6.5 (6-7.5)
0.9% NaCl	154	154	0	--	--	--	--	308	286	5.6 (4.5-7)
0.45% NaCl	77	77	0	--	--	--	--	154		5.6 (4.5-7)
0.225% NaCl + D5W	38.5	38.5	0	0	0	0	0	329		4.5 (3.5-6.5)

*Multiple electrolyte injection, Type 1, USP is the generic name for Plasma-Lyte® A and 148, and Normosol®-R and Normosol®-R pH 7.4.
Strong ion difference, SID

Moritz ML, Ayus JC. *New Engl J Med* 2015;373(14):13350-60.
Hall AM. *J Hosp Med* 2018; 13(9): 637-40.

Chloride Effects in Critically Ill Adults

Objective	To assess the association of a chloride-restrictive vs chloride-liberal IVF strategy with AKI in critically ill patients	
Design	Single-center, prospective, open-label	N = 1533
Comparison	Chloride-rich (control) vs chloride-poor IVF (intervention)	760 vs 773 patients
Inclusion	ICU admission Feb 18 – Aug 17, 2008 (control) Feb 18 – Aug 17, 2009 (intervention)	
Primary Outcome	Change in Scr Incidence of AKI (injury/failure)	+0.25 vs +0.16, p=0.03 14% vs 8.4%, p<0.001
Secondary Outcome	Hospital mortality ICU LOS Hospital LOS	112 (15%) vs 59 (8%), p=0.44 Median 4.29 vs 42.8 hours, p=0.52 Median 11 vs 11 days, p=0.57

Acute kidney injury, AKI; intensive care unit, ICU; length of stay, LOS; serum creatinine, Scr; renal replacement therapy, RRT

Yunos NM, et al. *JAMA* 2012;308(15):1566-72.

Hyperchloremia in Critically Ill Adults

Objective	Examine the association of serum chloride levels with hospital mortality in septic ICU patients	
Design	Single-center, observational, retrospective	N = 1940
Comparison	Chloride ≥ 110 mEq/L and < 110 mEq/L on admission	615 (32%) vs 1325 (68%) patients
Inclusion	ICU admission Severe sepsis and septic shock May 2007 – Apr 2012	
Primary Outcome	Hospital mortality	147 (23.9%) vs 284 (21.4%)

Intensive care unit, ICU

For each 5 mEq/L increase in chloride by 72-hours of ICU admission was associated with 12% increase in odds for mortality, p = 0.03

If hyperchloremic on presentation, for each 5 mEq/L increase in chloride by 72-hours of ICU admission was associated with 38% increase in odds for mortality, p = 0.003

Neyra JA, et al. *Crit Care Med* 2015;43:1938-44.

Adult Experience with Balanced Fluids

	SPLIT (Young 2015)	SALT (Semler 2017)	SALT-ED (Self 2018)	SMART (Semler 2018)
Population	2278	974	13,347	15,802
Design	Multi-center Prospective Double-blind Cluster randomized Double-crossover trial ICU only	Single center Prospective Open-label Randomized Multiple-crossover ICU only	Single-center Prospective Open-label Cluster-randomized Multiple-crossover ED → Ward	Single center Prospective Open-label Cluster-randomized Multiple-crossover ICU and ED → ICU
Comparison	NS vs BC (PL-148)	NS vs BC (LR or PL)	NS vs BC (LR or PL)	NS vs BC (LR or PL)
Primary outcome	Proportion of patients with AKI	Proportion of IVF that was NS	Hospital-free days (days alive after discharge before day 28)	Proportion of patients who met one or more criteria for a major adverse kidney event within 30 days (MAKE30)

Acute kidney injury, AKI; balanced crystalloids, BC; emergency department, ED; intensive care unit, ICU; intravenous fluids, IVF; lactated ringers, LR; major adverse kidney event within 30 days, MAKE30; normal saline, NS; Plasma-Lyte, PL

Young P, et al. *JAMA* 2015;314(16)1701-10.
Semler MW, et al. *Am J Respir Crit Care Med* 2017;195(10)1362-72.
Self WH, et al. *N Engl J Med* 2018;378(9):819-28.
Semler MW, et al. *N Engl J Med* 2018;378(9):829-39.

Adult Experience with Balanced Fluids

	SPLIT (Young 2015)	SALT (Semler 2017)	SALT-ED (Self 2018)	SMART (Semler 2018)
Primary outcome	Proportion with AKI 9.6% BC and 9.2% NS (p=0.77)	Proportion of IVF that was NS 21.2% BC and 91.2% NS (p<0.001)	Hospital-free days 25 days BC and 25 days NS (p=0.41)	Proportion of patients who met MAKE30
MAKE30		24.6% BC and 24.7% NS (p=0.98)	4.7% BC and 5.6% NS (p=0.01)	14.3% BC and 15.4% NS (p=0.04)
Mortality				
In-hospital			1.4% BC and 1.6% NS (p=0.36)	
30-day hospital		13.8% BC and 15% NS (p=0.62)		10.3% BC and 11.1% NS (p=0.06)
60-day hospital		16.7% BC and 18.3% NS (p=0.53)		11.7% BC and 12.4% NS (p=0.13)
90-day hospital	7.6% BC and 8.6% NS (p=0.4)			
90-day ICU	6.6% BC and 7.2% NS (p=0.62)			
ICU-free days		21.1 BC and 21 NS (p=0.58)		21.8 BC and 21.7 NS (p=0.94)
Ventilator-free days		23.2 BC and 22.9 NS (p=0.85)		24.2 BC and 23.9 NS (p=0.22)
Vasopressor-free days		23.9 BC and 23.5 NS (p=0.78)		24.7 BC and 24.4 NS (p=0.26)
RRT-free days		24 BC and 23.7 NS (p=0.42)		25 BC and 24.8 NS (p=0.01)

Acute kidney injury, AKI; balanced crystalloid, BC; intensive care unit, ICU; major adverse kidney event within 30 days, MAKE30; normal saline, NS; renal replacement therapy, RRT

Young P, et al. *JAMA* 2015;314(16):1701-10.
Semler MW, et al. *Am J Respir Crit Care Med* 2017;195(10):1362-72.
Self WH, et al. *N Engl J Med* 2018;378(9):819-28.
Semler MW, et al. *N Engl J Med* 2018;378(9):829-39.

Adult Balanced Fluid Studies: Take Away Points

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- Likely benefit of balanced fluids in renal endpoints
  → Number needed to treat with balanced IVF
  SALT-ED trial = 111
  SMART trial = 94

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- No mortality benefit of balanced fluid over NS
- No impact on length of stay, ventilator or vasopressor-free days

Self WH, et al. *N Engl J Med* 2018;378(9):819-28.
Semler MW, et al. *N Engl J Med* 2018;378(9):829-39.

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Hyperchloremia in Critically Ill Children

Hypothesis	Hyperchloremia prior to CRRT initiation is independently associated with higher mortality	
Design	Single-center, retrospective	N = 66
Comparison	Chloride ≥ 110 mmol/L and < 110 mmol/L	39 patient (59%) vs 27 patients (41%)
Inclusion	PICU admission Age > 90 days to 25 years Required CRRT Jan 2008 – Dec 2016	Median age 12.5 years (4.1–17.1)
Primary Outcome	Hospital mortality	26 patients (67%) vs 6 patients (29%), p=0.006
Secondary Outcome	Duration of mechanical ventilation Hospital LOS Duration of RRT	Median 13 vs 8 days, p<0.0001 Median 27 vs 15 days, p=0.02 Median 7 to 6 days, p=0.01

Acute kidney injury, AKI; continuous renal replacement therapy, CRRT; length of stay, LOS; normal saline, NS; pediatric intensive care unit, PICU; renal replacement therapy, RRT

10.9 times greater odds of death with hyperchloremia (≥110 mmol/L)

Barhight MF, et al. *Pediatr Nephrol.* 2018;33(6):1079-85

Pediatric Experience with Balanced Fluids

Hypothesis	Resuscitation with balanced fluids is associated with improved outcomes compared with normal saline in pediatric sepsis	
Design	Multi-center, retrospective database review	N = 12,529
Comparison	NS (unbalanced fluid) and LR (balanced fluid)	NS-only = 10,379, LR-only = 459
Inclusion	< 18 years Admitted to PICU Jan 2000 – Dec 2013 Diagnosis of pediatric severe sepsis or septic shock	
Duration	3 days from hospital admission	
Primary Outcome	30-day hospital mortality	21 (4.6%) vs 23 (5%), p=0.69
Secondary Outcome	Presence of AKI PICU LOS Hospital LOS	49 (10.7%) vs 45 (9.8%), p=0.32 Median 5.5 vs 5.8 days, p=0.27 Median 10.5 vs 11.9 days, p=0.01

Acute kidney injury, AKI; continuous renal replacement therapy, CRRT; length of stay, LOS; lactated ringers, LR; normal saline, NS; pediatric intensive care unit, PICU

Weiss SL, et al. *J Pediatr* 2017; 182;304-10.

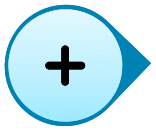
Pediatric Experience with Balanced Fluids

Objective	Evaluate outcomes in children receiving balanced fluids for resuscitation in pediatric sepsis	
Design	Multi-center, retrospective database review	N = 36,908
Comparison	NS (unbalanced fluid) and multiple electrolyte solutions (balanced fluid)	NS-only = 30,166 and MES-only = 2,398
Inclusion	< 18 years Admitted to PICU Jan 2004 – Dec 2012 Diagnosis of pediatric severe sepsis	Mean 7.4 and 5.5 years, p<0.001
Duration	72 hours from end of first bolus	
Primary Outcome	In-hospital mortality	15.9% vs 12.5%, p=0.007
Secondary Outcome	Prevalence of AKI CRRT use Vasoactive infusion days Hospital LOS	19.2% vs 16%, p=0.028 7.2% vs 5.4%, p=0.028 3.3 vs 3 days, p<0.001 18.1 vs 21 days, p<0.001

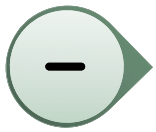
Acute kidney injury, AKI; continuous renal replacement therapy, CRRT; length of stay, LOS; multiple electrolyte solution, MES; normal saline, NS; pediatric intensive care unit, PICU

Emrath ET, et al. *Crit Care Med* 2017;. 45:1177-83.

Pediatric Balanced Fluid Studies: Take Away Points



- Large heterogeneous populations reviewed, few exclusions
- Hyperchloremia is likely not helpful
- Trend favoring balanced fluids for improved renal outcomes



- All retrospective studies
- Outcomes have not had consistent association favoring balanced fluids

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Patient Case #2 *Revisited*

18-month old, 12-kilogram, previously well child admitted to the PICU with acute hypoxic respiratory failure and septic shock.

Labs:

138	3.7	16
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Which is the best choice for an IV fluid bolus?

a. 5% Albumin
b. LR
c. 0.9% NaCl
d. Plasmalyte-A

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Summary and Final Thoughts

WHAT WE KNOW
Isotonic fluids are recommended mIVF for children to protect from hyponatremia
Unbalanced fluids have been associated with poor mortality and renal outcomes in children and adults
WHAT WE DO NOT KNOW
What is the best IVF in special populations? (i.e., CVICU, ECMO, neonates)
Will the widespread use of 0.9% NaCl for mIVFs increase clinically significant hyperchloremic metabolic acidosis?
Is there a true causation of balanced fluids and improvement of ICU-related outcomes in children?
Are isotonic-balanced solutions superior to 0.9% NaCl for the mIVF in the pediatric ICU?

Future study: PRoMPT BOLUS – Pragmatic pediatric trial of balanced versus normal saline fluid in sepsis: a pilot feasibility study
Sponsor: Children's Hospital of Philadelphia
Status: Active, not recruiting

Study information available at https://clinicaltrials.gov

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AAP POSITION PAPER

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