PRoMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

A research study information for the ACH Inpatient Units/PICU

Protocol: PRoMPT BOLUS-01

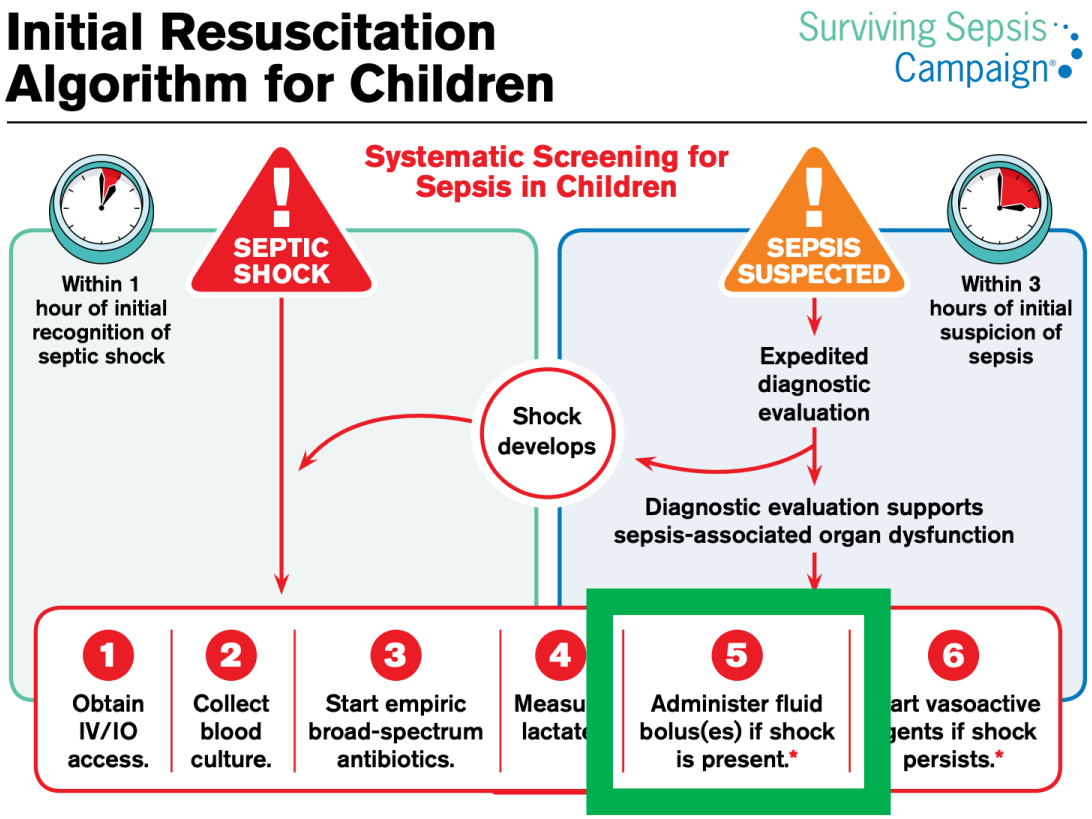
Protocol Version: 4.0, 17-May-2023

Sepsis…

…20-30 million patients are afflicted every year
…around 24 000 people die every day
…6 million children die every year in developing countries
…Sepsis is one of the most expensive conditions treated in North America

This international clinical trial will determine whether resuscitation with Balanced Fluids improves clinical outcomes in children with sepsis compared to resuscitation with Normal Saline.

Fluid boluses are a cornerstone of resuscitation in children presenting with suspected sepsis.



PCCM 2020 21(2):e52

Traditionally we use Normal Saline.

But really… which crystalloid is the best option?

0.9% NaCl PlasmaLyte Lactated Ringers

Balanced Fluids

Crystalloid Fluid Composition

	Blood	Normal Saline	Lactated Ringers	Plasma-Lyte
Na (mEq/L)	140	154	130	140
Cl (mEq/L)	100	154	109	98
K (mEq/L)	4	0	4	5
Ca (mEq/L)	5	0	2-3	0
Buffer	multiple	None	Lactate	Acet/Gluc
pH	7.4	5	6.5	7.4
SID	24	0	28	49
Osmolality	290	308	273	295

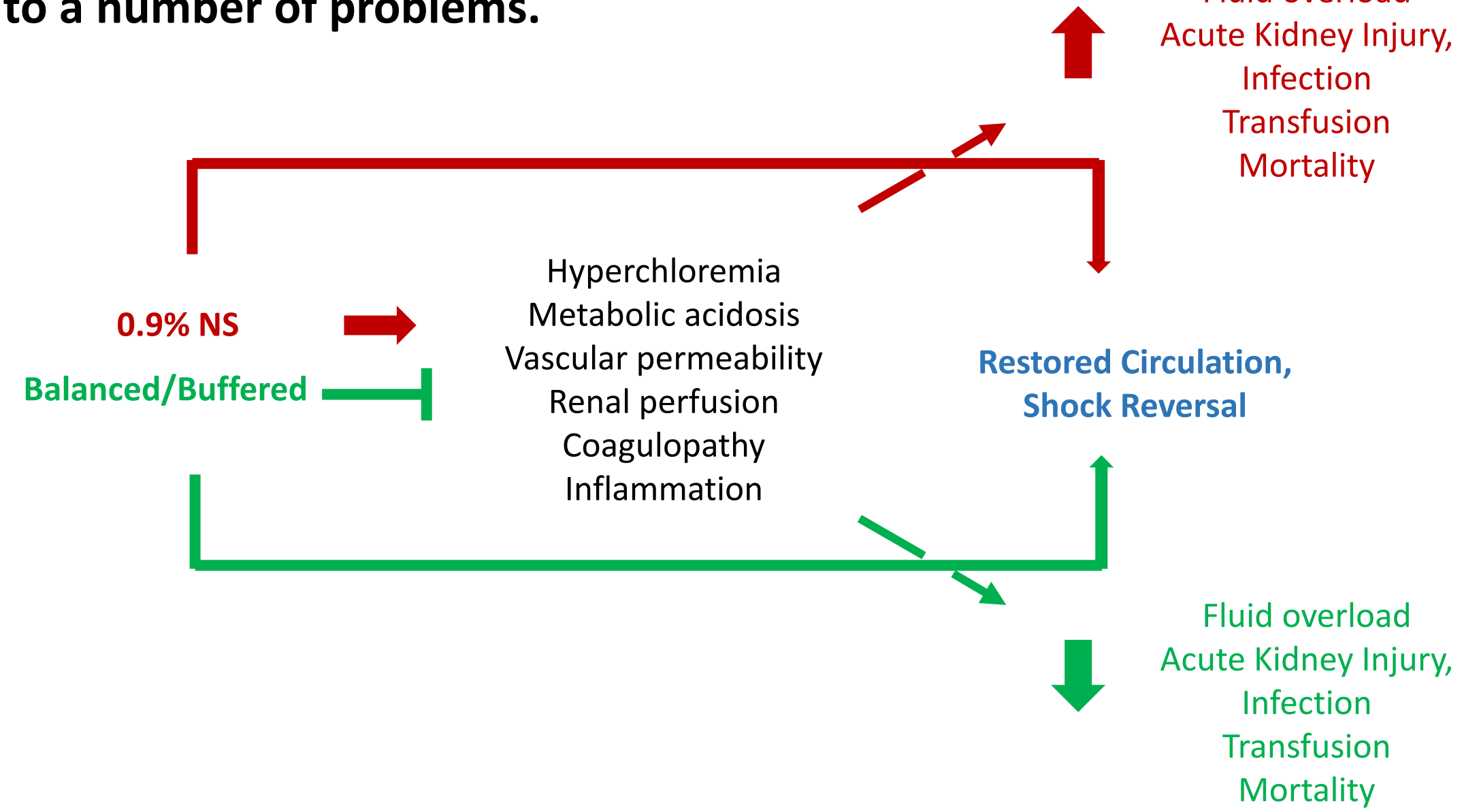
SID = Strong Ion Difference

If we compare Crystalloid Fluids to Blood we see some significant differences.

Particularly in the amount of Chloride, the pH and the Strong Ion Difference

Crit Care 2013; *JAMA* 2012

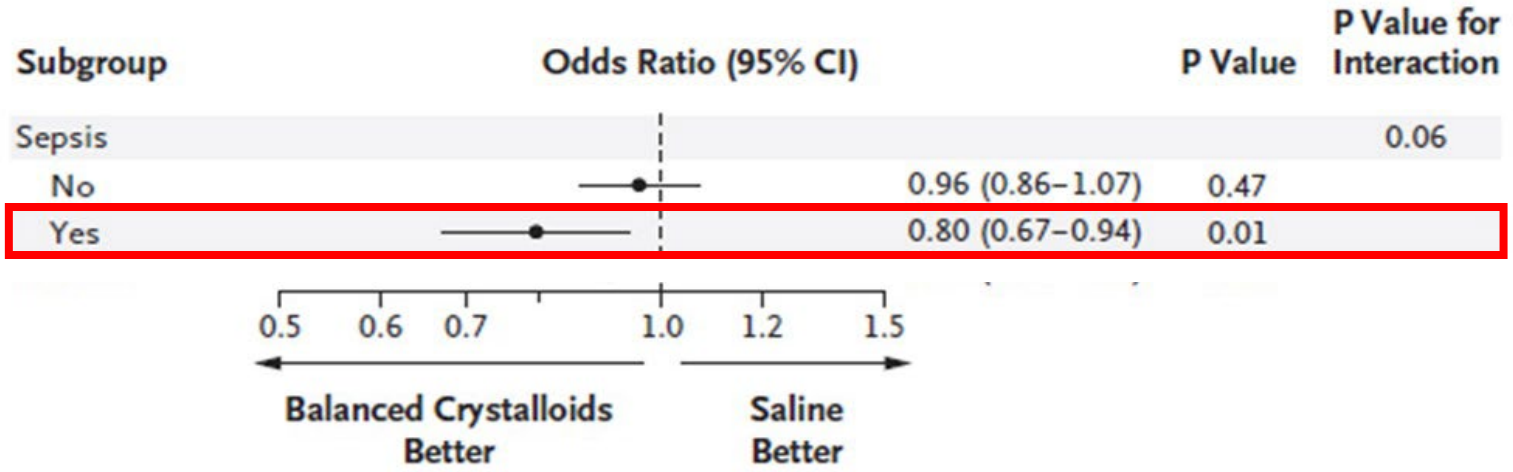
Excessive use of NaCl has the potential to lead to a number of problems.



ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Some studies in Adults have shown lower mortality rates in those treated with Balanced Fluids



NEJM 2018

Hyperchloremia is associated with acute kidney injury in pediatric patients with septic shock

Erin K. Stenson[1*], Natalie Z. Cvijanovich[2], Geoffrey L. Allen[3], Neal J. Thomas[4], Michael T. Bigham[5], Scott L. Weiss[6], Julie C. Fitzgerald[6], Parag N. Jain[7], Keith Meyer[8], Michael Quasney[9], Mark Hall[10], Rainer Gedeit[11], Robert J. Freishtat[12], Jeffrey Nowak[13], Riad Lutfi[14], Shira Gertz[15], Jocelyn R. Grunwell[16], Hector R. Wong[17] and Nick Anas[18]

Exposure	Outcome	aOR (95% CI)
Minimum Chloride **≥ 110 mmol/L**	Stage 2/3 AKI	2.4 (1.2-4.9)
Minimum Chloride **≥ 110 mmol/L**	Mortality	4.1 (2.1-8.1)

aOR – adjusted Odds Ratio

Septic children with higher chloride levels were more likely to have acute kidney injury (AKI) and more likely to die.

Ped Crit Care Med 2018

Crystalloid Fluid Choice and Clinical Outcomes in Pediatric Sepsis: A Matched Retrospective Cohort Study

Scott L. Weiss, MD, MSCE[1], Luke Keele, PhD[2], Fran Balamuth, MD, PhD, MSCE[3,4], Neika Vendetti, MPH[3], Rachael Ross, MPH[3], Julie C. Fitzgerald, MD, PhD[1], and Jeffrey S. Gerber, MD, PhD[3,5]

Resuscitation With Balanced Fluids Is Associated With Improved Survival in Pediatric Severe Sepsis*

Elizabeth T. Emrath, MD[1]; James D. Fortenberry, MD, MCCM[1,2]; Curtis Travers, MPH[3]; Courtney E. McCracken, PhD[3]; Kiran B. Hebbar, MD, FCCM[1,2]

BUT.....

2 large health record studies comparing children with sepsis who received
Normal Saline vs Balanced Fluids had conflicting results.

J Peds 2017

Crit Care Med 2017

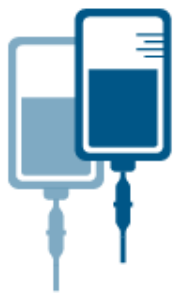
Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

Current Surviving Sepsis Campaign Guidelines State:

"We suggest balanced crystalloids, rather than 0.9% saline, for resuscitation of children with septic shock"
(weak recommendation, very low quality of evidence)

Balanced crystalloid vs 0.9% saline is a
knowledge gap and research opportunity

PCCM 2020
ICM 2020



PRoMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

Our Research Question

In children aged 2 months to < 18 years

presenting to the Emergency Department in septic shock,

does resuscitation with Balanced Fluids

improve clinical outcomes

compared to resuscitation with Normal Saline?

PRoMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

Study Summary

- **Design:** International pragmatic open-label RCT
- **Population:** Suspected septic shock, 2 mo to <18 yr
- **Setting:** Emergency Department (extension to wards, PICU)
- **Intervention:** Balanced Fluids (LR or PlasmaLyte) vs Normal Saline
- **1° outcome:** Major adverse kidney events (MAKE30)
- **Duration:** 4.5 years enrolment

PRoMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

perc
Pediatric Emergency Research Canada

PECARN

PREDICT
Paediatric Research in Emergency Departments International Collaborative

3 PEM Networks

4 Countries

8800 Participants

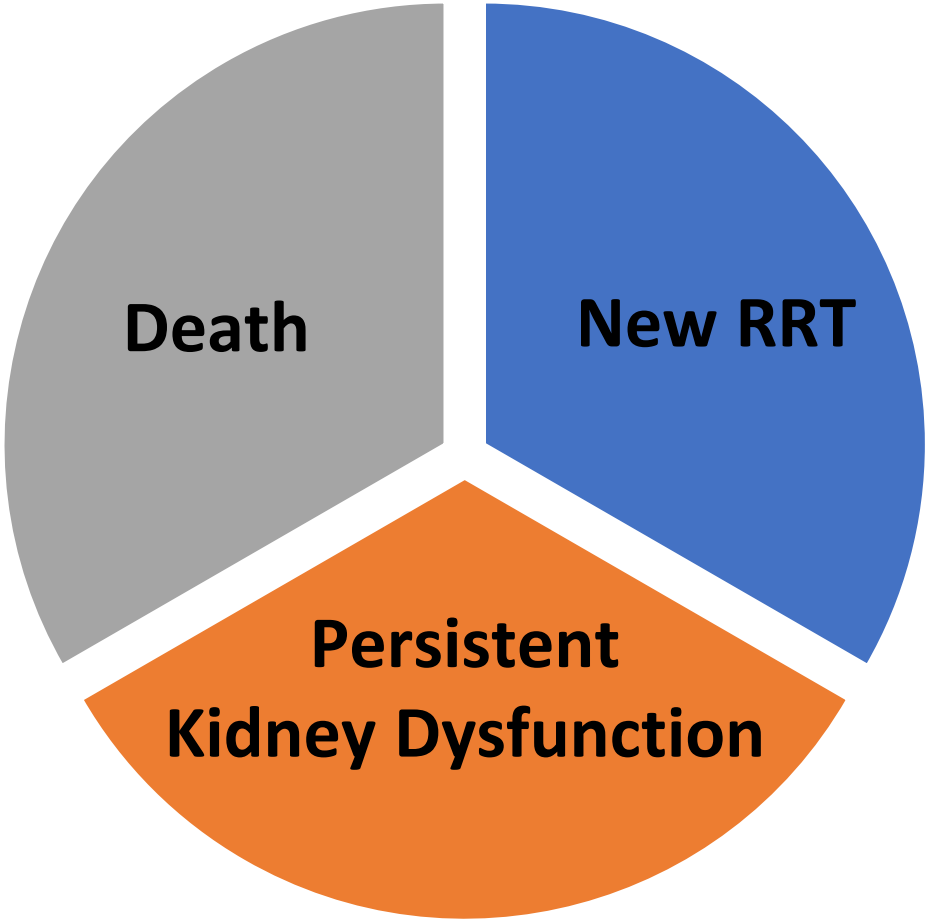
perc

Pediatric Emergency Research Canada

n= 2718

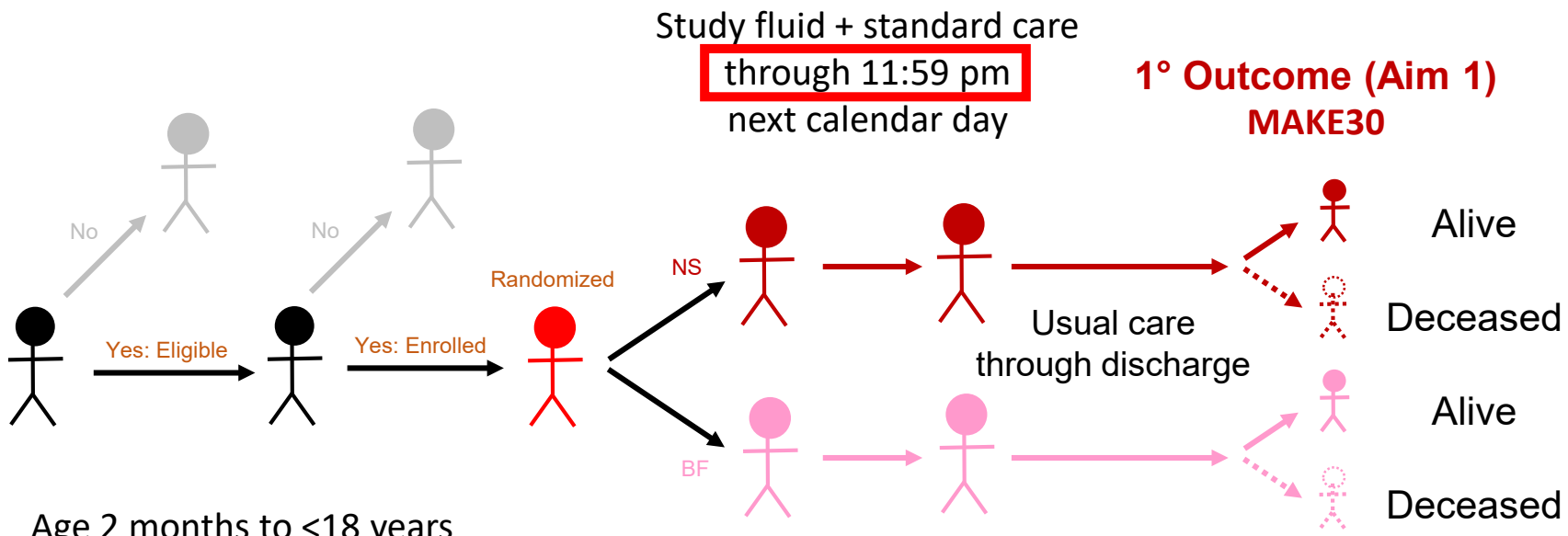
Primary Endpoint

Major Adverse Kidney Events within 30 days (MAKE30)



MAKE30 has been recommended by NIH as a patient-centred outcome for phase 3 clinical trials.

Study Design Overview



- Age 2 months to <18 years
- Suspected septic shock
  - Parenteral antibiotics
  - Blood culture
  - 20 mL/kg for abnormal perfusion or hypotension

  OR
  - Initiate sepsis pathway
  - Expect >1 fluid bolus

Observe for safety and efficacy outcomes (Aim 2)

Tri-Council Policy Statement

Ethical Conduct for Research Involving Humans

TCPS2 2018

Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada
Social Sciences and Humanities Research Council

Article 3.8 Consent for Research in Individual Medical Emergencies

(Deferred Consent)

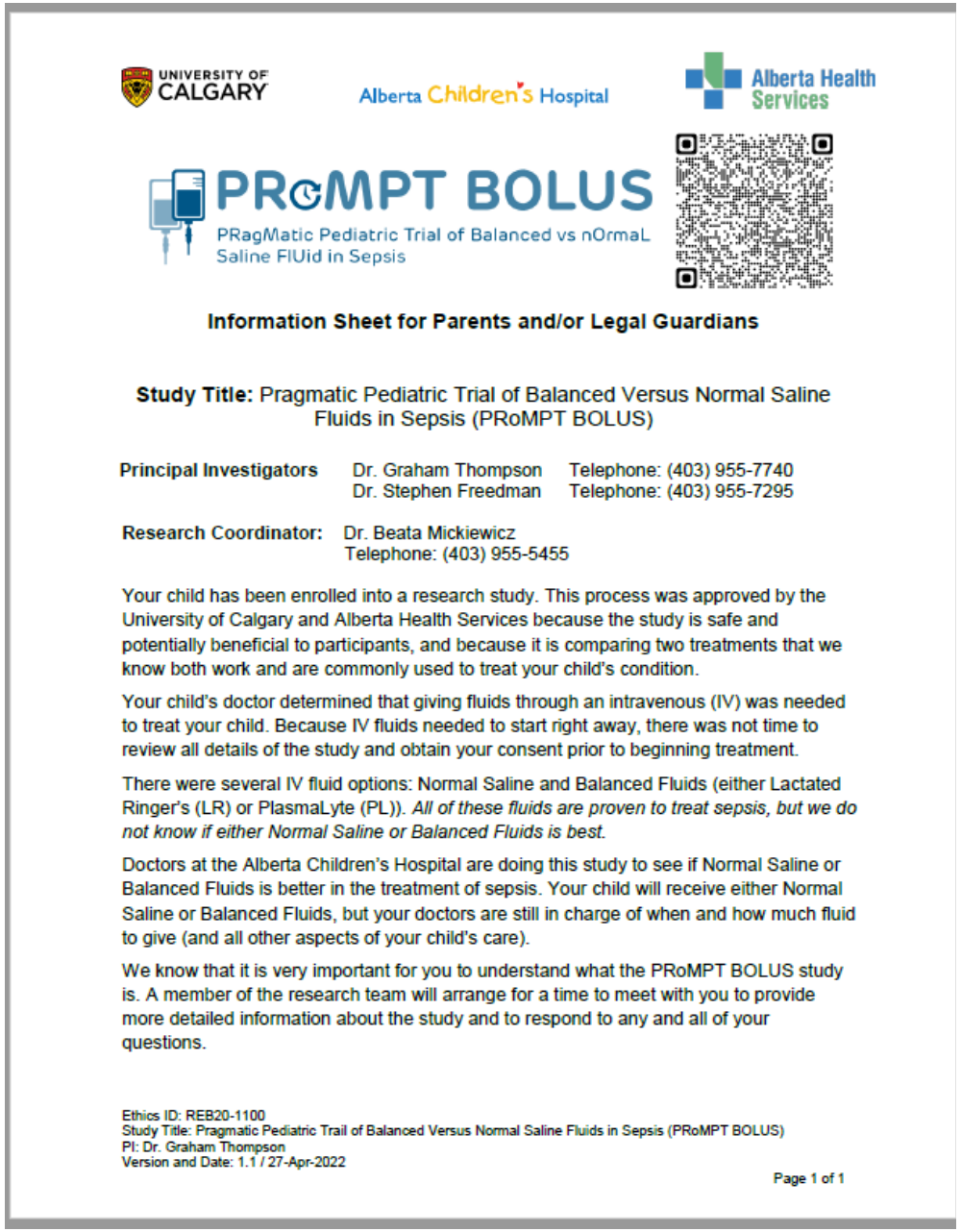
Deferred Consent

- Participant requires immediate intervention;
- No standard efficacious care exists OR research offers a realistic possibility of direct benefit
- Risk is not greater than standard efficacious care OR is clearly justified by the prospect for direct benefits
- Participant is unconscious or lacks capacity
- Third party authorization cannot be secured in sufficient time
- No relevant prior directive by the participant is known to exist.

PRoMPT BOLUS has been approved by our local Research Ethics Board to operate using Deferred Consent.

Caregiver Information Form

Given to Caregiver
by the ED Team.
Research Team will come
and talk with family.



UNIVERSITY OF CALGARY | Alberta Children's Hospital | Alberta Health Services

PRoMPT BOLUS
PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

Information Sheet for Parents and/or Legal Guardians

Study Title: Pragmatic Pediatric Trial of Balanced Versus Normal Saline Fluids in Sepsis (PRoMPT BOLUS)

Principal Investigators Dr. Graham Thompson Telephone: (403) 955-7740
Dr. Stephen Freedman Telephone: (403) 955-7295

Research Coordinator: Dr. Beata Mickiewicz
Telephone: (403) 955-5455

Your child has been enrolled into a research study. This process was approved by the University of Calgary and Alberta Health Services because the study is safe and potentially beneficial to participants, and because it is comparing two treatments that we know both work and are commonly used to treat your child's condition.

Your child's doctor determined that giving fluids through an intravenous (IV) was needed to treat your child. Because IV fluids needed to start right away, there was not time to review all details of the study and obtain your consent prior to beginning treatment.

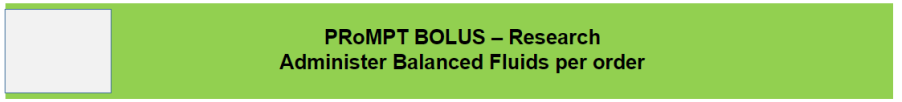
There were several IV fluid options: Normal Saline and Balanced Fluids (either Lactated Ringer's (LR) or PlasmaLyte (PL)). *All of these fluids are proven to treat sepsis, but we do not know if either Normal Saline or Balanced Fluids is best.*

Doctors at the Alberta Children's Hospital are doing this study to see if Normal Saline or Balanced Fluids is better in the treatment of sepsis. Your child will receive either Normal Saline or Balanced Fluids, but your doctors are still in charge of when and how much fluid to give (and all other aspects of your child's care).

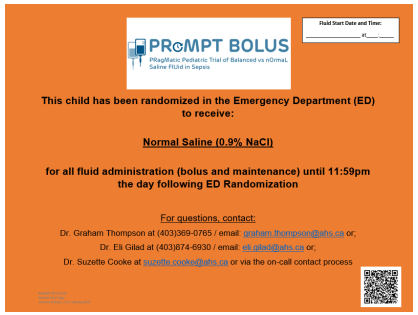
We know that it is very important for you to understand what the PRoMPT BOLUS study is. A member of the research team will arrange for a time to meet with you to provide more detailed information about the study and to respond to any and all of your questions.

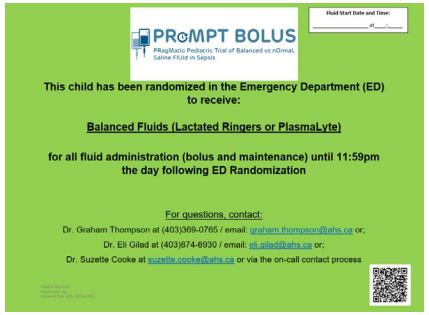
So what does all this mean for me?
(i.e. Inpatient/PICU Responsibilities)

1. Identify if your patient has been enrolled
2. Manage your patient!!
    - Allocated Fluids
    - Stopping Criteria
    - Other Clinical Care
3. Communication is key
    - Clinical teams
    - Study team

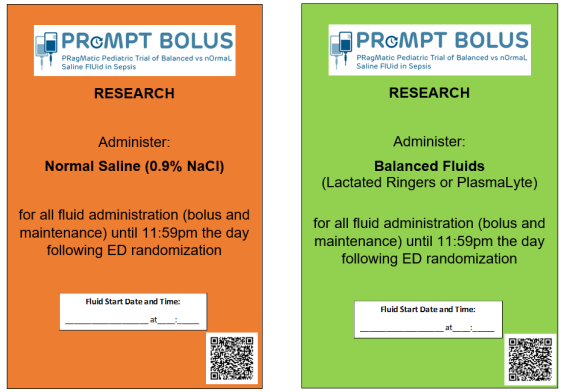


Participant Wrist Bands

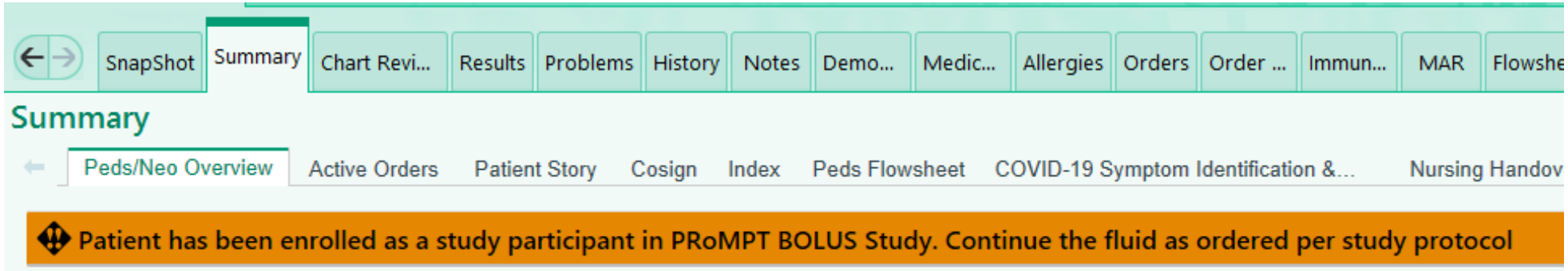




Inpatient Door Signs

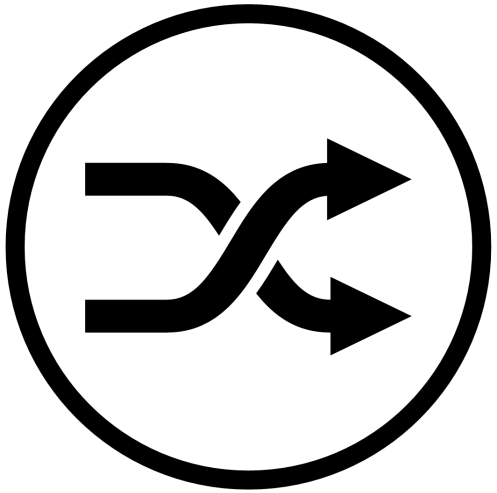


IV Pole Hang Tag



Study banner in Connect Care (Summary Peds/Neo Overview)

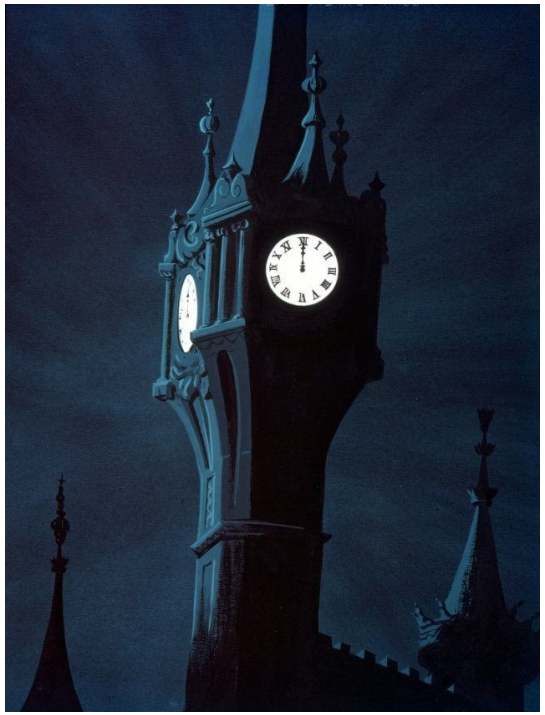
Study Intervention



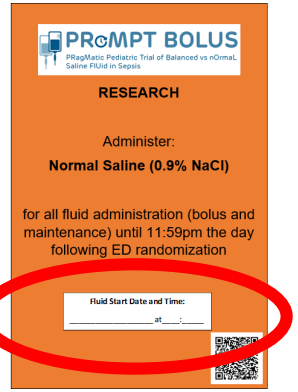
Randomization

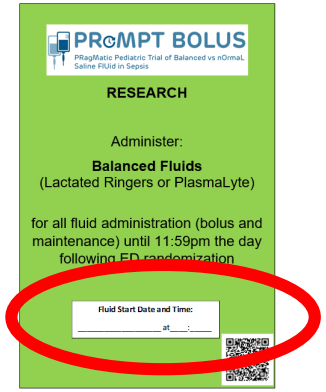
BF

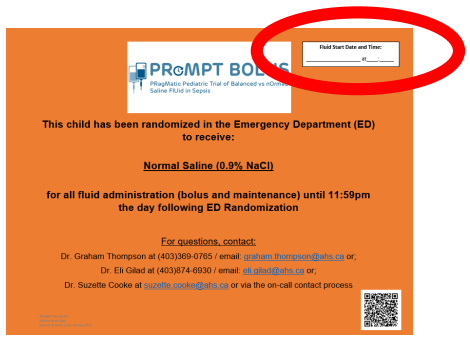
NS

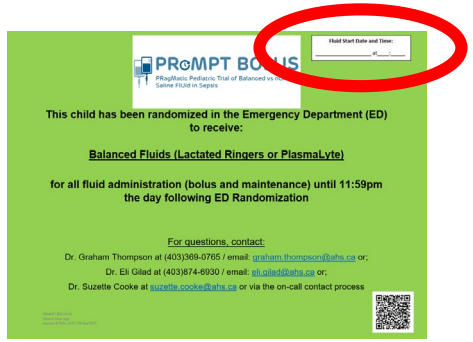


Midnight the day after randomization









Fluids Available for Use

Base	Solution	Location
0.9% NaCl (NS)	NS	ED/PICU/wards
	NS + 20KCl	ED/PICU/wards
	NS + 40KCl	ED/PICU/wards
	NS + 60KCl	Unit 4
	D5NS	ED/PICU/wards
	D5NS + 20KCl	ED/PICU/wards
	D12.5NS + 40KCl	Unit 4
	D12.5NS + 60KCl	Unit 4
	Other dextrose mixtures	Mix in ED^
Lactated Ringers (LR)	LR	ED/PICU/wards
	LR + 20KCl	PICU/Unit1/Unit2
	D5LR	PICU/OR
	(LR + 20KCl) + D5	Mix in ED^
PlasmaLyte (PL)	PL*	ED/PICU/wards

* AHS Pharmacy does not endorse additives to PL

^ IV Solution mixtures as per ED/PICU/Pharmacy policy.

What about Fluid Additives?

- Dextrose, K^+ etc. can be used as clinically indicated
- Available ACH stock bags are listed on the next slide.
- More complicated additives can be done using ACH PICU calculators

WARNING: Compatibilities

- Lactated Ringers is NOT compatible with the following items:
  - Ceftriaxone
  - Some Blood Products

- Please use a 2nd line if available. If not, exceptional IV flushing standards are vital.

- Please comply with all AHS compatibility protocols and procedures.

Stopping Criteria (for NS and BF)

Item	Definition
Hyperkalemia*	K^+ >6 mEq/L
Hypercalcemia*	Ca^{+2} >3 mmol/L *OR* iCa^{+2} >1.35 mmol/L
Severe hepatic impairment	ALT > 10 000 U/L *OR* total bilirubin >205 umol/L
Severe renal impairment	Urine output <0.5 ml/kg for 16 hrs (continuous) *OR* Initiation of new Renal Replacement Therapy
Hypersensitivity to allocated fluids	Based on managing clinical team

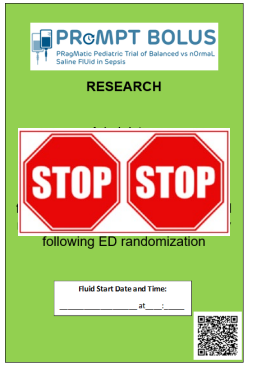
***confirmed by immediate retesting**

Stopping Criteria (for NS and BF)

Stopping Criteria stickers

If a child meets one of the Stopping Criteria, they are no longer required to receive the allocated study fluid. Manage the child at your discretion. However, the child is still a study participant and we need to collect safety data outcomes. Please follow the following steps:

1) Place a Stopping Criteria sticker (red sticker) on the child's wrist band and IV hang tag



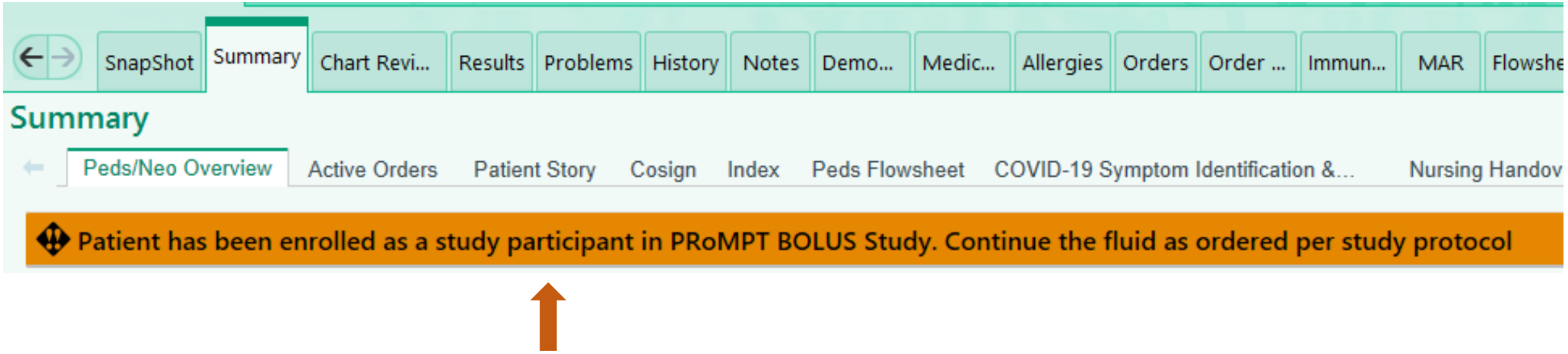
2) Notify the study team that the child had been enrolled but met stopping criteria

3) Place a note in Connect Care in the child's chart using the SmartPhrase **.PBSTOP**

Ongoing Care

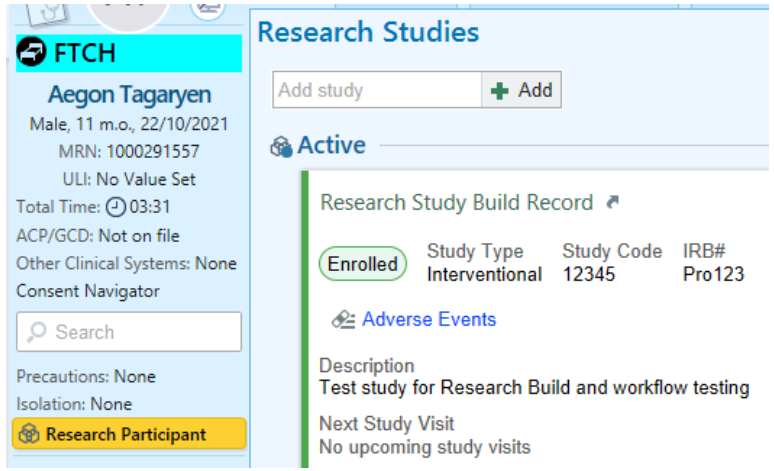
The timing and amount of fluids, use of antibiotics, vasoactive meds and all other care is at the discretion of the managing clinical team

Study Banner/Notification in Connect Care



1) A bright **orange** Banner located on Summary Peds/Neo Overview
   This is specific to PRoMPT BOLUS

2) A **yellow** Research Participant notification on the Story Board
   This is generic to all research study enrolments



These will stay in place during the intervention window (until 23:59 the day after randomization) after which they will disappear.

What do I do if I see the Study Banner?

- The Study Banner is a communication tool!
- It is there to remind you that the patient is on study.
- Ensure that the participant receives the allocated fluids for all future fluid boluses and maintenance (until midnight the day following randomization).

If you see other PRoMPT BOLUS identification items (coloured wristband, IV hangtag etc.), but nothing in Connect Care, that child <u>is still in the study.</u>

Communication is Key!!

- Inform consulting teams of study participation
- Inform accepting teams if any transfer of care (i.e PICU ⇢ Ward or Ward ⇢ PICU)
- Let the study team know when/where a participant is admitted
- Add PRoMPT BOLUS **Connect Care SmartPhrase** to clinical notes:
  - for NS arm use **.PBNS**
  - for BF arm use **.PBBF**

FLUIDS?

SEPSIS?

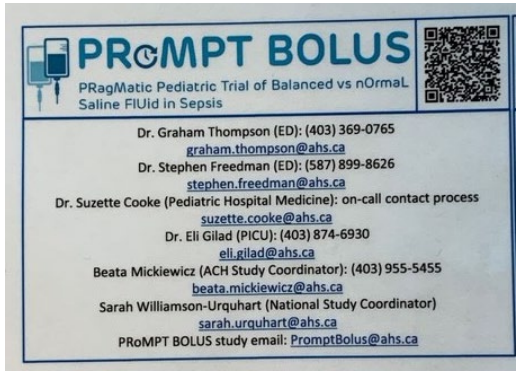
THINK

PRoMPT BOLUS

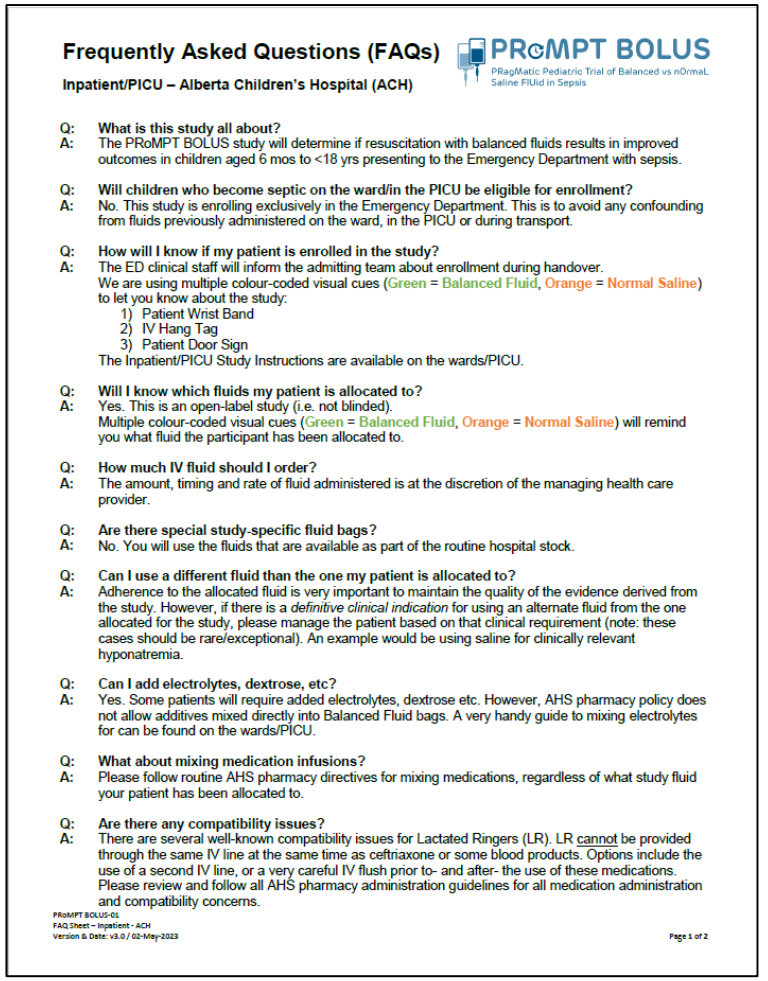
PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis

Found on all study documents

Study Summary
Eligibility Criteria
ED Study Information
Inpatient/PICU Study Information
Fluid Additives
Stopping Criteria
FAQ



PromptBolus@ahs.ca



Frequently Asked Questions (FAQs) — PRoMPT BOLUS (PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis)

Inpatient/PICU – Alberta Children's Hospital (ACH)

Q: What is this study all about?
A: The PRoMPT BOLUS study will determine if resuscitation with balanced fluids results in improved outcomes in children aged 6 mos to <18 yrs presenting to the Emergency Department with sepsis.

Q: Will children who become septic on the ward/in the PICU be eligible for enrollment?
A: No. This study is enrolling exclusively in the Emergency Department. This is to avoid any confounding from fluids previously administered on the ward, in the PICU or during transport.

Q: How will I know if my patient is enrolled in the study?
A: The ED clinical staff will inform the admitting team about enrollment during handover.
We are using multiple colour-coded visual cues (Green = Balanced Fluid, Orange = Normal Saline) to let you know about the study:
1) Patient Wrist Band
2) IV Hang Tag
3) Patient Door Sign
The Inpatient/PICU Study Instructions are available on the wards/PICU.

Q: Will I know which fluids my patient is allocated to?
A: Yes. This is an open-label study (i.e. not blinded).
Multiple colour-coded visual cues (Green = Balanced Fluid, Orange = Normal Saline) will remind you what fluid the participant has been allocated to.

Q: How much IV fluid should I order?
A: The amount, timing and rate of fluid administered is at the discretion of the managing health care provider.

Q: Are there special study-specific fluid bags?
A: No. You will use the fluids that are available as part of the routine hospital stock.

Q: Can I use a different fluid than the one my patient is allocated to?
A: Adherence to the allocated fluid is very important to maintain the quality of the evidence derived from the study. However, if there is a *definitive clinical indication* for using an alternate fluid from the one allocated for the study, please manage the patient based on that clinical requirement (note: these cases should be rare/exceptional). An example would be using saline for clinically relevant hyponatremia.

Q: Can I add electrolytes, dextrose, etc?
A: Yes. Some patients will require added electrolytes, dextrose etc. However, AHS pharmacy policy does not allow additives mixed directly into Balanced Fluid bags. A very handy guide to mixing electrolytes for can be found on the wards/PICU.

Q: What about mixing medication infusions?
A: Please follow routine AHS pharmacy directives for mixing medications, regardless of what study fluid your patient has been allocated to.

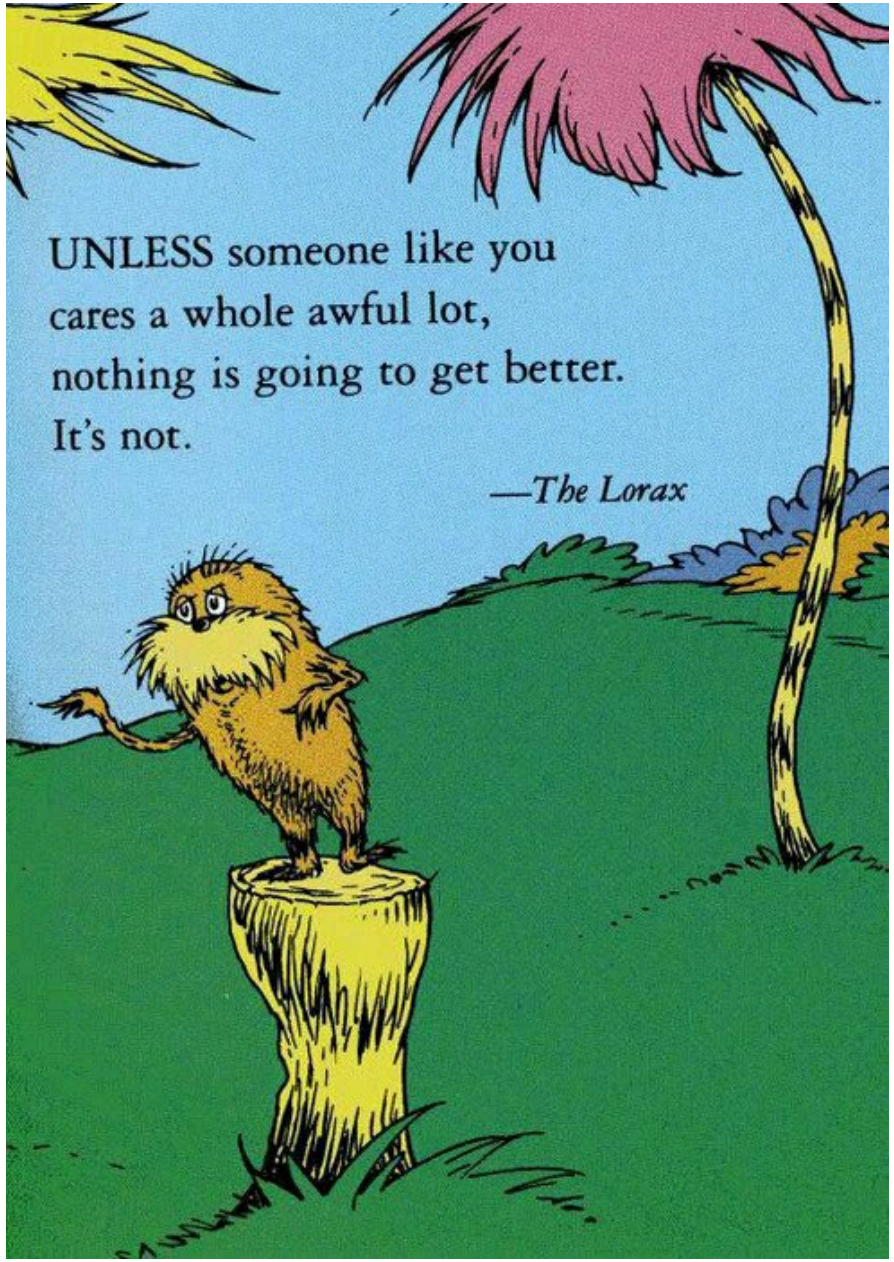
Q: Are there any compatibility issues?
A: There are several well-known compatibility issues for Lactated Ringers (LR). LR cannot be provided through the same IV line at the same time as ceftriaxone or some blood products. Options include the use of a second IV line, or a very careful IV flush prior to- and after- the use of these medications. Please review and follow all AHS pharmacy administration guidelines for all medication administration and compatibility concerns.

PRoMPT BOLUS-01
FAQ Sheet – Inpatient - ACH
Version & Date: v3.0 / 02-May-2023
Page 1 of 2

☐ Any questions, please contact
- **Dr. Graham Thompson** at **(403) 369-0765** / graham.thompson@ahs.ca
- Study team pager (Mon-Fri, 10:00-17:00): **#11316**

Contact Information

- Dr. Graham Thompson at **(403) 369-0765** graham.thompson@ahs.ca
- **Dr. Eli Gilad** at **(403) 874-6930** eli.gilad@ahs.ca
- **Dr. Suzette Cooke** at suzette.cooke@ahs.ca or via the on-call contact process
- Study team pager (Mon-Fri, 10:00-17:00): **#11316**
- Study email: PromptBolus@ahs.ca



The Lorax, Dr. Seuss

Anticipated Impact

1,275 fewer cases of MAKE30

242 fewer cases of CKD

50 fewer deaths

$35 million less in health care costs

US estimates

Weiss, Balamuth et al *CJASN* 2019

Acknowledgements

perc
Pediatric Emergency Research Canada

PECARN

PREDICT

PALISI
Pediatric Acute Lung Injury & Sepsis Investigators

ANZICS

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

NIH
NICHD

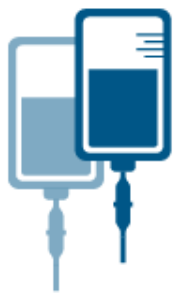
NHMRC

BUILDING A HEALTHY AUSTRALIA

Alberta Children's Hospital Research Institute

HC6-24-c251146
NCT04102371


CAN'T DO IT
WITHOUT YOU



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