Title:

Fluid resuscitation therapy for paediatric sepsis

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Abstract:

Sepsis and septic shock are the final common pathway for many decompensated paediatric infections. Fluid resuscitation therapy (FRT) has been the cornerstone of haemodynamic resuscitation in these children. Good evidence for equivalence between 0.9% saline and 4 % albumin, with the relative expense of the latter, has meant that 0.9% saline is currently the most commonly used resuscitation fluid worldwide. Evidence for harm from the chloride load in 0.9% saline has generated interest in balanced solutions as first line resuscitation fluids. Their safety has been well established in observational studies, and they may well be the most reasonable default fluid for resuscitation. Semi-synthetic colloids have been associated with renal dysfunction and death, and should be avoided. There is evidence for harm from excessive administration of any resuscitation fluid. Resuscitation fluid volumes should be treated in the same way as the dose of any other intravenously administered medication, and the potential benefits versus harms for the individual patient weighed prior to administration.

Key words: fluid resuscitation, sepsis, child, crystalloid, colloid

Key points:

1. The type and volume of fluid resuscitation therapy administered for paediatric sepsis are directly linked to patient outcome.

2. Balanced salt solutions may be the safest option for fluid resuscitation therapy.
3. The volume of fluid resuscitation therapy should be carefully titrated to avoid harms associated from overzealous administration.

Historical Background:

Intravenous fluid administration to human beings was first described by British physician Thomas Latta in 1832. He administered an alkalised salt solution to adults with severe cholera (1). In Latta's account, he 'proceeded with much caution, injecting ounce by ounce of fluid, closely observing the patient' (one ounce of fluid is 29.6ml).

In 1885, British physiologist Sidney Ringer discovered that experimental animal hearts maintained their function for a longer time when his laboratory assistant replaced distilled water with tap-water. Ringer's solution contained small amounts of calcium and potassium in addition to sodium and chloride. The solution was subsequently modified by American paediatrician Alexis Hartmann through the addition of sodium lactate and used to treat children with severe gastroenteritis. In 1882, Dutch physiologist Hartog Hamburger developed a 0.9% salt solution for in vitro use in experiments on red cell lysis. His postulation that 0.9% saline was isotonic with human plasma was in fact incorrect, with the correct tonicity of plasma resembling that of 0.6% saline. The development of blood fractionation in 1941 led to the use of human albumin as a resuscitative fluid for the first time in the attack on Pearl Harbour during World War II. Subsequently, cost and the limited supply of

human albumin have led to the development of multiple semisynthetic colloids that are either starch or gelatin based (2). Plasmalyte 148[®] is a balanced crystalloid solution designed to have similar osmolality and electrolyte composition to human plasma. It contains no calcium and is therefore safe for co-administration with most drugs and citrated blood products (2).

Pathophysiology:

The rationale for bolus administration of resuscitation fluid in sepsis is to increase cardiac output and vital organ perfusion. From a physiological point-of-view, this occurs through a series of steps. Fluid bolus administration into the systemic venous circulation increases the total volume of this vascular compartment (total venous volume). The component of total venous volume that contributes to venous return is the stressed volume (figure 1).

This volume generates transmural pressure that, when greater than right atrial pressure, leads to flow of venous blood into the right atrium. The relationship between right atrial pressure and venous return is depicted graphically as the Guyton Venous Return curve. Increased venous return following fluid bolus administration increases cardiac output through the Frank-Starling effect (depicted graphically as the Frank-Starling curve), as venous return must be equal to cardiac output. Preload, for which right atrial pressure is a surrogate, plays a pivotal role in the cardiac response to fluid bolus administration. It opposes venous return while at the same time increasing

cardiac output. This tension is depicted graphically as the intersection of the Guyton Venous Return curve and the Frank-Starling curve (figure 2) (3).

The determinants of the position and slope of the Guyton venous return curve are venous compliance, blood viscosity, and right atrial pressure. For the Frank-Starling curve they are preload, cardiac contractility, and afterload. In children, septic myocardial dysfunction may result in flattening of the Frank-Starling curve and limited preload responsiveness (4-6).

The theoretical premise supporting FRT for sepsis is that cardiac output is inadequate to maintain vital organ perfusion, and that fluid bolus administration will improve vital organ perfusion (microcirculatory resuscitation) by increasing cardiac output (macrocirculatory resuscitation). There is experimental, adult, and paediatric evidence, however, that in sepsis, cardiac output and vital organ perfusion may be elevated (7, 8), that oxygen delivery and metabolism may not be impaired (9, 10), and that macrocirculatory resuscitation may not normalise microcirculatory function (11, 12). It is therefore possible that the rationale for the use of FRT for sepsis is fundamentally flawed, and that excessive FRT may contribute to end-organ dysfunction through tissue oedema and metabolic effects (13).

Fluid Content:

Fluid types used for FRT in sepsis are broadly categorised as crystalloids or colloids. Crystalloids can be further divided into isotonic (0.9% saline), compounded sodium

lactate (Ringers lactate, Hartmann's solution), and balanced solutions (eg- Plasmalyte®), depending on their chloride content and primary buffer (lactate, acetate, or gluconate) (table 1). Colloids are suspensions of high molecular weight proteins in a carrier (crystalloid) solution. The two main types are albumin and semi-synthetic colloids. Colloids are purported to have a volume sparing effect, with a described ratio of 1:3 compared to crystalloids to achieve the same haemodynamic goals (2), but are expensive and semi-synthetic colloids require metabolism prior to excretion. In systematic reviews of randomised comparative trials, neither 0.9% saline nor albumin has been shown to confer a survival advantage over the other in critical illness (including sepsis) in children or adults (14, 15). Furthermore, the volumes of colloid actually used for FRT have been found to be comparable to volumes of crystalloid (with an actual ratio of 1:1.4) (16). This may result from compromised vascular integrity due to damage to the endothelial glycocalyx in sepsis, altering fluid movement across semi-permeable membranes as described in the classic Starling model (17). Semi-synthetic colloids have been shown to increase the risk of acute kidney injury and death when compared to crystalloids (18, 19), and therefore are no longer recommended for FRT. Importantly, the use of 0.9% saline as a resuscitative fluid has its own risk profile. It contains supra-physiological levels of sodium and chloride, and can lead to hyperchloraemic metabolic acidosis through the strong ion effect (20, 21). This has been associated with damage to the endothelial glycocalyx, which may worsen capillary leak, resulting in pulmonary, renal, and myocardial oedema and dysfunction (22). Hyperchloraemia is thought to contribute to renal

dysfunction, acute kidney injury (AKI), and requirement for renal replacement therapy (RRT) (23, 24), and has been independently associated with death in adult ICU patients (25) independent of total volume of fluid received (26). This has led to interest in the use of balanced solutions as resuscitative fluids (23, 27-29).

Observational studies of FRT comparing 0.9% saline with balanced solutions show worse outcome using solutions with supra-physiological chloride concentration (23, 28). Initial randomised trials of low volume balanced versus isotonic crystalloids as maintenance fluids in relatively well adult ICU patients, however, have not shown a difference in subsequent development of renal failure (30). [Head-to-head trials of isotonic versus balanced crystalloids in unwell children and adults using mortality as a primary outcome are underway.](#) Published international consensus statements support the use of balanced solutions in preference to 0.9% saline for adults with acute illness (31). Current published paediatric sepsis guidelines do not advocate the use of one resuscitative fluid over another (32-34).

[Recommendation: Given that 0.9% saline was not originally intended for use in vivo, that it is not physiological or “normal”, that its use has been associated with iatrogenic adverse outcomes, and that safe alternatives exists, it seems reasonable to shift to the use of balanced solutions as a default resuscitation fluid pending the results of externally valid comparative trials.](#)

Fluid Volume:

No clinical trials in humans have used fluid volume as a treatment variable for resuscitation. Large observational studies in critically ill adults have demonstrated the best survival was associated with the administration of a mean volume of 3.2L of FRT, equating to ~45ml/kg (35). Some paediatric guidelines suggest using 40-60 ml/kg of FRT, with up to 200ml/kg in some patients (32). The patient group that may benefit from large volume FRT has not been defined. These guidelines have informed the Surviving Sepsis Campaign paediatric bundle (33) and are the basis for Advanced Paediatric Life Support (APLS) teaching. More recently, the International Liason Committee on Resuscitation (ILCOR) published a guideline advocating an initial bolus of 20ml/kg for children with sepsis, followed by frequent patient re-assessment (34). The use of fluid resuscitation for febrile illness' with associated poor perfusion is discouraged.

Using physiological principles, it seems logical in the face of continued haemodynamic instability to continue fluid resuscitation while still on the ascending portion of the Frank-Starling curve. This is termed fluid (or preload) responsiveness, and theoretically is less likely to result in interstitial oedema compared to administering FRT when on the flat portion of the Frank-Starling curve. In the early stages of resuscitation in spontaneously ventilating children without invasive monitoring (where the majority of FRT occurs), it can be challenging to determine fluid responsiveness. In adults, the passive leg raise (PLR) delivers an auto-transfusion of venous blood pooled in the legs, which can be "withdrawn" when the

legs are laid flat, and has excellent test characteristics in predicting fluid responsiveness, with a pooled area under the receiver operating characteristics curve (AUC) of 0.95 (95% confidence interval 0.92-0.97) (36). An alternative approach is to administer an intravenous fluid challenge and monitor the response in terms of change in cardiac output. There is, however, no consensus definition for what constitutes fluid responsiveness in adults or children, and the use of a reversible fluid challenge in the form of PLR in children is limited by the relatively small size of their legs. The use of a fluid-responsiveness based resuscitative strategy for sepsis has recently been described in adults (37), and awaits study in larger trials. [The validation of several non-invasive cardiac output monitors in children may pave the way for similar trials in a younger age group \(38-40\).](#)

FRT volumes administered for sepsis are based historically on the results of several studies. Over a decade ago, Rivers popularised early and aggressive initial fluid resuscitation as a component of early goal-directed therapy (EGDT) in septic adults (41). This approach was mirrored in paediatric consensus based guidelines (42), citing single-centre observation evidence. Over the following decade, consistent evidence for harm from overzealous FRT accumulated in children and adults. Large volume FRT and a positive net fluid balance have been associated with worsening renal function, acute respiratory distress syndrome (ARDS), prolonged ICU and hospital length of stay, and mortality when corrected for disease severity (35, 43-49).

The Fluid Expansion as Supportive Therapy (FEAST) trial raised serious questions about the safety of aggressive FRT in children (50). This randomised controlled trial in Sub-Saharan Africa compared mortality at 48 hours with FRT versus maintenance fluid only in children with acute febrile illness and associated poor perfusion. This is the only study of FRT for sepsis to include a control arm (no fluid bolus). The key finding was that mortality was higher in the group receiving FRT compared to no FRT (10.5% with fluid bolus, 7.3% standard maintenance fluid). The majority (87%) of these deaths occurred within 24 hours of randomisation. Many contextual factors need to be taken into account when interpreting the results of the FEAST study, including the heterogeneous patient population, entry criteria (only 2% of children met the WHO definition of shock, most others had lesser degrees of poor perfusion), the presence of severe malarial anaemia in >50% of patients, the inclusion of patients with respiratory or neurological compromise prior to randomisation (who might be harmed by fluid bolus therapy), as well as the study setting (where no positive pressure ventilation, diuretics, or inotropes were available). However, in the population studied, the authors could identify no patient subgroup who benefited from FRT, based on intention to treat and partly based on post hoc analyses (51). In addition, there was a dose effect, with more FRT administered being associated with higher mortality. Systematic reviews and meta-analyses of mortality following fluid bolus administration in children with sepsis have been driven by the results of the FEAST trial, with the majority of all randomised evidence pointing to FRT being harmful when compared to no FRT (52).

Recommendation: All resuscitation fluids can contribute to organ oedema and dysfunction, and fluid balance may be more important than fluid type (31). The ideal volume for FRT in the individual patient, and a method for determining this volume, has yet to be elucidated. In the interim, caution with large volume fluid resuscitation (>40ml/kg) is warranted.

Therapeutic targets:

Current guidelines suggest titrating fluid resuscitation to improving cold extremities, central capillary refill, peripheral pulse character, and conscious state (32, 33). These vital signs have, however, been shown to have limited value in predicting illness severity or response to treatment (53-55). Indeed in a systematic review of FRT in adult sepsis, the median reduction in heart rate immediately post bolus was 2 beats per minute (56). The poor performance characteristics of clinical examination are further compounded by the heterogenous and dynamic cardiovascular response to sepsis in children (4-6), and variability in haemodynamic response to fluid resuscitation (57). Validated therapeutic targets used in adult sepsis resuscitation include achieving a mean arterial blood pressure (MAP) >65 and lactate clearance >10% (33, 58, 59). Blood pressure is not used to define sepsis in children, and no age-based lower limit for mean arterial blood pressure associated with adverse outcome has been established in children. This makes the use of blood pressure as a therapeutic target problematic. The role of serum lactate in screening for paediatric sepsis has not yet been established (60), and its utility in monitoring for response to treatment has not been

studied. Harms from fluid bolus therapy (such as pulmonary or cerebral oedema) are also monitored by using clinical examination findings (rales, hepatomegaly, and conscious state) (32, 33). It remains unclear, however, at what stage during fluid resuscitation these clinical signs develop. If they are late signs of fluid overload, their use as a stop point for FRT may result in systematic over-resuscitation, with its inherent associated harms.

Non-invasive methods for measuring end-organ perfusion may provide valuable targets for sepsis resuscitation in the future. Direct visualisation of sub-lingual microcirculation using sidestream dark field microscopy and analysis of tissue oxygen saturation using near-infrared spectroscopy are currently being evaluated as targets for sepsis resuscitation. Bedside ultrasound may be another tool for dynamic monitoring and titration of fluid resuscitation in sepsis. It may allow rapid evaluation of cardiac function, response to a fluid challenge, and monitoring for the development of early signs of harm from fluid resuscitation through examination of the heart, lungs, and inferior vena cava (IVC) (5, 61-63). Whether this is superior to clinical acumen in deciding when and how much fluid to give paediatric patients is yet to be determined (64).

Recommendation: Clinical signs are the current standard for monitoring response to fluid resuscitation in children (65), though they may not accurately reflect volume status. Research into appropriate therapeutic targets for paediatric sepsis and valid methods for measuring them are needed.

Conclusion:

Fluid resuscitation for sepsis and septic shock in children remains a widely and commonly used intervention, despite evidence for harm from this practice in some settings. Differences in efficacy between resuscitation fluids may be modest, but differences in safety are significant (31). The words of Dr Thomas Latta are as true today as when they were originally published over 180 years ago. When administering resuscitation fluids, we should proceed with much caution, injecting ounce by ounce of fluid, closely observing the patient.

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References:

1. Cosnett JE. The origins of intravenous fluid therapy. *Lancet*. 1989;1(8641):768-71.
2. Myburgh JA, Mythen MG. Resuscitation fluids. *The New England journal of medicine*. 2013;369(25):2462-3.
3. Henderson WR, Griesdale DE, Walley KR, Sheel AW. Clinical review: Guyton--the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Critical care (London, England)*. 2010;14(6):243.
4. Deep A, Goonasekera CD, Wang Y, Brierley J. Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. *Intensive care medicine*. 2013;39(9):1602-9.
5. Ranjit S, Aram G, Kissoon N, Ali MK, Natraj R, Shresti S, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study*. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2014;15(1):e17-26.
6. Brierley J, Peters MJ. Distinct hemodynamic patterns of septic shock at presentation to pediatric intensive care. *Pediatrics*. 2008;122(4):752-9.
7. Di Giantomasso D, May CN, Bellomo R. Vital organ blood flow during hyperdynamic sepsis. *Chest*. 2003;124(3):1053-9.
8. Schiffmann H, Erdlenbruch B, Singer D, Singer S, Herting E, Hoeft A, et al. Assessment of cardiac output, intravascular volume status, and extravascular lung water by transpulmonary indicator dilution in critically ill neonates and infants. *Journal of cardiothoracic and vascular anesthesia*. 2002;16(5):592-7.
9. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *Jama*. 1992;267(11):1503-10.
10. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *Jama*. 1993;270(14):1724-30.
11. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004;32(9):1825-31.

12. Dubin A, Pozo MO, Casabella CA, Palizas F, Jr., Murias G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care*. 2009;13(3):R92.
13. Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. *Critical care (London, England)*. 2012;16(1):302.
14. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *The Cochrane database of systematic reviews*. 2013;2:Cd000567.
15. Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *BMJ (Clinical research ed)*. 2010;341:c4416.
16. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *The New England journal of medicine*. 2004;350(22):2247-56.
17. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovascular research*. 2010;87(2):198-210.
18. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *The New England journal of medicine*. 2012;367(20):1901-11.
19. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *The New England journal of medicine*. 2012;367(2):124-34.
20. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90(5):1265-70.
21. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. *Critical care medicine*. 2011;39(11):2419-24.
22. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. *Critical care (London, England)*. 2010;14(4):226.
23. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *Jama*. 2012;308(15):1566-72.
24. Wilcox CS. Regulation of renal blood flow by plasma chloride. *The Journal of clinical investigation*. 1983;71(3):726-35.
25. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. *Journal of critical care*. 2011;26(2):175-9.
26. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkievicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive care medicine*. 2014;40(12):1897-905.
27. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal

- surgery: 0.9% saline compared to Plasma-Lyte. *Annals of surgery*. 2012;255(5):821-9.
28. Raghunathan K, Shaw A, Nathanson B, Sturmer T, Brookhart A, Stefan MS, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Critical care medicine*. 2014;42(7):1585-91.
29. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Annals of internal medicine*. 2014;161(5):347-55.
30. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *Jama*. 2015;1-10.
31. Raghunathan K, Murray PT, Beattie WS, Lobo DN, Myburgh J, Sladen R, et al. Choice of fluid in acute illness: what should be given? An international consensus. *British journal of anaesthesia*. 2014;113(5):772-83.
32. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Critical care medicine*. 2009;37(2):666-88.
33. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical care medicine*. 2013;41(2):580-637.
34. Maconochie IK, de Caen AR, Aickin R, Atkins DL, Biarent D, Guerguerian AM, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e147-e68.
35. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Critical care medicine*. 2011;39(2):259-65.
36. Cavallaro F, Sandroni C, Marano C, La Torre G, Mannocci A, De Waure C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive care medicine*. 2010;36(9):1475-83.
37. Richard JC, Bayle F, Bourdin G, Leray V, Debord S, Delannoy B, et al. Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. *Crit Care*. 2015;19(1):5.
38. Cote CJ, Sui J, Anderson TA, Bhattacharya ST, Shank ES, Tuason PM, et al. Continuous noninvasive cardiac output in children: is this the next generation of operating room monitors? Initial experience in 402 pediatric patients. *Paediatr Anaesth*. 2015;25(2):150-9.
39. Garisto C, Favia I, Ricci Z, Romagnoli S, Haiberger R, Polito A, et al. Pressure recording analytical method and bioreactance for stroke volume index monitoring during pediatric cardiac surgery. *Paediatr Anaesth*. 2015;25(2):143-9.

40. Beltramo F, Menteer J, Razavi A, Khemani RG, Szmuszkovicz J, Newth CJ, et al. Validation of an Ultrasound Cardiac Output Monitor as a Bedside Tool for Pediatric Patients. *Pediatr Cardiol*. 2015.
41. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *The New England journal of medicine*. 2001;345(19):1368-77.
42. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Critical care medicine*. 2002;30(6):1365-78.
43. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2012;13(3):253-8.
44. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Critical care medicine*. 2004;32(8):1771-6.
45. Rosenberg AL, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *Journal of intensive care medicine*. 2009;24(1):35-46.
46. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. *Annals of intensive care*. 2012;2(Suppl 1 Diagnosis and management of intra-abdominal hyperten):S1.
47. Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Critical care (London, England)*. 2013;17(5):R246.
48. Selewski DT, Cornell TT, Lombel RM, Blatt NB, Han YY, Mottes T, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. *Intensive care medicine*. 2011;37(7):1166-73.
49. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2010;55(2):316-25.
50. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. *The New England journal of medicine*. 2011;364(26):2483-95.
51. Maitland K, George EC, Evans JA, Kiguli S, Olupot-Olupot P, Akech SO, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. *BMC medicine*. 2013;11:68.

52. Ford N, Hargreaves S, Shanks L. Mortality after fluid bolus in children with shock due to sepsis or severe infection: a systematic review and meta-analysis. *PloS one*. 2012;7(8):e43953.
53. Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. Effectiveness of physical exam signs for early detection of critical illness in pediatric systemic inflammatory response syndrome. *BMC emergency medicine*. 2014;14(1):24.
54. Saugel B, Ringmaier S, Holzapfel K, Schuster T, Phillip V, Schmid RM, et al. Physical examination, central venous pressure, and chest radiography for the prediction of transpulmonary thermodilution-derived hemodynamic parameters in critically ill patients: a prospective trial. *Journal of critical care*. 2011;26(4):402-10.
55. Nowak RM, Sen A, Garcia AJ, Wilkie H, Yang JJ, Nowak MR, et al. The inability of emergency physicians to adequately clinically estimate the underlying hemodynamic profiles of acutely ill patients. *The American journal of emergency medicine*. 2012;30(6):954-60.
56. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. *Critical Care*. 2014;18(6).
57. Pladys P, Wodey E, Betremieux P, Beuchee A, Ecoffey C. Effects of volume expansion on cardiac output in the preterm infant. *Acta paediatrica (Oslo, Norway : 1992)*. 1997;86(11):1241-5.
58. Holley A, Lukin W, Paratz J, Hawkins T, Boots R, Lipman J. Review article: Part one: Goal-directed resuscitation--which goals? Haemodynamic targets. *Emergency medicine Australasia : EMA*. 2012;24(1):14-22.
59. da Silva Ramos FJ, Azevedo LC. Hemodynamic and perfusion end points for volemic resuscitation in sepsis. *Shock (Augusta, Ga)*. 2010;34 Suppl 1:34-9.
60. Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2012;19(11):1276-80.
61. Kanji HD, McCallum J, Sirounis D, MacRedmond R, Moss R, Boyd JH. Limited echocardiography-guided therapy in subacute shock is associated with change in management and improved outcomes. *Journal of critical care*. 2014;29(5):700-5.
62. Klugman D, Berger JT. Echocardiography as a hemodynamic monitor in critically ill children. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2011;12(4 Suppl):S50-4.
63. Griffie MJ, Merkel MJ, Wei KS. The role of echocardiography in hemodynamic assessment of septic shock. *Critical care clinics*. 2010;26(2):365-82, table of contents.
64. Farris RW. Working toward "just right": fluid balance in pediatric septic shock. *Critical care medicine*. 2014;42(2):470-1.
65. Long E, Babl F, Dalziel S, Dalton S, Etheridge C, Duke T. Fluid resuscitation for paediatric sepsis: A survey of senior emergency physicians in Australia and New Zealand. *Emergency medicine Australasia : EMA*. 2015;27(3):245-50.

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Table 1. Type and composition of resuscitation fluids.

Variable	Human plasma	0.9% saline	4% albumin	Compounded sodium lactate	Balanced salt solution
Trade name		Normal saline	Albumex®	Ringer's lactate or Hartmann's solution ¹	Plasmalyte®
Osmolarity (mmol/L)	291	308	250	280.6	294
Sodium (mmol/L)	135-145	154	140	131	140
Chloride (mmol/L)	94-111	154	128	111	98
Potassium (mmol/L)	4.5-5.0			5.4	5.0
Calcium (mmol/L)	2.2-2.6			2.0	
Magnesium (mmol/L)	0.8-1.0				3.0
Acetate (mmol/L)					27
Lactate (mmol/L)	1-2			29	
Gluconate (mmol/L)					23
Bicarbonate (mmol/L)	23-27				
Octanoate (mmol/L)			6.4		

1. Ringer's lactate and Hartmann's solution have minor differences in ion concentrations that are not clinically significant.

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