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REVIEW ARTICLE

Fluid resuscitation therapy for paediatric sepsis

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Sepsis and septic shock are the final common pathway for many decompensated paediatric infections. Fluid resuscitation therapy 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 world-wide. 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: child; colloid; crystalloid; fluid resuscitation; sepsis.

Historical Background

Intravenous fluid administration to human beings was first described by British physician Thomas Latta in 1832. He administered an alkalinised 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 29.6 mL). 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 that was isotonic with NSW, Australia) is a balanced crystalloid solution designed to have similar osmolarity 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]

Key points

- The type and volume of fluid resuscitation therapy administered for paediatric sepsis are directly linked to patient outcome.
- Balanced salt solutions may be the safest option for fluid resuscitation therapy.
- The volume of fluid resuscitation therapy should be carefully titrated to avoid harms associated from overzealous administration.

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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 (Fig. 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 (Fig. 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

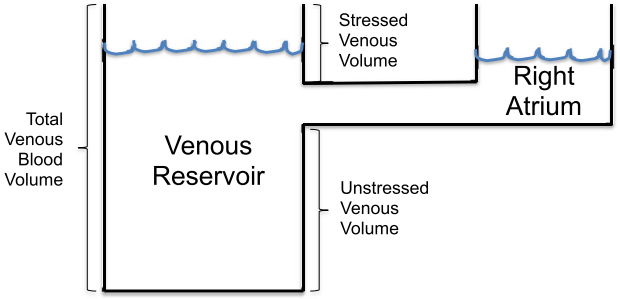

Fig. 1 Venous compartments contributing to venous return.

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 and Hartmann's solution) and balanced solutions (e.g. 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 with 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 with 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 with 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 and requirement for renal replacement therapy[23,24] and has been independently associated with death in adult intensive care unit (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.

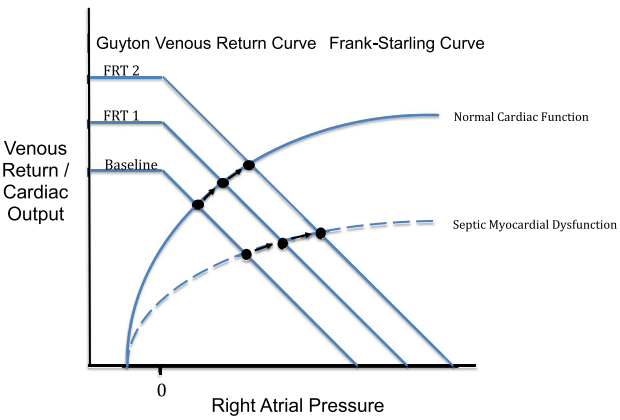

Fig. 2 Superimposed Guyton venous return curve and Frank–Starling curve demonstrating the decremental increase in cardiac output with repeat fluid resuscitation therapy (FRT). The impact of septic myocardial dysfunction on response to FRT is also shown.

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 that the best survival was

Table 1 Type and composition of resuscitation fluids

Variable Trade name	Human plasma	0.9% saline Normal saline	4% albumin Albumex	Compounded sodium lactate Ringer's lactate or Hartmann's solution	Balanced salt solution 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	0	0	5.4	5.0
Calcium (mmol/L)	2.2–2.6	0	0	2.0	0
Magnesium (mmol/L)	0.8–1.0	0	0	0	3.0
Acetate (mmol/L)	0	0	0	0	27
Lactate (mmol/L)	1–2	0	0	29	0
Gluconate (mmol/L)	0	0	0	0	23
Bicarbonate (mmol/L)	23–27	0	0	0	0
Octanoate (mmol/L)	0	0	6.4	0	0

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

associated with the administration of a mean volume of 3.2 L of FRT, equating to ~45 mL/kg.[35] Some paediatric guidelines suggest using 40–60 mL/kg of FRT, with up to 200 mL/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 teaching. More recently, the International Liason Committee on Resuscitation published a guideline advocating an initial bolus of 20 mL/kg for children with sepsis, followed by frequent patient reassessment.[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 with 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 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 passive leg raise 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]

Fluid resuscitation therapy 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 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, 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 h 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 with no FRT (10.5% with fluid bolus and 7.3% standard maintenance fluid). The majority (87%) of these deaths occurred within 24 h 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 World Health Organization 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) and 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 with 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 (>40 mL/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 >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.[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] although 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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To discover the world through a feather by Samantha Li (15) from Operation Art 2014.