Point of view

Coming full circle: thirty years of paediatric fluid resuscitation

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Summary
Fluid bolus therapy (FBT) is a cornerstone of the management of the septic child, but clinical research in this field is challenging to perform, and hard to interpret. The evidence base for independent benefit from liberal FBT in the developed world is limited, and the Fluid Expansion as Supportive Therapy (FEAST) trial has led to conservative changes in the World Health Organization–recommended approach to FBT in resource-poor settings. Trials in the intensive care unit (ICU) and emergency department settings post-FEAST have continued to explore liberal FBT strategies as the norm, despite a strong signal associating fluid accumulation with pulmonary pathology in the paediatric population. Modern clinical trial methodology may ameliorate the traditional challenges of performing randomised interventional trials in critically ill children. Such trials could examine differing strategies of fluid resuscitation, or compare early FBT to early vasoactive agent use. Given the ubiquity of FBT and the potential for harm, appropriately powered examinations of the efficacy of FBT compared to alternative interventions in the paediatric emergency and ICU settings in the developed world appear justified and warranted.

Key Words: paediatric critical care, fluid resuscitation, fluid bolus therapy, sepsis, severe sepsis

Introduction

Prior to the introduction of the Paediatric Advanced Life Support (PALS) course and textbook in 1988[1], the standard of care in paediatric shock states was the slow infusion of 10 to 20 ml/kg of intravenous (IV) fluid over 20 to 30 minutes with close monitoring[2,3]. Subsequent international consensus recommendations for the management of sepsis and septic shock in children advocated the use of aggressive fluid bolus therapy (FBT), with 10 to 20 ml/kg to be given over five to ten minutes, and up to 40 to 60 ml/kg, or more over the first hour[4–7]. Where and how this shift to a liberal approach to fluid resuscitation in children arose is unclear. Furthermore, concerns are emerging regarding an association between fluid administration and accumulation, and mortality in critically ill children in both developed, and resource-poor settings (Figure 1, see next page).

Incorporating evidence from the sub-Saharan Fluid Expansion as Supportive Therapy (FEAST) trial[8], the 2016 World Health Organization's (WHO) Updated guideline: paediatric emergency triage, assessment and treatment has suggested returning to a more conservative approach[9]. Given uncertainties regarding the external validity of these findings outside of resource-poor settings, the recently published 2016 Surviving Sepsis Campaign (SSC) guidelines[10] recommend "that clinicians restore euvolemia with IV fluids, more urgently initially, and then more cautiously as the patient stabilises," with the 2012 Surviving Sepsis Campaign guidelines advocating a more aggressive approach to fluid resuscitation[6] (Table 1, see next page).

The existence of differing guidelines provides a unique opportunity to review the evidence for fluid resuscitation in paediatric sepsis, and may offer the first opportunity for a randomised controlled trial examining the efficacy of FBT in paediatric sepsis in the resource-rich critical care environment.

The evidence base for liberal paediatric fluid resuscitation

In Section C (Fluid Resuscitation) of the Paediatric Considerations in Severe Sepsis component of the 2012 edition of the SSC guidelines, none of the studies directly referenced as providing evidence for the use of FBT in these circumstances demonstrates an independent survival advantage from the administration of fluid in the absence of other intensive care supports (Table 2)[6,11–24]. No new such studies have been added in the four years to 2016[10].

Trials identified as key in the derivation of the clinical recommendations were performed in rats and mice[25,26],

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anaesthetised monkeys[27], rabbits challenged with toxic shock syndrome toxins[28], or pigs with peritonitis[29]. In general, they were small and examined biochemical or physiological endpoints without relating them to outcome[26,30,31], or were in adults and were produced by a group whose leader was involved in extensive research fraud[32]. Attempts at extrapolating from animal experimental models to clinical human sepsis have remained problematic[33–35]. Children are not simply small adults; they have different distributions of intracellular and extracellular fluid than adults, and neonates and infants have a greater proportion of blood volume by weight than older children,

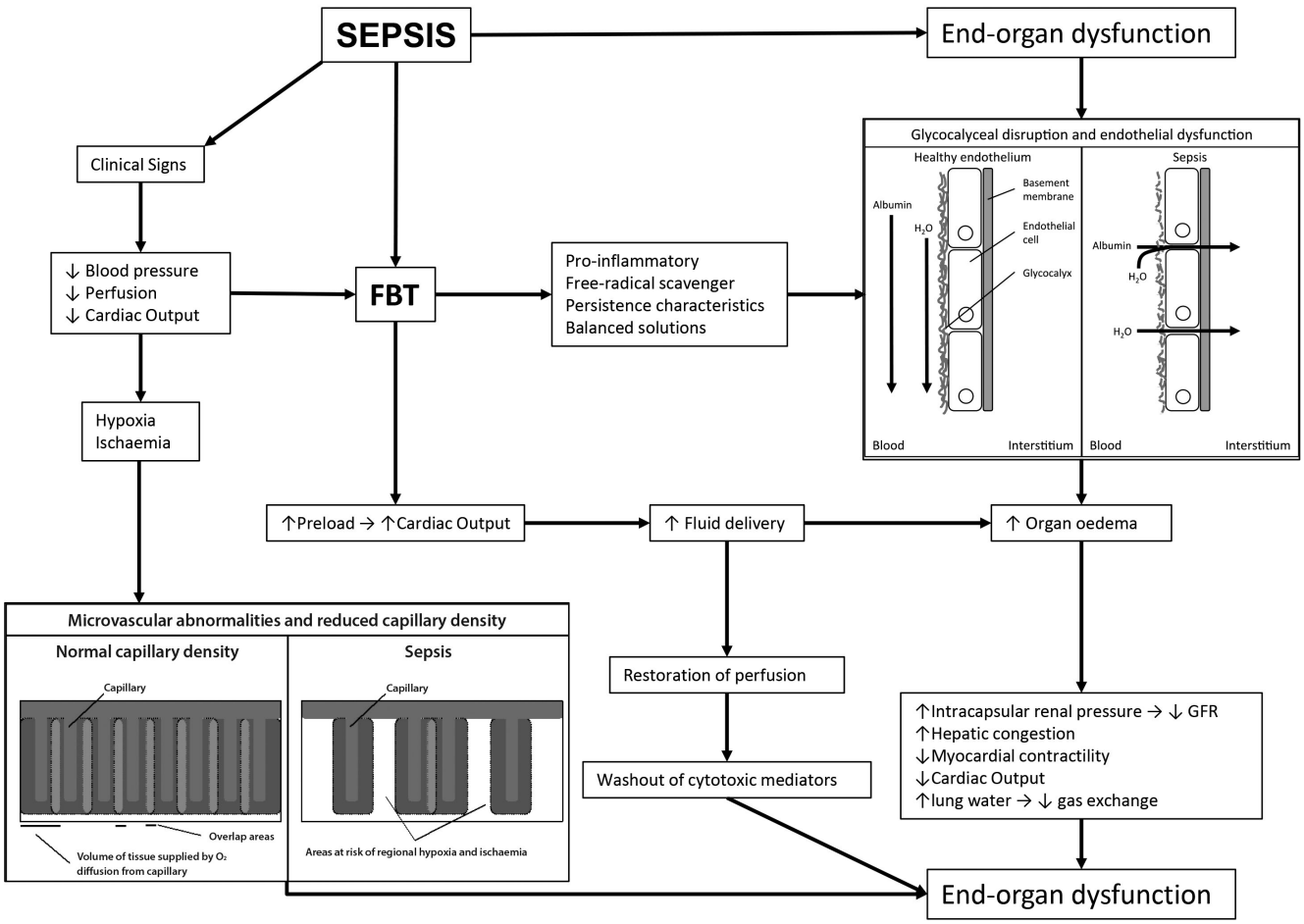

Figure 1: Potential mechanisms for harm as a consequence of FBT administration in children. FBT, fluid bolus therapy; GFR, glomerular filtration rate.

Table 1

Comparison of the Surviving Sepsis Campaign and the World Health Organization guidelines

	Guidelines		
	SSC 2012	SSC 2016	WHO 2016
Who gets fluid?	Fluid resuscitation is recommended for normotensive and hypotensive children in hypovolaemic shock.	In children where euvolaemia needs to be restored.	Children with all 3 signs of shock:1) cold extremities 2) capillary refill time > 3 seconds, 3) weak and fast pulse.
How much?	FBT of up to 20 ml/kg for crystalloids (or albumin equivalent) over 5 to 10 minutes.	No specific fluid or volume recommendations.	FBT of 10 to 20 ml/kg crystalloid over 30 to 60 minutes.
Maximum?	Up to 40 to 60 ml/kg for initial resuscitation.	No recommendations.	Further infusion of 10 ml/kg over 30 minutes for persistent shock.
Cessation?	Hepatomegaly and/or rales as signs of hypervolaemia.	No recommendations.	Signs of fluid overload, cardiac failure or neurological deterioration.

SSC, Surviving Sepsis Campaign; WHO, World Health Organization; FBT, Fluid Bolus Therapy.

Table 2

Summary of paediatric studies directly referenced by the 2012 Surviving Sepsis Guidelines as supporting liberal paediatric fluid resuscitation in sepsis

Study information				Fluid interventions		Additional interventions			Outcomes		
Author, year	**Study type**	**Aim**	**Location**	**Population**	**Intervention**	**Volume of fluid**	**% Vasoactives**	**% on IPPV**	**% with PRC transfusion**	**Mortality**	**Fluid overload**
Kanter 1986[16]	Single centre observational study	To test the effectiveness and rapidity of emergency intravenous catheterisation to a novel protocol.	ED, paediatric services, New York, USA.	38 children requiring resuscitation (2 days to 15 years).	Sequential timed attempts at peripheral, then simultaneous femoral central and surgical saphenous venous, then intraosseous access.	ND	ND	ND	ND	ND	ND
Carcillo 1991/3[7]	Single centre observational study	Explore the association between FBT, volume and survival, ARDS and hypovolaemia, 6 hours from ED presentation.	ED, Washington, USA.	34 children (1 to 192 months) with septic shock and PAC insertion by 6 hours.	Analysed as whole group then dependent on volume of resuscitation at 1 hour: Group 1 <20 ml/kg; Group 2 20 to 40 ml/kg; Group 3 >40 ml/kg.	All patients: 33±26 ml/kg at 1 hour, 9 ml/kg colloid; 95±42 ml/kg at 6 hours, 37 ml/kg colloid. Survivors: 42±28 ml/kg at 1 hour; 97±49 ml/kg at 6 hours. Non-survivors: 23±18 ml/kg at 1 hour; 94±37 ml/kg at 6 hours. Group 1: 11±6 ml/kg at 1 hour; 71±29 ml/kg at 6 hours. Group 2: 32±5 ml/kg at 1 hour; 108±54 ml/kg at 6 hours. Group 3: 69±19 ml/kg at 1 hour; 117±29 ml/kg at 6 hours.	100%	82% by 6 hours	ND	Overall: 47.1% Group 1: 57.1% Group 2: 63.6% Group 3: 11.1%	Overall: 14.7% Group 1: 14.3% Group 2: 9% Group 3: 22%
Dung 1999[15]	Single centre RCT	A comparison of four resuscitation fluids for treatment of children with dengue shock syndrome.	ICU, Ho Chi Minh City, Vietnam.	50 patients (mean age 8.2 ± 2.5 years); all with serological dengue infection.	Randomised to Dextran 70, Gelatin 3%, RL and NS solutions. All patients given 20 ml/kg over first hour then 10 ml/kg over the subsequent hour. Additional fluid as per treating clinician from end of hour 2.	Total study volume infused + additional D: 30 ml/kg + median 100 ml crystalloid G: 30 ml/kg + median 200 ml crystalloid RL: 30 ml/kg + median 200 ml crystalloid NS: 30 ml/kg + median 0 ml crystalloid	ND	ND	ND	Nil	ND
Ngo 2001[18]	Single centre RCT	To identify the immediate and ongoing therapeutic response in children with severe DHF to different crystalloid and colloid solutions.	ICU, Vietnam.	230 children (2 to 15 years); 89% with serological confirmation of dengue infection.	Randomised to Dextran 70, Gelatin 3%, RL and NS solutions. Grade III DHF: 20 ml/kg over 1 hour with resuscitation fluid. Grade IV DHF: 20 ml/kg over 15 minutes then 20 ml/kg over 1 hour. Additional fluid ongoing RL thereafter and/or rescue Dextran.	Total volume infused D: 89 to 189 ml/kg G: 93 to 212 ml/kg RL: 103 to 182 ml/kg NS: 106 to 172 ml/kg	None available	Not available	G: 1 child	Nil	ND
Booy 2001[12]	Single centre observational study	To investigate if ongoing changes in management of meningococcal disease have resulted in improved outcome over a 5 year period.	University ICU, London, UK.	331 children (5 weeks to 17 years) with meningococcal disease.	Provision of specialist PICU services and mobile ICU team for the management of meningococcal disease, aggressive fluid resuscitation with 4.5% albumin, early ETI and IPPV, inotropes, correction of coagulopathy and metabolic derangement, and early renal replacement therapy.	ND	ND	ND	ND	Yearly mortality reduction (OR 0.41, 95% CI: 0.27 to 0.62)	ND
Ninis 2005[19]	Nationwide case-control study	To determine if the outcome of meningococcal disease is dependent on the quality of healthcare early in the disease process.	England, Ireland and Wales.	498 children (<1 to 16 years) with meningococcal disease; 143 deaths.	Standardised management assessment tool created using PALS guidelines.	If evidence of cardiovascular failure then standard management identified as to be 40 ml/kg fluid resuscitation at 1 hour, as 2 x 20 ml/kg FBT.	Failure to give appropriately is an independent risk factor for mortality.	ND	ND	Fluid administration not independently associated with mortality	ND
Ranjit 2005[20]	Single centre observational study	To determine if changes to the management of severe DHF had resulted in improved patient-centred outcomes.	Private ICU, Channai, India.	172 children, 86 before and 86 after the introduction of a new protocol for dengue.	RL or NS solutions. Grade III DHF: 10 to 20 ml/kg over 20 to 30 minutes until hypotension reversed. Grade IV DHF: 20 ml/kg over 3 to 5 minutes until hypotension reversed.	Median volume at 1 hour: Before: 20 (20 to 40) ml/kg After: 30 (20 to 60) ml/kg	ND	Before: 30.2% After: 26.7%	Before: 53.5% After: 47.7%	Before: 22.1% After: 7%	Fluid Removal Before: 5.8% After: 52.3%

Study information				Fluid interventions		Additional interventions			Outcomes		
Author, year	**Study type**	**Aim**	**Location**	**Population**	**Intervention**	**Volume of fluid**	**% Vasoactives**	**% on IPPV**	**% with PRC transfusion**	**Mortality**	**Fluid overload**
Willis 2005[23]	Single centre RCT	A comparison of three resuscitation fluids for primary resuscitation of children with dengue shock syndrome.	ICU, Ho Chi Minh City, Vietnam.	512 patients (median age 9 to 10 years); 93% with serological years dengue infection; 129 with severe shock.	MS: Randomised to RL, Dextran 70 or HES 200/0.5. SS: Randomised to Dextran 70 or HES 200/0.5. All patients: 15 ml/kg over 1 hour, then 10 ml/kg over the next hour. Additional fluid: ongoing RL thereafter and/or rescue Dextran.	Median volume received MS D: 25 ml/kg MS HES: 25 ml/kg MS RL: 25 ml/kg SS D: 25 ml/kg SS HES: 25 ml/kg	ND	ND	MS D: <1% MS HES: <1% MS RL: 2% SS D: 3% SS HES: 2%	MS D: 0% MS HES: 0% MS RL: 0% SS D 0%: SS HES: 1.6%	MS D: 35% MS HES: 30% MS RL: 30% SS D: 40% SS HES: 39%
Thomson 2006[22]	Post hoc analysis of a nationwide case-control study	To determine the frequency and time of onset of clinical features of meningococcal disease to enable early pre-hospital diagnosis.	England, Ireland and Wales.	448 children with meningococcal disease; 103 deaths.	ND	ND	ND	ND	ND		
Maat 2007[17]	Single centre, retrospective observational study.	To analyse the variation in severity and survival of children presenting with sepsis and purpura with respect to age, gender, ethnicity, and serogroup of *N. meningitidis*.	University ICU, Rotterdam, Netherlands.	287 children (0.1 to 17.9 years); 82.2% with *N. meningitidis*	ND	ND	ND	ND	ND	Case fatality rate 15.7%	
Santhanam 2008[21]	Single centre RCT	Comparison of two EGDT protocols differing in FBT resuscitation strategy on shock reversal and short-term clinical outcomes.	ICU, Chennai, India.	147 paediatric patients (1 month to 12 years) presenting to ED with septic shock.	RL solution. Intervention: 40 ml/kg over 15 minutes + dopamine. Control: 60 ml/kg over 60 minutes + dopamine.	Total fluids intervention: 72.5 (60 to 90) ml/kg Control: 60 (60 to 60) ml/kg	Intervention: 100% Control: 98.6%	Intervention: 51.4% Control: 43.8%	ND		Intervention: 17.6% Control: 17.8%
Akech 2010[11]	Systematic review	To synthesise the evidence comparing the use of crystalloid and colloid for fluid resuscitation in paediatric severe infection.	London/Kenya	1,198 children across nine studies.	Comparison of mortality in studies of severe paediatric sepsis treated with colloid or crystalloid.	Data not pooled due to heterogeneity. Single study demonstrating potential survival advantage in children with malaria treated with colloid.					
Cruz 2011[14]	Single centre, retrospective observational	Assess tool for recognition of septic shock and adherence to local guideline	ED, Texas, USA	167 children where a shock protocol had been implemented for sepsis; 64% previously healthy.	Change to rapid vascular access within 5 minutes, rapid administration of isotonic crystalloid via rapid infuser or manual syringe instead of pump-delivered FBT over 1 hour.	Protocol: Median time to 1st FBT: 22 minutes; to 3rd FBT: 61 minutes. Total volume of FBT: 38.9 ml/kg. Control: Median time to 1st FBT: 72min; to 3rd FBT: 280 minutes. Total volume of FBT: 58.8 ml/kg.	Vasoactives in ED: Protocol: 10.1% Control: 16%	Intubated in ED: Protocol: 3.2% Control: 20%	ND	During admission: Protocol: 2.5% Control: 4%	
de Oliviera 2008[24]	Multicentre RCT	To determine if smaller volumes of rapid FBT would achieve similar resolution of shock, less need for ventilation and similar outcomes as compared to standard practice.	ED/ICU, Sao Paulo, Brazil	102 children with fluid-refractory (40 ml/kg) septic shock.	A comparison of ACCCM/PALS guideline with and without using $ScvO_2$ >70% on morbidity and mortality of children with severe sepsis and septic shock.	Median FBT volume over first 6 hours Intervention: 28 (20 to 40) ml/kg Control: 5 (0 to 20) ml/kg	Any agent at 72 hours. Intervention: 78.4% Control: 72.5%	Intervention: 70.6% Control: 80.4%	At 72 hours: Intervention: 68.6%% Control: 58.5%	28-day mortality Intervention: 11.8% Control: 39.2% 60-day mortality Intervention: 15.7% Control: 41.2%	

PRC, packed red cells; ED, emergency department; FBT, fluid bolus therapy; ARDS, acute respiratory distress syndrome; PAC, pulmonary artery catheter; RCT, randomised controlled trial; ICU, intensive care unit; D, dextran solution; G, gelatin solution; RL, Ringer's lactate solution; NS, 0.9% sodium chloride solution; DHF, dengue haemorrhagic fever; ETI, endotracheal intubation; IPPV, invasive positive pressure ventilation; OR, odds ratio; 95% CI, 95% confidence interval; PALS, Paediatric Advanced Life Support; HES, hydroxyethyl starch solution; MS, moderate shock; SS, severe shock; EGDT, early goal-directed therapy; $ScvO_2$, central venous oxygen saturation; ACCCM/PALS, American College of Critical Care Medicine/Paediatric Advanced Life Support; ND, not documented.

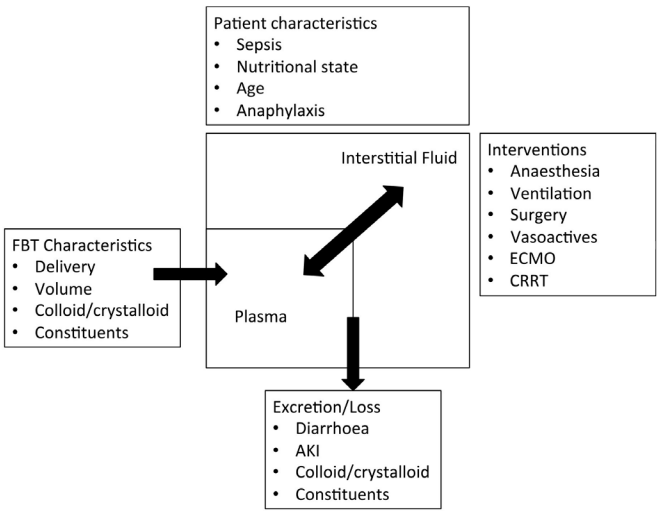

Figure 2: Factors influencing intravascular persistence in children. ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; AKI, acute kidney injury; FBT, fluid bolus therapy.

with the effects of volume expansion being likely to differ with age. Moreover, the intravascular persistence of such fluid expansion is highly variable, and is dependent on the fluid characteristics, the clinical state of the patient, and the effect of intercurrent interventions (Figure 2)[36]. The only published paediatric study examining the clearance of FBT from the circulation suggests that, in well paediatric patients awaiting minor surgery, the median half-life of Ringer's lactate solution is 30 minutes, with an interquartile range of 11 to 70 minutes (Table 3)[37].

Early observational work

The study central to the use of large volume resuscitation in children is an uncontrolled, methodologically weak study of aggressive early fluid resuscitation in 34 participants[13]. These patients had been recruited over a six-year period; all were deemed sick enough that they were thought to require pulmonary artery catheter placement for cardiac output monitoring within six hours of admission. Minimal demographic information was provided. They were divided into three groups based on the amount of fluid delivered in the first hour, with patients receiving more than 40 ml/kg having the lowest rate of mortality on parametric analysis. The composition of the fluid delivered to each group was not presented. No association was found between increasing fluid volume delivered over the first 24 hours and the development of cardiogenic pulmonary oedema or acute respiratory distress syndrome (ARDS), though 82% of patients had to be ventilated within the first six hours of admission for respiratory distress. Although a pulmonary artery catheter was in situ, minimal haemodynamic information was presented. This trial has since shaped the international approach to paediatric fluid resuscitation[4,7,38-41].

Subsequent studies have focused on how rapidly fluid could be given to paediatric patients, not on whether it was appropriate[42,43]. Other attempts to investigate paediatric fluid resuscitation have occurred outside of the intensive care unit (ICU) environment in resource-poor settings without advanced therapeutic interventions, or examined fluid resuscitation in specific pathophysiological conditions such as dengue fever, malaria, or malnutrition[15,18,23,44–46].

Evidence from randomised controlled trials

A recent systematic review identified only three randomised controlled trials (RCTs)[21,24,47] and eight observational studies comparing different FBT-based resuscitation strategies in hospitalised paediatric patients with sepsis where critical care support was available[48]. Of the three RCTs, two were single-centre studies from India[21,47], and one a multicentre trial from Brazil[24]. Different interventions, with different additional therapies (mechanical ventilation, vasoactive agents, blood product and steroid administration) to different triggers aiming for different endpoints were used in different studies, in a total of only 309 patients[48]. Mortality reporting was inconsistent across trials, and only the Brazilian trial, comparing resuscitation with or without central venous oxygen saturation ($ScvO_2$) guidance, demonstrated a mortality benefit of $ScvO_2$–guided resuscitation at both 28 days (11.8% versus 39.2%; *P*=0.002) and 60 days (15.7% versus 41.2%; *P*=0.002)[24]. There was no significant difference in time to shock reversal as defined by the authors, or in reported length of stay, using the interventions described in the studies presenting these outcomes. Given the clinical and methodological heterogeneity of the studies, meta-analysis was impossible. The observational data was similarly heterogeneous across a group of similarly small trials[48].

The FEAST trial: surprising findings, important implications

In 2011 the New England Journal of Medicine published the FEAST trial, a multicentre, randomised controlled study from sub-Saharan Africa comparing the effects of a 20 ml/kg bolus of 0.9% saline or 5% albumin with maintenance therapy only on mortality in more than 3000 children with clinical evidence of impaired perfusion. The findings of FEAST were provocative, and fully challenged the extant paradigm of paediatric FBT-based fluid resuscitation[49].

In intention-to-treat analyses of well-matched groups with no significant baseline differences, minimal loss to follow-up, and more than 99% adherence to allocated therapy, the risk of mortality at 48 hours was significantly higher in patients receiving FBT than in those receiving no bolus (RR 1.45; 95% confidence interval [CI] 1.13 to 1.86; *P*=0.003), though there was no significant difference in mortality between those receiving albumin and those receiving saline

(RR 1.0; 95% CI 0.78 to 1.29; *P*=0.96). FBT with albumin or saline increased the absolute risk of death by 3.3% in children with suspected severe infection. Most deaths occurred within the first 24 hours, and the majority within 48 hours. A dose-response may also have been evident, with a strong trend towards higher mortality in patients recruited following the protocol amendment to increase the volume of fluid bolus administered (RR 1.72, 95% CI 0.98 to 3.05 versus RR 1.38, 95% CI 1.05 to 1.83), a trend that would have likely been significant had recruitment been completed. This mortality difference persisted across all pre-specified, pathophysiologically logical sub-groups including patients with and without malaria, coma (defined as inability to localise to painful stimulus), severe anaemia (haemoglobin concentration <50 g/l), and severe illness (base deficit ≥8 mmol/l, lactate ≥5 mmol/l), with no heterogeneity between centres or across age groups[49].

While only a small fraction of included patients met the WHO Emergency Triage Assessment and Treatment criteria for shock[38], a larger proportion met the American College of Critical Care Medicine[4,7] or the PALS criteria[50]. Of note, the definition of shock used in the FEAST trial is very similar to that used in the original *Journal of the American Medical Association* paper from which these clinical guidelines appear to have been extrapolated[13]. Although not powered to explore the effects of FBT in children with hypotension or dehydration, with both of these conditions being rare in the examined cohort (only 29 children had severe hypotension and only 236 had severe dehydration without diarrhoea), a trend toward increased mortality was found in those groups receiving boluses when compared to controls[51,52].

After the FEAST, a famine?

When FEAST was released, rapid, large-volume fluid resuscitation was the norm in paediatric septic shock, and in other conditions involving fluid loss in children[53]. It may be impossible to directly translate the findings of FEAST into practice change internationally; however, as it represents the current purest examination of the effects of FBT in isolation in critically ill children, it should have prompted further investigation into the safety and efficacy of FBT in this population in the developed world.

A prospective observational trial assessing the implementation of a protocol for the management of septic shock according to the current guidelines in a United States emergency department (ED) demonstrated no survival advantage, despite significantly more patients receiving 20 ml/kg of 0.9% saline solution over 15 or 60 minutes. A significant increase in the number of patients receiving 60 ml/kg of fluid resuscitation over the first hour was also observed. Despite being effectively cost neutral, an increased rate of paediatric intensive care unit (PICU) admission appeared to be balanced by a shorter hospital stay for survivors[54].

A prospective, observational, before and after study in a tertiary referral Australian paediatric ED examined the effect of introducing a local guideline in accordance with SSC recommendations, in association with removal of barriers to adherence and an extensive education program, in 102 pre-intervention and 113 post-intervention children presenting with sepsis. Children in the pre-intervention group were more likely to be over 12 months of age, with a greater proportion possessed indwelling central venous access, but no statistical test of significance is presented in the paper. Post-intervention, children received both antibiotics and fluid more quickly, and although the volumes of fluid given are not presented, it is stated in the manuscript that they did not vary between groups. There was a significant reduction in the median length of hospital stay following intervention, even following adjustment for multiple potential confounders. However, this did not translate into an improvement in mortality[55]. In contrast, in a prospective observational study of 79 children admitted to a Canadian tertiary PICU with sepsis, the volume of fluid boluses administered over the first two hours from presentation was independently associated with longer PICU stays and longer duration of mechanical ventilation[56].

The most recent international epidemiological study of paediatric severe sepsis prevalence, outcomes and therapies fails to present or account for fluid accumulation, or the use of FBT[57]. Several recent Canadian trials have examined the most efficient strategies to deliver rapid large-volume fluid resuscitation, and barriers to that delivery[58,59]. Despite acknowledging the findings of FEAST, a survey of medical and nursing staff from the same institution only asked how to rapidly administer fluid to shocked children, not if it should be done. Of note, no respondent offered a potential concern related to FBT in children as in the FEAST trial[60]. A recent survey of senior Australian and New Zealand emergency physicians suggests that current practice among clinicians managing the presentation of a child with septic shock is still to treat with large volume FBT of isotonic crystalloids[61].

Fluid accumulation and outcome

Post-FEAST, several studies have examined fluid balance in the resource-rich PICU setting. A single-centre, retrospective observational study in a tertiary referral university hospital in the US demonstrated, in a cohort of critically ill children not requiring renal replacement therapy, that peak fluid overload percentage was independently associated with both a higher peak oxygenation index and longer hospital and PICU stays, even when controlled for age, gender and illness severity. Though no independent association with mortality was demonstrated, those with greater peak fluid overload percentages also spent longer mechanically ventilated[62]. A similar study from the UK demonstrated

no significant difference in degree of fluid overload between survivors and non-survivors in 636 patients, but demonstrated that it was a significant predictor of oxygenation index at 48 hours and duration of mechanical ventilation as ventilation days[63].

The Calfactant in Acute Respiratory Distress Syndrome Trial was a masked RCT of calfactant surfactant versus placebo, performed across 24 PICUs from six countries[64]. In a post hoc analysis of their data, the investigators suggest that paediatric intensivists in resource-rich countries tend towards liberal fluid administration even when encouraged to be conservative, with patients in this study demonstrating a mean fluid accumulation of 1.96 ± 4.2 l/m^2 over the first seven days of inclusion. Increasing fluid accumulation was independently associated with worsening oxygenation, increasing duration of ventilation and higher mortality on robust multivariable assessment, with the mean fluid accumulation being approximately seven times greater in those who died[65].

In a tertiary referral US PICU, 42 patients with fluid accumulation ≥10% of admission bodyweight over the first three days of admission were matched to 72 controls. Matching was complex and varied by analysis. Mortality was four-fold greater among cases. The presence, degree and duration of early fluid overload was shown to be independently associated with mortality when adjusted for multiple potential confounders, though how robust such conclusions are in the face of probable significant over-fitting of the multivariable analysis is questionable[66]. Given the sample size and methodology, these results should be interpreted with caution, but appear consistent with the other investigations presented.

In a prospective observational study of 100 younger children (mainly between the ages of two to 36 months) consecutively admitted to a South African PICU, fluid overload as represented by peak fluid overload percentage was smaller than in the other studies discussed. Daily peak fluid overload percentage correlated with illness severity, PICU length of stay, ventilation days and oxygenation index, and non-survivors had a fluid overload percentage 1.44 times that of survivors on PICU admission. Meaningful regression analysis was precluded by the small sample size and limited number of outcomes, with ten deaths in the population[67].

A retrospective Canadian cohort study, published in 2015, but examining 173 patients undergoing 196 cardiac surgeries with subsequent postoperative management in

Table 3

Haemodilution by weight and age as a consequence of fluid bolus therapy

Age Category	Blood Volume	Time post-administration	Percentage volume expansion by FBT volume			
	(ml/kg)		10 ml/kg	20 ml/kg	40 ml/kg	60 ml/kg
Neonate	90	End of infusion	11%	22%	33%	44%
		30 minutes	6%	11%	17%	22%
		60 minutes	3%	6%	8%	11%
Infant	85	End of infusion	12%	24%	35%	47%
		30 minutes	6%	12%	18%	24%
		60 minutes	3%	6%	9%	12%
Child	80	End of infusion	13%	25%	38%	50%
		30 minutes	7%	13%	19%	25%
		60 minutes	3%	6%	10%	13%
Adolescent	75	End of infusion	13%	27%	40%	53%
(Male)		30 minutes	7%	14%	20%	27%
		60 minutes	3%	7%	10%	13%
Adolescent	65	End of infusion	15%	31%	46%	62%
(Female)		30 minutes	8%	16%	23%	31%
		60 minutes	4%	8%	12%	16%

This is a simplified model of potential haemodilution making the following assumptions: 1)The fluid being administered is lactated Ringer's solution (RL); the only published study of fluid bolus therapy (FBT) volume kinetics and intravascular persistence in children used this fluid[78]. 2) The half-life for RL in a child's circulation is 30 minutes. By 30 minutes 50% of the administered volume will have been excreted or redistributed, by 60 minutes 75%[79]. 3) All of the fluid is given at the same time. According to guidelines, 60 ml/kg would normally be given over 1 hour in divided doses; the peak effect is likely to be less than that stated. 4) These children are well. In sepsis or other states of inflammation and increased vascular leak it is likely that the half-life of RL in the circulation would be much reduced. 5) There is no neurohormonal or pathophysiological process promoting the retention, or preventing the excretion, of the fluid delivered.

PICU between 2005 and 2007, explored the associations between fluid overload and patient-centred outcomes. Higher fluid overload percentages were seen on day two in patients following first surgery, with underlying cyanotic heart disease or those given early postoperative fluids, and were independently associated with increased length of PICU stay and increased duration of mechanical ventilation. In those without cyanotic heart disease, increasing fluid overload percentages were independently associated with a worsening oxygenation index[68].

A strong signal suggesting an association between fluid accumulation and pulmonary pathology is present across these clinically and methodologically heterogeneous studies. While there is no increase in mortality in many of these studies, they are small and inadequately powered to detect such outcomes. The relationship between fluid administration and fluid accumulation in children is unclear, but fluid must be given to accumulate, and the association has been demonstrated in children undergoing cardiac surgery[68]. Moreover, the absence of an increase in mortality does not automatically translate into a survival advantage.

The complex nature of an intervention and translating research to practice

Personal belief in the efficacy of FBT is so strong that recent evidence has failed to disrupt current clinical equipoise in resource-rich settings[8,49,52,69,70]. Paediatric clinicians indicate that their experience of the beneficial effects of FBT administration in shocked and septic children has been overwhelming, to the point that the current clinical paradigm is nigh unassailable[71–73]. However, such experiences remain associative, and it is possible that this belief in the efficacy of FBT is merely a complex logical fallacy. It remains the role of well-conducted RCTs to disrupt this sort of circular thinking and demonstrate causality.

Recent evidence actually agrees with global experience—FBT does improve signs of impaired perfusion within the first hour following administration[4–6]. However, the major cause of death in the FEAST trial was cardiovascular collapse, occurring between two and 11 hours post-FBT administration[52]. In resource-rich settings invasive monitoring, vasoactive medication and/or invasive ventilation may have commenced by this point, in keeping with international guidelines[54–56]. Such interventions may prevent or ameliorate the severity of the phenomenon underlying these terminal clinical events[74], but it is possible that FBT administration contributes directly to the persistent mortality observed in paediatric severe sepsis and septic shock[57].

Minimal new evidence in emergency paediatric care was felt to have emerged prior to 2010 by the international experts reviewing the WHO guidelines on the management of common childhood illnesses that year[75]. Emergency care was therefore not identified as a priority for review, though a caution was included regarding rapid fluid administration in malaria and anaemia in the 2013 publication[75,76]. The association between FBT and increased mortality was confirmed in systematic review in 2012[77], and again in low-income countries in 2014[78]. The publication of the 2016 update to the WHO paediatric emergency triage, assessment and treatment guidelines was important because it demonstrated the first consensus shift away from aggressive FBT in paediatric shock for almost 30 years. This new edition now recommends that initial fluid resuscitation in shocked children should be undertaken with 10–20 ml/kg of isotonic fluid to be administered over 30 to 60 minutes, with a subsequent infusion of 10 ml/kg over 30 minutes in children in persistent shocked states[9]. The uptake of these changes in practice in resource-rich or other settings has not yet been presented in the literature.

How to disrupt the circle, and the shape of things to come

The lack of interventional work indicates just how hard clinical research in the critically ill paediatric population can be. As most paediatric critical illnesses may be classed as rare diseases, the evidence base for most interventions in paediatric intensive care is limited[79,80]. Multiple centres, research networks or other collaborations may be needed to ensure adequate potential populations for screening for inclusion[81]. Cluster randomised crossover trial designs could be used for trials of fluid administration, and may overcome some of the challenges of recruitment[82], though current methods of statistical analysis for such designs lose fidelity with low prevalence outcomes[83]. Given the falling incidence of mortality in paediatric critical care practice, using the 'gold-standard' outcome measure of 28- or 30-day mortality will become impractical, as demonstrating the effectiveness of an intervention will require impossibly large sample sizes. Length of ICU or hospital stay, number of 'intervention-free' or 'complication-free' days, or duration of mechanical ventilation may offer patient-centred outcomes suitable for smaller study sizes. Bayesian techniques could be used to leverage the results of well-designed adult trials, allowing for smaller sample sizes in follow-on paediatric studies[84].

Recruiting patients to paediatric trials is challenging; despite the time pressure for urgent intervention, appropriate information must be provided for informed decision-making[85]. In those jurisdictions amenable to such an approach, consent to continue in interventional trials and opt-out models for observational research would offer a way to maximise recruitment, particularly in situations with true equipoise, and may offer parents or guardians the opportunity to consider enrolment under less psychologically stressful conditions[85,86]. Consent to continue has been used in several studies of paediatric emergency care in the UK and Africa and appears to be acceptable

to participants when sensitively implemented[86–88]. Illness severity is important, with parents of very unwell children being more likely to refuse consent for even observational studies[89,90]. Further challenges include: the burden of study involvement on the child[91], therapeutic misconception[92], and clinicians attempting to act as both doctors and scientists[91].

The area of paediatric sepsis has specific challenges. While the incidence of sepsis in children in developed countries is increasing, the majority of this increase is seen in the neonatal population; neonatal, infantile, childhood and adolescent sepsis are likely to be essentially differing conditions[57,93,94]. In adults the presence of comorbidities was found to significantly alter risk of mortality in critically ill adults with sepsis[95]. Without such information in paediatric populations, using power calculations to appropriately size trials may be difficult. Power calculations should take into account likely recruitment rates stratified by age group. The blurred distinction between infections, sepsis, severe sepsis and septic shock may lead to heterogeneous study populations, diluting the effectiveness of any studied intervention. This may be ameliorated by new definitions of sepsis and septic shock, though these will require adaptation for use in critically ill children[96].

The lack of information regarding current practice and both the expected and true age-normalised haemodynamic responses to FBT in children provides a specific barrier to further interventional trials[48]. The generic triggers for initiation of FBT in children need to be identified, as does how they vary depending on underlying diagnosis. Majority definitions of what clinicians believe constitutes FBT, and the expected haemodynamic changes indicating a response to FBT in adults have been published[97]. These have been demonstrated to be divorced from the actual clinical effects of FBT in this population, which appear to be very brief, and, though statistically significant, clinically insignificant[98–101]. Surveys of practice, observational studies identifying the independent effects of FBT while accounting for age and diagnosis, and an assessment of the epidemiology of fluid administration and accumulation would provide the platform upon which future randomised interventional studies could be planned. Pilot data would inform, not only the acceptability of the trial design to clinicians, but also the expected age-dependent rates of recruitment.

Such randomised trials could take several forms, with the most obvious being a comparison between the recommendations made in the 2012 SSC, and those in the 2016 WHO guidelines. Alternatively, immediate FBT could be compared to subsequent reassessment after ten to 15 minutes, with delayed FBT in the presence of persisting triggers for initiation. Lastly, further FBT could be compared to peripheral catecholamine administration following an initial, restricted phase of controlled FBT. Careful follow-up of participants could allow the medium- to long-term consequences of different resuscitation strategies to be identified. Certainly, the assessment of the efficacy of a paediatric intervention should not be based only on short-term outcomes.

Conclusion

Paediatric fluid resuscitation appears to have come full circle, with these most recent WHO recommendations being near identical to those of the original PALS textbook, now approaching 30 years old[1]. The FEAST data has been appropriately integrated into WHO recommendations for practice in the developing world. While these results cannot be easily applied to practice in ICUs in the developed world, it is clear that the current evidence for FBT in this setting is primarily experimental, uncontrolled, extrapolated from work in adults, or subject to small-trial bias. If FBT was being introduced as a new intervention to paediatric acute care it is difficult to see how it could be widely acceptable to modern medical sensibilities with the current evidence base. Fifteen years ago, a methodologically flawed trial of approximately 300 adults[102] led to massive networks of basic scientific and clinical research, widely adopted consensus guidelines[5,6,103], and millions of dollars of international funding[104]. In contrast, little specific evidence-based guidance for FBT in septic children has been generated over the same period. Despite the challenges of performing randomised interventional trials in critically ill children, appropriately powered examinations of the efficacy of FBT compared to alternative interventions in the developed paediatric ED and ICU settings appear justified and warranted.

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