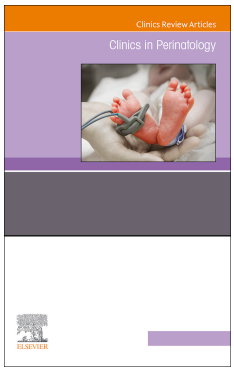
Journal Pre-proof



Fluid therapy: Friend or Foe?

Erin Grace, BBMSc MBBS(Hons) DCHGradDipNeo, Amy K. Keir, MBBS MPH FRACP PhD

PII: S0095-5108(20)30057-9

DOI: https://doi.org/10.1016/j.clp.2020.05.005

Reference: CLP 1173

To appear in: *CLINICS IN PERINATOLOGY*

Please cite this article as: Grace E, Keir AK, Fluid therapy: Friend or Foe?, *CLINICS IN PERINATOLOGY* (2020), doi: https://doi.org/10.1016/j.clp.2020.05.005.

ARTICLE TITLE

Fluid therapy: Friend or Foe?

AUTHOR NAMES AND DEGREES

Erin Grace BBMSc MBBS(Hons) DCH GradDipNeo
Amy K Keir MBBS MPH FRACP PhD

AUTHOR AFFILIATIONS

Department of Neonatal Medicine, Women's and Children's Hospital, North Adelaide, South Australia
SAHMRI Women and Kids, South Australian Health and Medical Research Institute, Adelaide, South Australia
Adelaide Medical School and the Robinson Research Institute, University of Adelaide, Adelaide, South Australia

AUTHOR CONTACT INFORMATION

Mailing address: Department of Neonatal Medicine, Zone F, Women's and Children's Hospital, 72 King William Road, North Adelaide, South Australia, 5006
Email: amy.keir@adelaide.edu.au
Twitter handle: @AmyKKeir

CORRESPONDING AUTHOR

Dr. Amy Keir

DISCLOSURE STATEMENT

AK receives funding from the Australian National Health and Medical Research Council (NHMRC) (APP1161379). The contents of this paper are solely the responsibility of the individual authors and do not reflect the views of the NHMRC.

KEY WORDS

Infant, newborn; fluid therapy/methods

KEY POINTS

1. The most commonly used fluid for volume expansion in neonates is 0.9% sodium chloride given at a volume of 10mL/kg over 30 minutes to manage hypotension.
2. It is not clear if fluid bolus therapy provides benefit, has no clinical benefit, or is associated with harm in neonatology. Or it simply may be a marker of critical illness.
3. A negative fluid balance in the first 7 days of age is associated with a degree of improved clinical outcomes in preterm and term infants.
4. Further studies examining fluid bolus therapy and fluid management in the first 7 days of age in preterm and term infants are needed to adequately inform this important area of practice.

SYNOPSIS

Many questions surround fluid bolus therapy and subsequent fluid management in neonatal critical care as they do in paediatric and adult critical care. This review explores the known key clinical aspects of fluid bolus therapy and fluid balance in the first 7 days of life and provides suggestions for further work in this area. It draws on the paediatric and adult critical care literature to provide thought-provoking data around the potential harms of excessive intravenous fluids, which may prove relevant to neonatology. Current data suggests that fluid bolus therapy and early life positive fluid balance in neonates may be associated with harm.

INTRODUCTION

Administration of fluids remains a key intervention during the stabilisation phase of critically ill neonates with the basic aim to increase cardiac output and to improve oxygen delivery. However, there remains little conclusive evidence to guide healthcare professionals about what type of fluids to use, when to use them, at what rate and how to assess the efficacy or potential harm of these practices in neonatology. With increasing evidence in the paediatric and adult critical care settings that fluid bolus therapy and positive fluid balances are linked with adverse outcomes, it is timely to appraise what is known in neonatology. This review will explore the known key clinical aspects of fluid bolus therapy and early life fluid balance in neonatal care as well as providing suggestions for further work in this area.

WHEN AND WHY DO WE USE FLUID BOLUSES IN NEONATOLOGY?

When is fluid bolus therapy used?

Volume expansion is used in neonatology not only in the setting of hypovolaemia but in situations where hypovolaemia is unlikely, for example in preterm neonates with hypotension with signs of systemic hypoperfusion. Consequently, the majority of preterm neonates who receive fluid bolus therapy for the management of suspected haemodynamic compromise are unlikely to be hypovolaemic and, in recent times with increased uptake of deferred cord clamping, hypovolaemia is perhaps even less likely. Of course, hypovolaemia does occur in neonatology in the setting of blood loss at delivery and in septic shock. However, these are not the most common indications for fluid bolus therapy in preterm or term neonates.[1]

A Canadian survey reported that neonatologists routinely treated suspected haemodynamic compromise in neonates with a birthweight <1500 grams with a fluid bolus (97%) and the most commonly used fluid was 0.9% sodium chloride (95%).[2] Use of a fluid bolus to treat

suspected haemodynamic compromise is further illustrated by a prospective study of 367 preterm neonates <27 weeks gestational age (GA) investigating the relationship between early blood pressure changes, receipt of anti-hypotensive therapy and longer term neurodevelopmental outcome. Of the 203 neonates (55%) who received anti-hypotensive therapy, 135 (67%) received a fluid bolus, 102 (50%) received a blood product and 92 (45%), 25 (12%), 18 (9%) and 1 (<1%) received dopamine, hydrocortisone, dobutamine and vasopressin, respectively.[3] A recent international multicentre observational study of fluid bolus therapy in preterm and term neonates found the most frequent indication was low blood pressure (34%), followed by decreased perfusion on clinical assessment (12%), then metabolic acidosis (12%), and an elevated lactate level (8%).[1] Although it is challenging to gain a comprehensive understanding of the prevalence of fluid bolus therapy in neonatology, it is likely it is very commonly used. In the Management of Hypotension in Preterm Infants (The HIP Trial) both arms of this randomised controlled trial included a bolus of 10mL/kg of 0.9% sodium chloride.[4]

Unfortunately, there is no validated clinical scoring system or tool to reliably diagnose systemic hypoperfusion or haemodynamic compromise in neonates, situations in which volume expansion may be beneficial. Assessment of the adequacy of end-organ blood flow remains primarily subjective.[4] We lack consensus on what constitutes hypotension or haemodynamic compromise in neonates, and what clinically relevant outcomes are sought when a treatment is given to manage perceived haemodynamic compromise.

Who receives fluid bolus therapy?

In a multicentre international observational study including perinatal, surgical, cardiac and mixed centres, neonates identified to have received fluid bolus therapy had a bimodal

distribution of birth gestational ages. The two peaks were neonates < 28 weeks gestational age (GA) and term neonates. This likely reflects a combination of the reported bimodal patterns of admission to tertiary neonatal units,[5] and, in the case of extremely preterm neonates, the increased rates of suspected haemodynamic compromise in this group.[3]

WHAT TYPE, HOW MUCH AND OVER HOW LONG?

Fluid therapy in resuscitation is given with the goal of maintaining an adequate intravascular volume to maintain cardiovascular stability, organ perfusion and sufficient tissue oxygenation. Various fluids are used for fluid resuscitation in neonates, including crystalloids such as 0.9% sodium chloride and Ringers lactate, or colloids like albumin or blood products, namely red blood cells (RBCs) and fresh frozen plasma (FFP). The types of fluid reported as used for fluid bolus therapy in preterm and term neonates include 0.9% sodium chloride (*n* = 129; 79%), RBCs (*n* = 15; 9%), 4 or 5% albumin (*n* = 5; 3%), Ringer's lactate (*n* = 9; 5%), FFP (*n* = 4; 3%) and 0.45% sodium chloride (*n* = 1; <1%).[1]

Dose and infusion time

The most common dose of intravenous fluid seems to be 10mL/kg given over a median duration of 30 (interquartile range (IQR) 20-60) minutes.[1] Fluid boluses appear to be relatively consistently administered at 10mL/kg over 30 minutes (IQR 10-60 minutes).[1] Faster infusion times have been associated with worse outcomes in neonates.[6]

PHYSIOLOGICAL BASIS FOR FLUID BOLUS THERAPY

In a preload responsive individual whose heart is functioning at the steep portion of the Frank-Starling curve, additional intravascular volume will increase stroke volume and increase cardiac output.[7] The assumed consequence is improved tissue perfusion, leading to

improved cell and organ function. These are the physiologic principles on which fluid bolus therapy is based and this is supported by data revealing an increase in cardiac output post-fluid bolus in preterm neonates.[8,9] The characteristics of neonates that will respond to a fluid bolus and in what clinical settings remains unclear.

The understanding of the physiological basis of fluid therapy continues to evolve. In Earnest Starling's original model of fluid shifts between intravascular and extravascular compartments net fluid flux across a capillary was said to favour filtration at the arterial end and fluid resorption at the venule end.[10] This was attributed to differences in hydrostatic and colloid oncotic pressure in the capillary in relation to the interstitial compartment.[10] This principle provided a rationale for fluid resuscitation with hyperoncotic fluids such as 20% albumin. However, Starling's equation has been revised in recent years[11,12] after it was demonstrated that filtration actually occurs over the over the entire length of a capillary[13] and net absorption does not occur when intravascular colloid oncotic pressure exceeds that of the interstitial fluid compartment. Additionally, the integral role of the glycocylx, a layer of glycoproteins and proteoglycans on the inner surface of vascular endothelial cells, in fluid exchange has now been recognised.[11 14] The oncotic pressure difference across the glycocylx opposes, but does not reverse, filtration.[12] This colloid oncotic pressure of the subglycoclyx space is an important factor in determining vascular fluid shifts.[14] The increase in circulating intravascular volume seen with an albumin infusion[15] is thought to be due to 'drawing' fluid out of the noncirculating sub-glycocalyx fluid compartment, rather than the interstitial space. Thus the physiological basis of using albumin to increase intravascular colloid oncotic pressure to 'draw' interstitial fluid back into the intravascular space is no longer feasible. This further negates any rational basis for using colloids to manage oedema or in the setting of sepsis.[11]

EVIDENCE-BASE FOR VOLUME EXPANSION IN NEONATOLOGY

Preterm neonates

There are no randomised studies primarily designed to investigate a fluid bolus compared to no fluid bolus in preterm neonates with haemodynamic compromise.[16] Several studies,[17-21] published between 1976 to 2000, compared a fluid bolus to no fluid bolus in preterm neonates. However, the majority of included neonates did not have signs of haemodynamic compromise. Meta-analysis of these studies found no differences in clinical outcomes, including mortality, grade 3-4 intraventricular haemorrhage and/or neurodevelopmental impairment.[22]

The largest, and best-known study examining the use of fluid boluses in preterm neonates is the Northern Neonatal Nursing Initiative (NNNI) Trial Group study.[21] The study was designed to determine whether early volume expansion, including with FFP administration, would reduce morbidity and mortality in neonates < 32 weeks' gestation (GA) (n=776). Prophylactic FFP (20 ml/kg initially and then a further 10 ml/kg after 24 hours) or a similar volume of an inert gelatin plasma substitute or a control fluid with a maintenance infusion of 10% dextrose were compared. The primary study found no effect of use of FFP as early volume expansion on cranial ultrasound abnormalities or mortality prior to discharge. In the 2-year follow-up study,[23] no significant differences between groups in disability or mortality were reported. Critically, volume expansion was used prophylactically as opposed to part of management of haemodynamic compromise, again limiting the conclusions that are able to be drawn. As all infants received a fluid bolus of some type, including a control fluid of 10% dextrose, the study did not actually assess the effects of no fluid bolus, in essence it assessed the type of fluid used.

Two further studies are available comparing the use of 0.9% sodium chloride versus 5% albumin in hypotensive preterm infants.[24,25] One is a small randomised study (n=100) comparing the use of 10mL/kg of 0.9% sodium chloride versus 5% albumin over 20 minutes in hypotensive preterm (mean GA 30 weeks) infants. Hypotension was defined as mean arterial blood pressure (MAP) less than the 5th percentile for at least 10 minutes.[25] A second bolus was given for ongoing hypotension as previously defined. Dopamine therapy was commenced for hypotension after the second bolus if hypotension persisted. The primary outcome was an increase in MAP towards a pre-defined 'normal' range one hour post-infusion. The study found infants receiving albumin were more likely to achieve this outcome (57.1% versus 32.1%; p<0.01) following the first bolus. Interestingly, the infants in the 0.9% sodium chloride group had more grade 3-4 intraventricular haemorrhages (7/31; 22.6%) than the albumin group (2/25; 8%). The authors suggest this may have been related to the ongoing hypotension in the 0.9% sodium chloride group and subsequent use of inotropes. However, it does raise concerns about the potential independent harm fluid boluses with 0.9% sodium chloride may cause. The second study is a small randomised trial in 50 infants (mean GA 28-31 weeks) assigned to receive either 5% albumin or 0.9% sodium chloride for volume expansion in the setting of hypotension.[24] Hypotension was defined as >30 minutes of a MAP of <30 mmHg for infants weighing <2500 grams or a MAP of <40 mmHg for those weighing >2500 grams. The main outcome was the resolution of hypotension, as previously described, sustained for >30 minutes. Infants received intravenous fluids at 10mL/g over 15 minutes, which could be repeated if the infant initially did not respond with an increase in MAP to the desired level. Again, after the second bolus, if there was no increase in MAP to this pre-defined level, inotrope support was initiated. Successful treatment was observed in 17/21 (81%) of infants in the albumin group and 17/20 (85%) of infants in the 0.9% sodium chloride group. Seven of the 20 infants in the 0.9% sodium chloride group (35%) received a

second fluid bolus, and three of these infants received inotropic support. Nine of the 21 infants (43%) in the albumin group received a second volume infusion, and four of these 21 received inotropic support. These studies highlight the challenges of research in this area with each study defining hypotension differently, use of different treatment outcomes and exclusion criteria.

Late preterm and term neonates

Two retrospective studies with comparator groups that assess whether fluid bolus therapy in late preterm and term neonates has clinical benefit are available.[26,27] The studies found that receipt of fluid bolus therapy was more likely to be a marker of illness severity, rather than a cause of adverse effects in neonates with persistent pulmonary hypertension of the newborn[26] and hypoxic-ischaemic encephalopathy.[27]

POTENTIAL FOR HARM

Adverse effects for all types of fluid boluses in neonates may occur and include volume overload, dilutional coagulopathy, hypothermia and electrolyte abnormalities (Table 1). Observational studies suggest dose-related adverse effects of volume overload; in preterm neonates, multiple fluid boluses are associated with increased mortality[28] and intraventricular haemorrhages,[6] whereas lower total fluid intakes in the first week of age were correlated with decreased chronic lung disease and mortality.[29,30] Whether adverse effects are precipitated by the properties of the fluid infused and/or the volume of fluids remains unclear.

As each fluid has different biochemical and physicochemical properties, different solutions may be indicated in different situations and may have different potential adverse effects (Table 1). Crystalloids can be balanced or unbalanced. For example, 0.9% sodium chloride,

an unbalanced crystalloid, has high concentrations of sodium and chloride thus large volume infusions of 0.9% sodium chloride can result in hyperchloraemic acidosis. In balanced crystalloids, such as Ringers lactate and Plasma-Lyte, chloride is partially replaced by other anions,[31] reducing the risk of this side effect. Yet, balanced crystalloids contain more potassium than 0.9% sodium chloride, consequently hyperkalaemia can occur with large volumes of infusion. In terms of colloids, albumin 4% or 5% are commonly used in neonates, as well as RBCs and FFP. Blood products have additional potential adverse effects beyond the scope of this review.

Potential mechanisms for harm due to fluid bolus

There are a several plausible mechanisms by which fluid boluses may cause harm,[32] including:

- Tissue oedema leading to increased requirement for ventilatory support, translocation of gut organisms and increased renal venous pressure compromising renal perfusion
- Opening of shut-down capillary beds leading to ‘flooding’ of the systemic circulation with cytokine-rich blood, thereby, exacerbating systemic inflammation
- Degradation of the glycocalyx layer lining the luminal wall of the vascular endothelium; loss of integrity of the glycocalyx is a critical step in endothelial cell activation and drives a systemic inflammatory state as well as increasing vascular permeability precipitating oedema
- Animal data suggests rapid infusion of intravenous fluids may disrupt haemostasis mechanism with a resultant coagulopathy[33]

WHAT DOES THE BROADER LITERATURE TELL US?

What does the Cochrane tell us?

The Cochrane review examining liberal versus conservation fluid therapy in adults and children with sepsis or septic shock[34] found moderate quality evidence from 2 randomised controlled studies[35,36] (n=3288) indicating that liberal fluid therapy may increase in hospital mortality risk by 38% compared with conservative fluid therapy. These 2 studies were paediatric studies performed in lower resourced settings and included the Fluid Expansion as Supportive Therapy (FEAST) study, which will be discussed in greater detail later on.[36] The other included study compared the effects of more intravenous fluid intake (i.e. liberal fluid therapy defined as 40 mL/kg of fluid over 15 minutes) versus less intravenous fluid intake (i.e. conservative fluid therapy defined as 20 mL/kg over 20 minutes) for children with septic shock.[35] An additional study was included in the review but excluded from meta-analysis due to lack of data and was published in abstract form only.[37]

It is worth reviewing what these Cochrane authors defined as conservative and liberal fluid regimens in paediatrics.[34] Conservative fluid therapy was defined for children as no fluid bolus, fluid titrated according to monitoring of heart rate, urine output, capillary refill, and level of consciousness (or total fluid amount less than that for liberal fluid therapy). Liberal fluid therapy was defined for children as a fluid bolus of 20 mL/kg of crystalloids over 5 to 10 minutes before titration (or total fluid amount greater than that for conservative fluid therapy). The liberal fluid therapy definition was based on the recommendation from the Surviving Sepsis Campaign.[38] What would conservative fluid therapy compared to liberal fluid therapy look like in neonatal care?

The FEAST study

The FEAST study published in 2011 found increased 48-hourly mortality in critically ill children randomised to receive fluid bolus therapy (0.9% sodium chloride or 5% albumin) in

a developing country setting.[36] The results of this study have reignited interest in this area of critical care management. A recent secondary analysis of the study data[39] was undertaken to explore the potential mechanisms for the increased mortality found in the intervention arm. The authors found 5% albumin and 0.9% sodium chloride boluses caused respiratory and neurological dysfunction, hyperchloraemic acidosis, and a reduction in haemoglobin concentration; they proposed that these were the mechanisms underlying the increased mortality in the fluid bolus arm. The rationale being that bolus fluids reduce haemoglobin concentration, resulting in decreased tissue oxygenation, increasing anaerobic metabolism, and resultant metabolic acidosis. The authors proposed that the combination of these adverse effects on haemoglobin concentration, acidosis, and respiratory and neurological function induced by the fluid boluses might have overwhelmed the compensatory mechanisms in the most severely ill children in the study, resulting in the increased mortality.[39]

What other studies are there in paediatrics?

Three other randomised studies examining the use of restrictive fluids in paediatric sepsis exist, but are either currently underway or recently completed, therefore they were not included in the previous discussed review.The Fluids in Shock (FiSh) pilot compared a restricted fluid bolus volume (10 mL/kg) with the current recommendation (20 mL/kg) to determine the feasibility of a large-scale trial. A larger FiSh trial, however, was found not feasible as participants had a lower severity of illness than expected in the pilot trial[40] making the numbers needed for a larger trial unrealistic.

Another small randomised controlled study published in 2017 compared children with septic shock to either fluid bolus therapy (40-60mL/kg in 20mL/kg aliquots) over either 15-20 minutes or 5-10 minutes. The authors found that compared with 5-10 minutes group, fewer

children in 15-20 minutes group required mechanical ventilation or had an increase in oxygenation index in the first 6 hours (36% vs 57%; relative risk, 0.62; 95% CI, 0.39-0.99) and 24 hours (43% vs 68%; relative risk, 0.63; 95% CI, 0.42-0.93) after fluid resuscitation.[41] A Canadian-based pilot trial to determine whether septic shock-reversal is faster in paediatric patients randomised to an early goal-directed fluid-sparing strategy versus usual care (SQUEEZE)[42] is underway and may provide some answers for the paediatric group.

Fluid bolus therapy in adults

In adult critical care, there are no multi-centre randomised controlled studies examining whether fluid bolus therapy should be given to critically ill patients or not. The majority of studies in adult critical care examining fluid bolus therapy focus on sepsis and hypotension.

The REFRESH pilot study demonstrated that a restricted volume and early vasopressor approach over the first 6 hours of resuscitation in adults presenting to the emergency department with suspected sepsis and hypotension resulted in a 30% relative reduction in total fluid administered up to 24 hours and was not associated with any harm.[32] The CLASSIC pilot study[43] found that restricting intravenous resuscitation fluid volumes compared with standard care in adult intensive care patients with septic shock is feasible. The restricted fluid approach resulted in lower resuscitation fluid volumes given in the first 5 days and during the entire intensive care stay. The study found no statistically significant difference in mortality, total fluid input or fluid balances. Fewer patients had worse acute renal injury amongst those who received less fluid.

WHAT ABOUT OTHER FLUID THERAPY PRACTICES IN NEONATOLOGY?

Liberal compared to restrictive fluid practices in neonatology

The Cochrane review in this area found that the 5 randomised controlled studies published between 1980 and 2000 that restricted water intake significantly increased postnatal weight loss and reduced the risks of patent ductus arteriosus and necrotising enterocolitis. All these studies included both parenteral and enteral fluids but with variation around the inclusion of medications and blood products. The authors of the Cochrane review warn clinicians against the over□interpretation of these findings due to under□representation of extremely preterm neonates. The age of the studies mean that they are unlikely to reflect current clinical practice in neonatology. A recent evidence-based review in this same area included the same randomised studies but also examined non-randomised studies.[44] The same conclusions were reached and it was again noted that no new primary studies have occurred in this area since 2000.

The AWAKEN study group

The Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study group recently published additional analyses from their primary dataset.[45] These secondary analyses describe the distribution and impact of fluid balance in preterm neonates (< 36 weeks GA) (n=1007)[46] as well as for near term and term neonates (n=645)[47] across the first postnatal week. Peak fluid balance in the first 7 days was associated with the need for mechanical ventilation on postnatal day 7 (adjusted odds ratio (OR) 1.12, 95% confidence interval (CI) 1.07-1.17) for ≥36 weeks GA compared to aOR 1.14 (95% CI 1.10 – 1.19 for < 36 weeks GA) and a negative fluid balance on postnatal day 7 was protective (aOR 0.33, 95% CI 0.16-0.67) for ≥36 weeks GA compared to aOR 0.21 (95% CI 0.12-0.35 for <36 weeks GA). These contemporary findings are consistent with the studies included in the reviews previously discussed.

WHAT DOES THE BROADER LITERATURE TELL US?

Fluid balance beyond initial resuscitation in paediatric and adult critical care

A recent systematic review and meta-analysis of fluid management beyond initial resuscitation in adults with acute respiratory distress syndrome and sepsis found a conservative or de-resuscitative (active removal of fluid using diuretics or renal replacement therapy) fluid strategy resulted in an increased number of ventilator-free days and a decreased length of intensive care stay compared with a liberal strategy or standard care.[48] The review included both randomised studies comparing fluid regimens with differing fluid balances between groups, and observational studies investigating the relationship between fluid balance and clinical outcomes.

Another systematic review and meta-analysis included a total of 44 studies (7507 children) and found strong evidence of an association between fluid overload and poorer outcomes in critically ill children.[49] Fluid overload, however it was defined in the studies, was consistently associated with increased in-hospital mortality (17 studies (n = 2853); odds ratio (OR) 4.34 (95% CI 3.01-6.26); I^2 = 61%). Fluid overload was associated with increased risk for prolonged mechanical ventilation (>48 hours) (3 studies (n = 631); OR 2.14 (95% CI 1.25-3.66); I^2 = 0%) and acute renal injury (7 studies (n = 1833); OR 2.36 (95% CI 1.27-4.38); I^2 = 78%).

The Fluid and Catheter Treatment Trial (FACTT) compared a conservative and a liberal strategy of fluid management using explicit protocols applied for 7 days in 1000 adults with acute lung injury. Management with the FACTT Conservative protocol resulted in a significantly lower cumulative fluid balance over the 7 days. While there was no difference in mortality, the FACTT Conservative group had more ventilator-free days and an improved

oxygenation index and lung injury score.[50] In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, a large European observational multicentre study, a positive fluid balance was associated with increased 60-day mortality.[51]

SUMMARY

Many similar questions surround fluid bolus therapy and subsequent fluid management in neonatal critical care as they do in paediatric and adult critical care. There is enough evidence to suggest that fluid bolus therapy and positive fluid balances in neonates may be associated with harm and require further careful exploration. Unfortunately, we remain hampered in neonatology due to a lack of consensus definitions. Is fluid given over 60 minutes even volume expansion? What is haemodynamic compromise in a neonate? How do we assess suspected haemodynamic compromise? What is the definition of fluid overload in neonatology? What outcomes are we looking for after a fluid bolus is given? How do we know that the perceived improvements would not have occurred if we had instituted 'watchful waiting'? An international consensus definition of haemodynamic compromise in neonates is required as well as development of a core outcome set. Core outcome sets are an agreed, standardised group of outcomes to be reported by all studies within a research field. This broad initiative is underway in neonatology through a United Kingdom based group.[52] The expansion of specific outcome sets for different areas of neonatal research is needed.

Fluid bolus therapy

Preliminary work is needed to determine if a study examining a fluid bolus compared to no fluid bolus is feasible. Would healthcare professionals be willing to withhold a fluid bolus in the setting of extreme prematurity and clinical signs of poor perfusion but no history of volume loss? A pilot randomised study could evaluate the feasibility of fluid bolus therapy

compared to no fluid bolus therapy for the management of suspected haemodynamic compromise in preterm infants (< 28 weeks GA) within the first 72 hours of age. The detailed development of the study will rely on the work to be carried out as described in the previous section, in particular, around definitions and outcomes.

Fluid balance and restrictive fluid practices

As previously discussed, data from the AWAKEN study group demonstrates an association between an early positive fluid balance and adverse outcomes in preterm and term neonates.[46,47] The group identified a negative fluid balance during the first 7 days as a potential therapeutic target for further study. A pilot, feasibility randomised controlled study may be required to assess healthcare professionals willingness to enrol neonates, as well as willingness of families to participate.

We do not know enough about the potential benefits or harms of fluid therapy in neonatology to call it a friend or foe. Box 1 provides a summary of some of the key unanswered research questions in this area. In an insightful editorial written by a critical care physician, critical care is described as a U shaped curve.[53] On the left side of the x-axis, inadequate provision of a particular therapy is associated with an increase in complications, demonstrated on the y-axis. On the right side of the x-axis, an overabundance of the same therapy will also increase complications and worsen outcome (Figure 1). Where we are on this U shaped curve in regards to fluid therapy in neonatology is unknown but perhaps we are more towards the right than we would like to believe.

Best Practices Box

What is the current practice?

Fluid Therapy in Neonatology

Best practice/guideline/care path objectives

- **Given the large variation in fluid bolus* practice, it is unlikely that current practice is best practice**
- **There is currently no high-quality evidence to support the development of best practice guidelines for fluid bolus therapy**
- **Restrictive* intravenous fluid practices within the first 7 days of age may be preferable**
- **Avoidance of fluid overload, reductions in morbidities, mortality and improved longer term outcomes are the ultimate goals of fluid management**

What changes in current practice are likely to improve outcomes?

Standardising a conservative approach to fluid therapy may improve outcomes whilst awaiting higher quality evidence from future research studies.

Major Recommendations

Fluid bolus therapy

- **Use fluid bolus* therapy judiciously outside the setting of hypovolaemia in preterm and term infants (GRADE C)**

Fluid balance and restrictive fluid practices

- **Consider restrictive* intravenous fluid practices within the first 7 days of age (GRADE B)**

Summary statement

Fluid therapy in neonatology has a limited evidence base. A pilot randomised study could evaluate the feasibility of fluid bolus therapy compared to no fluid bolus therapy for the management of suspected haemodynamic compromise outside the setting of hypovolaemia. A negative fluid balance during the first 7 days is a potential therapeutic target for further study.

Data from Refs.[1,22,46,47]

*Variable definitions

References

1. Keir AK, Karam O, Hodyl N, et al. International, multicentre, observational study of fluid bolus therapy in neonates. *J Paediatr Child Health.* 2018; 55(6):632-639.
2. Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. *J Perinatol.* 2006;26(11):677-681.
3. Batton B, Li L, Newman NS, et al. Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(3):F201-206.
4. Dempsey EM, Barrington KJ, Marlow N, et al. Management of hypotension in preterm infants (The HIP Trial): a randomised controlled trial of hypotension management in extremely low gestational age newborns. *Neonatology.* 2014;105(4):275-281.
5. Chow SSW, Le Marsney R, Hossain S et al. *Report of the Australian and New Zealand Neonatal Network 2013.* Sydney: ANZNN; 2015.
6. Goldberg RN, Chung D, Goldman SL, Bancalari E. The association of rapid volume expansion and intraventricular hemorrhage in the preterm infant. *J Pediatr.* 1980;96(6):1060-1063.
7. Nixon JV, Murray RG, Leonard PD, Mitchell JH, Blomqvist CG. Effect of large variations in preload on left ventricular performance characteristics in normal subjects. *Circulation.* 1982;65(4):698-703.
8. Osborn D, Evans N, Kluckow M. Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr.* 2002;140(2):183-191.
9. Pladys P, Wodey E, Betremieux P, Beuchee A, Ecoffey C. Effects of volume expansion on cardiac output in the preterm infant. *Acta paediatrica.* 1997;86(11):1241-1245.

10. Starling EH. On the Absorption of Fluids from the Connective Tissue Spaces. *J Physiol.* 1896;19(4):312-326.

11. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res.* 2010;87(2):198-210.

12. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth.* 2012;108(3):384-394.

13. Adamson RH, Lenz JF, Zhang X, Adamson GN, Weinbaum S, Curry FE. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. *J Physiol.* 2004;557(Pt 3):889-907.

14. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369(25):2462-2463.

15. Margarson MP, Soni NC. Changes in serum albumin concentration and volume expanding effects following a bolus of albumin 20% in septic patients. *Br J Anaesth.* 2004;92(6):821-826.

16. Dempsey EM, Barrington KJ. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. *J Perinatol.* 0000;27(8):469-478.

17. Beverley DW, Pitts-Tucker TJ, Congdon PJ. Prevention of intraventricular haemorrhage by fresh frozen plasma. *Arch Dis Child.* 1985;60(8):710-713.

18. Ekblad H, Kero P, Korvenranta H. Renal function in preterm infants during the first five days of life: influence of maturation and early colloid treatment. *Biol Neonate.* 1992;61(5):308-317.

19. Gottuso MA, Williams ML, Oski FA. The role of exchange transfusions in the management of low-birth-weight infants with and without severe respiratory distress

syndrome. II. Further observations and studies of mechanisms of action. *J Pediatr.* 1976;89(2):279-285.

20. Lundstrom K, Pryds O, Greisen G. The haemodynamic effects of dopamine and volume expansion in sick preterm infants. *Early Hum Dev.* 2000;57(2):157-163.
21. The Northern Neonatal Nursing Initiative [NNNI] Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. The Northern Neonatal Nursing Initiative [NNNI] Trial Group. *Eur J Pediatr.* 1996;155(7):580-588.
22. Osborn DA, Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev.* 2004.
23. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet.* 1996;348(9022):229-232.
24. Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. *J Perinatol.* 2003;23(6):473-476.
25. Lynch SK, Mullett MD, Graeber JE, Polak MJ. A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. *J Perinatol.* 2008;28(1):29-33.
26. Mydam J, Zidan M, Chouthai NS. A comprehensive study of clinical biomarkers, use of inotropic medications and fluid resuscitation in newborns with persistent pulmonary hypertension. *Pediatr Cardiol.* 2015;36(1):233-239.
27. Wyckoff MH, Perlman JM, Laptook AR. Use of volume expansion during delivery room resuscitation in near-term and term infants. *Pediatrics.* 2005;115(4):950-955.

28. Ewer AK, Tyler W, Francis A, Drinkall D, Gardosi JO. Excessive volume expansion and neonatal death in preterm infants born at 27-28 weeks gestation. *Paediatr Perinat Epidemiol.* 2003;17(2):180-186.

29. Tammela OK, Koivisto ME. Fluid restriction for preventing bronchopulmonary dysplasia? Reduced fluid intake during the first weeks of life improves the outcome of low-birth-weight infants. *Acta paediatrica.* 1992;81(3):207-212.

30. Van Marter LJ, Leviton A, Allred EN, Pagano M, Kuban KC. Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants. *J Pediatr.* 1990;116(6):942-949.

31. Boer C, Bossers SM, Koning NJ. Choice of fluid type: physiological concepts and perioperative indications. *Br J Anaesth.* 2018;120(2):384-396.

32. Macdonald SPJ, Taylor DM, Keijzers G, et al. REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial. *Trials.* 2017;18(1):399.

33. Mauch J, Madjdpour C, Kutter AP, et al. Effect of rapid fluid resuscitation using crystalloids or colloids on hemostasis in piglets. *Paediatr Anaesth.* 2013;23(3):258-264.

34. Li D, Li X, Cui W, Shen H, Zhu H, Xia Y. Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock. *Cochrane Database Syst Rev.* 2018;12:CD010593.

35. Santhanam I, Sangareddi S, Venkataraman S, Kissoon N, Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. *Pediatr Emerg Care.* 2008;24(10):647-655.

36. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364(26):2483-2495.

37. Benakatti G, Singhi S, Muralidharan J, Bansal A. 15 Conventional vs. Restrictive Maintenance Fluid Regime in Children with Septic Shock after Initial Resuscitation: A Randomized Open Label Controlled Trial. *Arch Dis Child.* 2012;97(Suppl 2):A5-A5.

38. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.

39. Levin M, Cunnington AJ, Wilson C, et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. *The Lancet Respiratory medicine.* 2019;7(7):581-593.

40. Inwald DP, Canter R, Woolfall K, et al. Restricted fluid bolus volume in early septic shock: results of the Fluids in Shock pilot trial. *Arch Dis Child.* 2019;104(5):426-431.

41. Sankar J, Ismail J, Sankar MJ, C PS, Meena RS. Fluid Bolus Over 15-20 Versus 5-10 Minutes Each in the First Hour of Resuscitation in Children With Septic Shock: A Randomized Controlled Trial. *Pediatr Crit Care Med.* 2017;18(10):e435-e445.

42. Parker MJ, Thabane L, Fox-Robichaud A, Liaw P, Choong K. A trial to determine whether septic shock-reversal is quicker in pediatric patients randomized to an early goal-directed fluid-sparing strategy versus usual care (SQUEEZE): study protocol for a pilot randomized controlled trial. *Trials.* 2016;17(1):556.

43. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med.* 2016;42(11):1695-1705.

44. Abbas S, Keir AK. In preterm infants, does fluid restriction, as opposed to liberal fluid prescription, reduce the risk of important morbidities and mortality? *J Paediatr Child Health.* 2019;55(7):860-866.

45. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health.* 2017;1(3):184-194.

46. Selewski DT, Gist KM, Nathan AT, et al. The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group. *Pediatr Res.* 2019; doi: 10.1038/s41390-019-0579-1.

47. Selewski DT, Akcan-Arikan A, Bonachea EM, et al. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. *Pediatr Res.* 2019;85(1):79-85.

48. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43(2):155-170.

49. Alobaidi R, Morgan C, Basu RK, et al. Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. *JAMA pediatrics.* 2018;172(3):257-268.

50. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354(24):2564-2575.

51. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care.* 2008;12(3):R74.

52. Webbe J, Sinha I, Gale C. Core Outcome Sets. *Archives of disease in childhood Education and practice edition.* 2018;103:163-166

53. Fuller BM. Fluid, Fluid Everywhere, and All the Organs Did Not Shrink; Fluid, Fluid Everywhere, Administered Without a Think. *Crit Care Med.* 2018;46(10):1692-1693.

Figure legends

Figure 1: The U shaped curve in critical care

Table 1: Types of fluids used for fluid bolus therapy in neonatal care

Solution/Properties	pH	Osmolality	Na	K	Cl	HCO3	Lactate	Acetate	Gluconate	Possible adverse effects	Comments
Human plasma	7.35 - 7.35	291	135-145	4.5-5.5	94-111	23-27	-	-	-		
0.9% sodium chloride	5.4	308	154	-	154	-	-	-	-	Hyperchloraemic acidosis	
Compound sodium lactate[a]	6.5	280.6	131	5.4	111	-	29	-	-		
Balanced salt solution [b]	7.4	294	140	5	98	-	-	27	23		
Albumin 4% (Albumex)		250	148		128					Fluid overload	Plasma expansion duration < 24 hours Plasma half-life 16-24

NB: Osmolality Units mOsol/L,
Na/K/Cl mmol/L
[a]Common examples: Ringers lactate/Hartmann's
[b]Common examples: Plasma-Lyte

Box 1: A few unanswered questions in fluid therapy in neonatology

What is haemodynamic compromise in neonatology?
What is considered a fluid bolus in neonatology?
What is restrictive fluid therapy defined as in neonatology?
What is liberal fluid therapy defined as in neonatology?

Potential study questions
In preterm infants ≤28 weeks GA at ≤72 hours of age [*patient*] does a fluid bolus for any indication (excluding septic shock and/or haemorrhagic shock) [*intervention*] compared to no fluid bolus [*comparator*] increase or decrease morbidity (e.g. intraventricular haemorrhage) and/or mortality [*outcome*]?

In term infants at ≤72 hours of age [*patient*] does a fluid bolus for any indication (excluding septic shock and/or haemorrhagic shock) [*intervention*] compared to no fluid bolus [*comparator*] increase or decrease morbidity and/or mortality [*outcome*]?

Is it feasible and safe to use restrictive versus liberal intravenous fluid therapy policy in preterm infants (≤28 weeks GA) in the first 7 days of admission?

Is it feasible and safe to use restrictive versus liberal intravenous fluid therapy policy in infants (>37 weeks GA) in the first 7 days of admission?