

# 2022 exceptional surveillance of intravenous fluid therapy in children and young people in multiple guideline (NICE guideline NG29, NG51, NG143, CG84, CG102 and NG18)

Wednesday 3<sup>rd</sup> August 2022

## Surveillance decision

We will update section 1.3 fluid resuscitation of the guideline on [intravenous fluid therapy in children and young people in hospital](#) (NICE guideline NG29).

We will update section 1.8 intravenous fluids in people with suspected sepsis of the guideline on [sepsis](#) (NICE guideline NG51).

We will update section 1.5 management by the paediatric specialist of the guideline on [fever in under 5's](#) (NICE guideline NG143).

We will update section 1.3 fluid management of the guideline on [diarrhoea and vomiting caused by gastroenteritis in under 5's](#) (NICE guideline CG84).

We will update section 1.4 management in secondary care of the guideline on [meningitis and meningococcal septicaemia in under 16's](#) (NICE guideline CG102).

We will update section 1.4 diabetic ketoacidosis of the guideline on [diabetes \(type 1 and type 2\) in children and young people](#) (NICE guideline NG18).

The updates will focus on the volume of fluid boluses given during intravenous fluid therapy for shock in children and young people.

## ***Reason for the exceptional review***

To assess the impact of the publication of the European Resuscitation Councils (ERCs) [paediatric life support \(PLS\) guideline](#) on NICE guidelines

which mention fluid therapy for the treatment of shock in children and young people.

## **Methods**

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Feedback from topic experts.
- Focussed literature searches to identify relevant evidence.
- Considering the evidence used to develop the guidelines.
- Examining related NICE guidance and quality standards.
- Consulting on the proposal with stakeholders.
- Considering comments received during consultation and making any necessary changes to the proposal.

For further details about the process and the possible update decisions that are available, see [ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual](#).

## **Information considered in this exceptional surveillance review**

### **Background information**

Early goal directed therapy/ early aggressive fluid resuscitation has been the main approach in treating shock, and many clinical guidelines on IV fluids therapy were based on this approach. The approach involves the administration of up to 60 ml/kg of isotonic fluid within 15 minutes after the diagnosis of shock ([Rivers et al. 2001](#)). However, recent studies have shed doubt on whether or not rapid, high volume, fluid therapy is the most appropriate form of treatment for shock.

A high profile study, conducted in hospitals in 3 countries in Africa (Fluid Expansion as Supportive Therapy; FEAST; [Maitland et al. 2011](#)) challenged this approach, and has opened up the debate surrounding the best approach for fluid therapy in children and young people with severe febrile illness. Inclusion criteria for the FEAST trial were broad but children and young

people with gastroenteritis, severe malnutrition, or noninfectious causes of shock were excluded. Of enrolled participants, 57% had malaria. The FEAST trial assessed the impact of bolus size (20 ml vs 40 ml) and fluid type (5% albumin vs 0.9% saline solution) in children and young people with severe febrile disease. It was conducted in 6 hospitals, across 3 countries, and 3,141 children and young people were enrolled. The primary outcome was 48 hour mortality. Recruitment was halted before the target of 3,600 children and young people due to safety concerns around the mortality rate in the bolus groups compared to the non-bolus group. Forty-eight hour mortality in the albumin bolus group was 10.6%, in the saline bolus group was 10.5%, and in the control non-bolus group was 7.3%. Relative risk for any bolus compared to the non-bolus group was 1.45; 95% (95% CI 1.13 to 1.86; p=0.003). This increased mortality risk persisted to the 4 week mark, with the albumin bolus, saline bolus and control group showing 12.2%, 12.0% and 8.7% of 4 week mortality respectively (p=0.004 for the comparison of any bolus vs control). Cases of neurological complications, pulmonary oedema and increased intracranial pressure were not significantly different between the 3 groups.

This study was designed to assess the most appropriate fluid therapy protocol for acutely ill children and young people with severe febrile illness and impaired perfusion, presenting in typical hospitals in African countries, where access to intensive care facilities, and diagnostic testing are often not available. As such, children and young people with a range of severe illnesses were included in the study including those with severe malaria, sepsis, pneumonia, and meningitis, and were not differentiated. The setting in which this research was conducted is different to the environment in which children and young people with shock would present in the UK.

### **Evidence considered in this exceptional surveillance review**

The ERC published their PLS guidelines in 2021 which contained recommendations for fluid therapy in children and young people with shock. The Resuscitation Council UK (RCUK) has adopted these guidelines. The guidelines were drafted and agreed by the Paediatric Life Support Writing

Group members of the ERC, and were posted for public comment prior to publication.

The ERC guidelines now recommend smaller volumes of resuscitation fluid in the initial management of children and young people presenting with signs of shock. They now state: Give one or more early fluid bolus(es) of 10 ml/kg in children and young people with recognised shock. Repeated fluid boluses (up to 40–60 ml/kg) might be needed in the first hour of treatment of (septic) shock. The smaller volume enables faster reassessment but does not limit the total amount of fluid given.

In order to develop these recommendations, a literature search was conducted. The review question in the ERC guideline was: do certain doses or types of fluid and how they are given in (different degrees of) circulatory failure compared to others impact outcome. The population was infants and children and young people who are being treated for circulatory failure in any setting, during the first hour of treatment. The intervention was “a certain dose or type of fluid given at a certain speed of delivery, compared to another”. All outcomes were considered, including mortality, adverse events, acute renal injury, organ system dysfunction and fluid overload. Exclusion criteria included infants or children in cardiac arrest, treatment beyond the first hour of treatment and diabetic ketoacidosis. A priori sub-groups for hypovolemic, haemorrhagic, septic and cardiogenic shock were decided upon. After de-duplication 771 articles were identified. Full text articles were ordered for 4 guidelines, 7 systematic reviews, 6 randomised control trials and 25 observational studies. Evidence from adults was also discussed when relevant.

Two studies were found that reanalysed FEAST data. One study reanalysed FEAST data conducting subgroup analyses according to different international definitions of shock applied to the participants ([Houston et al. 2018](#)), and found that there was a consistent risk of increased mortality in all sub-groups. The authors found that hypotension was rare in the children and young people with severe febrile illness, who were recruited to the study, with it impacting only 0.9% of participants. In the subgroup of children with WHO defined

shock, totalling 2% of participants, the increased relative risk of mortality was 240% ( $p=0.07$ ) for the bolus group compared to the non-bolus group.

The second study that conducted a post hoc analysis of the FEAST data to try and determine the mechanism underlying the increased mortality following bolus administration ([George et al. 2019](#)). They found that the increased risk of mortality from bolus therapy was not due to a mechanism occurring immediately after bolus administration, as mortality rates were similar between groups immediately following bolus administration. The excess mortality in the bolus group is due to a slower decrease in mortality risk over the ensuing 4 days compared to non-bolus group.

Additionally, a systematic review was identified that looked at cohort studies which compared high and low fluid volumes in severe sepsis/septic shock in adults ([Tigabu et al. 2018](#)). Fifteen studies were included ( $n=31,443$ ). Patients with a high fluid balance have an increased mortality risk, with a pooled risk ratio of 1.7 (95% confidence interval 1.2 - 2.41). This work found that survivors of severe sepsis/septic shock received higher fluid volume in the first 3 hours, however fluid volume administered in the first 24 hours was higher for non-survivors. Low volume resuscitation in the first 24 hours had a significant mortality reduction ( $p=0.02$ ). A meta-analysis of individual patient data in adults ([Prism Investigators 2017](#);  $n=3723$ ; 132 hospitals; 7 countries) found no difference in 90 day mortality between early goal directed therapy (EGDT) and usual care. EGDT was associated with greater mean use of intensive care ( $5.3\pm 7.1$  vs.  $4.9\pm 7.0$  days,  $p=0.04$ ), and cardiovascular support ( $1.9\pm 3.7$  vs.  $1.6\pm 2.9$  days,  $p=0.01$ ).

It was also noted that the [surviving sepsis guidelines](#) from Surviving Sepsis Campaign were updated in 2020 to recommend 10-20 ml/kg boluses, to a total volume of 40-60 ml/kg in the first hour.

The authors of the ERC guidelines recommend different approaches for different aetiologies of shock. For presumed septic shock they recommend a more restrictive approach to fluid resuscitation, with frequent reassessment, to minimise side effects. They recommend 10 ml/kg fluid boluses, to allow for

faster reassessment, without the limitation on the total fluid volume given in the first hour of treatment, which may be up 40-60 ml/kg. Early consideration of vasoactive or inotropic drugs and respiratory support is also strongly advised.

For hypovolemic non-haemorrhagic shock, ERC guidelines recommended fluid resuscitation protocols are the same as advised for septic shock, however there should be consideration of the underlying cause. The case of acute gastroenteritis is highlighted, as this can cause hypovolaemic shock, the ERC guideline authors considered that acute gastroenteritis most commonly occurs in situations where there are limited resources and with comorbidity and as such recommended a non-bolus approach to fluid resuscitation, except when septic shock is also present. They recommended the same approach for children and young people with severe malnutrition.

For cardiogenic shock, the authors note that clinical consensus is to avoid fluid resuscitation once confirmed, however there may be cause for cautious fluid resuscitation in some clinical situations.

The aetiology for haemorrhagic shock as a result of trauma differs from hypovolaemic shock, and there is a separate body of evidence.

Recommendations in the ERC guideline regarding haemorrhagic shock are in line with the current NICE guideline on [major trauma](#) (NICE guideline NG39).

### ***Search and selection strategy***

We searched for new evidence related to the safety of delivering fluid therapy with 20 ml/kg boluses vs 10 ml/kg boluses. We found 615 studies in a search for randomised controlled trials, systematic reviews, meta-analysis, case-series and observational studies published between 1<sup>st</sup> January 2011 and 16<sup>th</sup> May 2022.

Studies were included if they looked at any outcomes for 20 ml/kg boluses compared to 10 ml/kg boluses. Following a sift on abstract, 18 full texts were reviewed. Following full text review, a single UK based randomised control

trial (RCT) study that was relevant to the search question was included for consideration.

The Fluids in Shock (FiSH; [Inwald et al. 2019](#)) trial looked at giving children and young people, aged 0-16 years, in the UK a restricted fluid bolus volume of 10 ml/kg instead of current usual practice, which is 20 ml/kg. The trial was designed in response to the publication of the FEAST data. 75 participants were recruited, 2 were withdrawn. Participants were not as unwell as expected, 23 (59%) of 39 in the 10 ml/kg arm and 25 (74%) of 34 in the 20 ml/kg arm required a single trial bolus before the shock resolved. The Paediatric Index of Mortality-2 score was not significantly different between the groups. There were no deaths. Length of hospital stay, paediatric intensive care unit (PICU) admissions and PICU-free days at 30 days did not differ significantly between the groups. The study group determined that a larger trial of this design is not feasible in the UK due to the lack of seriously unwell patients they were able to recruit.

During literature searching, one study was identified as ongoing research. This study is a Canadian based trial to determine which fluid therapy strategy results in quicker septic shock reversal ([SQUEEZE trial](#)). We plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible.

### ***Topic expert feedback***

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We contacted 15 topic experts and received 8 responses. Two topic experts replied to say that they were unable to comment, and 1 topic expert declined to comment due to a conflict of interest. Six topic experts were consultant paediatricians, 1 topic expert was a specialist clinical pharmacist with a special interest in fluids, sedation and paediatrics, and 1 topic expert was a chair in paediatric infection.

We wanted to know whether topic experts were aware of a change in fluid bolus therapy practice due to either the findings of the FEAST trial, or the

updated ERC guidelines for paediatric life support. Seven of the topic experts were aware of a change in practice towards smaller fluid boluses. Both the FEAST trial and the ERC PLS guidelines were listed as reasons for this change in practice. One topic expert mentioned that some information resources used by trainees explicitly advise 10 ml/kg boluses.

We also wanted to know whether or not topic experts were aware of any evidence looking at the safety of 10 ml/kg fluid boluses compared to 20 ml/kg fluid boluses for children and young people. Three topic experts highlighted the FiSH study (Inwald et al. 2019), which did not find significantly different outcomes between 10 ml/kg and 20 ml/kg boluses in children and young people with shock. The study did not manage to recruit as many unwell patients as it had intended however, which limits the interpretation of its findings.

One topic expert noted a recent international randomised trial in Europe, looking at restrictive versus standard fluid therapy in adults with septic shock in the intensive care unit ([Meyhoff et al. 2022](#)). There was no difference in 90 day mortality found in this work. The topic expert acknowledged that this was a different population than being considered in this review, and that there was a need for research in children and young people with shock.

Finally, we asked topic experts whether or not there were any safety or equality issues related to fluid therapy for children and young people in shock that they would like to highlight. Four topic experts highlighted safety issues as a result of fluid overload from fluid bolus delivery, of these 2 explicitly mentioned the FEAST trial as the source of this understanding. Two of the topic experts acknowledged that there was little head to head evidence assessing 10 ml/kg vs 20 ml/kg fluid boluses, and that the impact in a UK clinical context was not certain.

Three topic experts raised the fact that NICE guidelines now differ from the ERC and RCUK guidelines on fluid therapy for children and young people in shock. They said that the inconsistency between these major guidelines, and



that this could cause confusion, conflict between different staff caring for a child, or delays in care.

One topic expert also raised the issue of using mean arterial blood pressure as a measurement of a child's response to a fluid bolus. They stated that in some patients fluid boluses may have a vasodilatory effect, reducing mean arterial blood pressure, despite increased cardiac output. They felt that both mean arterial blood pressure and cardiac output should be used to assess response to fluid boluses.

In regards to equalities issues, 1 topic expert raised that it may be an equality issue that it can be harder to evaluate dehydration in some groups compared to others, using the recommended clinical signs. The topic expert did not state which clinical signs, or which groups this may be an issue for.

### ***Information considered when developing the guideline***

The appropriate volumes of resuscitation fluid to use in the initial management of children and young people presenting with signs of shock occurs in many NICE guidelines. The mechanism of shock varies in these guidelines, and so the impact of the changes to the ERC PLS guideline has been assessed individually below. The recommendations and the evidence underlying them are also tabulated in Appendix A for ease of comparison.

### **Intravenous fluid therapy in children and young people in hospital (NICE guideline NG29) and Sepsis (NICE guideline NG51)**

Recommendations from the NICE guideline on intravenous fluid therapy in children and young people in hospital (NICE guideline NG29) were directly quoted in the NICE guideline on sepsis (NICE guideline NG51), and so the 2 guidelines will be discussed together here.

[Recommendation 1.3.1](#) in NICE guideline NG29 states that if children and young people need intravenous fluid resuscitation to deliver glucose free crystalloids that contain sodium in the range of 131-154 mmol/litre as a bolus of 20 ml/kg over less than 10 minutes. This recommendation was developed in 2015.

During the development of NICE guideline NG29 searches were conducted for systematic reviews, RCTs and cohort studies in children and young people. The guideline development group (GDG) did not consider that evidence in an adult population was relevant as the optimum rate of fluid administration is likely to differ for children and young people and adults as the fluid requirements for children and young people are higher. No relevant clinical studies comparing sodium chloride at different rates were identified. Children and young people with shock need immediate restoration of intravascular blood volume. It is current practice to administer 20 ml/kg over less than 10 minutes. No evidence was identified to change current practice. The GDG felt it important to reassess the circulation following completion of the fluid bolus and administer further fluids if indicated. No further evidence was found during the development of NICE guideline NG51.

During the development of NICE guideline NG29 the evidence from the FEAST trial was noted, however the GDG concluded that although this was an important finding, the situation was not directly applicable to the UK clinical setting. It was also discussed during the development of NICE guideline NG51, however the study was excluded from formal review because the study population consisted of children and young people with severe febrile illness or respiratory distress rather than sepsis. Only 16% of the study population had a working diagnosis of septicaemia.

### **Fever in under 5's (NICE guideline NG143)**

[Recommendation 1.5.16](#) states that children with shock should be given an immediate 20 ml/kg bolus, typically of 0.9% sodium chloride. They should then be actively monitored and given further fluid boluses as necessary. This recommendation was developed in 2007.

One case-control study found that too little fluid therapy versus “adequate” fluid therapy was significantly associated with death. No information was given in the guideline about the volume of “adequate” therapy given. A retrospective cohort study found that fluid boluses and early use of inotropes resulted in shock reversal and increased survival. There was no information on the volume of fluid boluses given.

The GDG concluded that children with fever and signs of circulatory insufficiency have reduced mortality when given intravenous fluid resuscitation. They stated that current practice would be to give a bolus of 20 ml/kg.

### **Diarrhoea and vomiting caused by gastroenteritis in under 5's (NICE guideline CG84)**

[Recommendation 1.3.3.2-3](#) states that suspected or confirmed shock should be treated with a rapid infusion of 20 ml/kg of 0.9% sodium chloride. If a child remains shocked after the initial rapid infusion, then another rapid infusion of 20 ml/kg of 0.9% sodium chloride should be given and causes of shock other than dehydration should be considered. This recommendation was developed in 2009.

There was no definitive evidence on the optimum IV fluid regimen for the management of hypovolaemic shock in the dehydrated child with gastroenteritis. However, there was widespread consensus that whatever the cause of shock, a bolus of IV fluid should immediately be given. There was no committee discussion of the different volumes for initial boluses in fluid therapy. Discussion was instead centered on the optimal fluid composition.

### **Meningitis and meningococcal septicaemia in under 16's (NICE guideline CG102)**

[Recommendation 1.4.30](#) states that for children and young people with suspected or confirmed meningococcal septicaemia and signs of shock, an immediate 20 ml/kg fluid bolus of 0.9% sodium chloride should be given over 5-10 minutes, followed immediately by reassessment. If signs of shock persist a second bolus of 20 ml/kg 0.9% sodium chloride or 4.5% human albumin over 5-10 minutes is recommended. If the signs of shock still persist after the first 40 ml/kg, a third bolus of 20 ml/kg 0.9% sodium chloride or 4.5% human albumin over 5-10 minutes is recommended. Additionally it is recommended to call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation; start treatment with vasoactive drugs; be aware that some children and young people may require large volumes of fluid over a

short period of time to restore their circulating volume; consider giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution over 5–10 minutes based on clinical signs and appropriate laboratory investigations including urea and electrolytes. This recommendation was developed in 2010.

No evidence was identified regarding the volume or rate of intravenous fluids to give and there was no committee discussion of the different volumes for initial boluses in fluid therapy. Discussion was instead centered on the optimal fluid composition.

### **Diabetes in children and young people (NICE guideline NG18)**

[Recommendation 1.4.24](#) in the NICE guideline on diabetes in children and young people recommends giving children and young people with diabetic ketoacidosis (DKA) with signs of shock an initial intravenous bolus of 20 ml/kg 0.9% sodium chloride as soon as possible. The fluid bolus volume is not detracted from the total fluid deficit. This recommendation was written in 2020. Recommendations were also made to highlight that shock is rare in children and young people with DKA, and that typical symptoms of shock can overlap with symptoms of DKA.

During an update in 2020, a combined search was conducted to identify studies which explored the route of fluid administration for rehydration, the type of fluids (including additives) that should be used for rehydration and the rate and volume these fluids should be administered. There were no studies identified that looked at 20 ml/kg vs 10 ml/kg fluid boluses in children with DKA and shock.

Diabetic ketoacidosis was an exclusion criteria for the ERC guidelines, and as such this population was not considered in their evidence review. The current recommendations for fluid therapy in children and young people with diabetic ketoacidosis (DKA) were based on clinical consensus of intravenous fluid therapy for children in shock.

The British Society for Paediatric Endocrinology and Diabetes (BSPED) updated their guideline on management of diabetic ketoacidosis in children and young people following the publication of the ERC guidelines.

### ***Other relevant NICE guidance***

No impact was identified on other NICE guidance.

### ***Equalities***

No equalities issues were identified at this point of the surveillance process.

### ***Overall decision***

We will update the NICE guidelines in which there are recommendations about fluid therapy for children and young people with shock. There has been a change in the thinking around fluid boluses for the treatment of shock in children and young people following the publication of the FEAST trial, which found increased mortality with any fluid bolus in a trial in African hospitals. This has led to some clinical guidelines recommending smaller fluid boluses, as in the case of the ERC, RCUK and the Surviving Sepsis Campaign. Across the NICE guidelines that mention fluid therapy for children and young people in shock, 20 ml/kg boluses are recommended, followed by reassessment and further boluses if necessary.

During our focussed literature search for evidence on the safety of 10 vs 20 ml/kg fluid boluses in a UK clinical context, we found only 1 relevant study. This work found no differences between 10 ml/kg and 20 ml/kg fluid boluses in mortality or length of PICU stay. The study did not manage to recruit as many seriously unwell patients as it had intended however, and the researchers concluded that studies of this design may not be feasible in the UK.

The majority of topic experts who responded told us that they were aware of clinical practice changing as a result of the ERC guidelines, with clinicians choosing smaller fluid bolus volumes and more frequent reassessment. Topic experts did not identify any further evidence for 10 vs 20 ml/kg fluid boluses in children and young people, in a UK clinical context. When asked about safety considerations, a number of topic experts raised the idea that fluid overload

from larger bolus volumes may be harmful. Topic experts also raised that the discrepancy between the ERC, surviving sepsis guidelines and NICE guidelines on fluid boluses for shock may cause confusion and therefore harm.

When writing recommendations on fluid therapy for children and young people in shock across multiple NICE guidelines, committee consensus was used, and recommendations were based on current clinical practice at the time of development. As a result of the FEAST trial, and concerns about the impact of fluid overload there has been a change in current clinical practice. Therefore, while we did not find evidence that existing NICE recommendations are unsafe, they are no longer in line with current clinical practice and we will therefore update NICE guidelines in which there are recommendations about fluid therapy for children and young people with shock.

ISBN: [digital editors will add this before publication]