ESPNIC clinical practice guidelines

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SYSTEMATIC REVIEW

ESPNIC clinical practice guidelines: intravenous maintenance fluid therapy in acute and critically ill children— a systematic review and meta-analysis

David W. Brossier[1] , Lyvonne N. Tume[2] , Anais R. Briant[3], Corinne Jotterand Chaparro[4,5] ,
Clémence Moullet[4] , Shancy Rooze[6], Sascha C. A. T. Verbruggen[7] , Luise V. Marino[8] , Fahad Alsohime[9],
Sophie Beldjilali[10], Fabrizio Chiusolo[11] , Leonardo Costa[12], Capucine Didier[13], Stavroula Ilia[14] ,
Nyandat L. Joram[15] , Martin C. J. Kneyber[16] , Eva Kühlwein[17], Jorge Lopez[18] , Jesus López-Herce[18] ,
Huw F. Mayberry[19] , Fortesa Mehmeti[20], Magdalena Mierzewska-Schmidt[21], Maria Miñambres Rodríguez[22] ,
Claire Morice[20], John V. Pappachan[23] , Florence Porcheret[24], Leonor Reis Boto[25] , Luregn J. Schlapbach[26] ,
Hakan Tekguc[27] , Konstantinos Tziouvas[28] , Jean-Jacques Parienti[29], Isabelle Goyer[30]
and Frederic V. Valla[13,31]* on behalf of the Metabolism Endocrinology and Nutrition section of the European
Society of Pediatric and Neonatal Intensive Care (ESPNIC)

Abstract

Purpose: Intravenous maintenance fluid therapy (IV-MFT) prescribing in acute and critically ill children is very variable among pediatric health care professionals. In order to provide up to date IV-MFT guidelines, the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) undertook a systematic review to answer the following five main questions about IV-MFT: (i) the indications for use (ii) the role of isotonic fluid (iii) the role of balanced solutions (iv) IV fluid composition (calcium, magnesium, potassium, glucose and micronutrients) and v) and the optimal amount of fluid.

Methods: A multidisciplinary expert group within ESPNIC conducted this systematic review using the Scottish Inter-collegiate Guidelines Network (SIGN) grading method. Five databases were searched for studies that answered these questions, in acute and critically children (from 37 weeks gestational age to 18 years), published until November 2020. The quality of evidence and risk of bias were assessed, and meta-analyses were undertaken when appropriate. A series of recommendations was derived and voted on by the expert group to achieve consensus through two voting rounds.

Results: 56 papers met the inclusion criteria, and 16 recommendations were produced. Outcome reporting was inconsistent among studies. Recommendations generated were based on a heterogeneous level of evidence, but consensus within the expert group was high. "Strong consensus" was reached for 11/16 (69%) and "consensus" for 5/16 (31%) of the recommendations.

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*Correspondence: frederic.valla@chu-lyon.fr
[31] Service de Réanimation Pédiatrique, Hôpital Femme Mère Enfant, 59
Boulevard Pinel, 69500 Bron, France
Full author information is available at the end of the article

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Conclusions: Key recommendations are to use isotonic balanced solutions providing glucose to restrict IV-MFT infusion volumes in most hospitalized children and to regularly monitor plasma electrolyte levels, serum glucose and fluid balance.

Keywords: Isotonic fluids, Balanced fluids, Hyponatremia, Fluid balance, Intensive care, Acutely ill children

Introduction

Intravenous maintenance fluid therapy (IV-MFT) has been defined as the water and electrolyte prescription designed to replace anticipated physiologic water and electrolyte losses over the ensuing 24-h period [1]. Maintenance fluid therapy is provided by enteral hydration and/or IV-MFT which comprises both specific IV-MFT prescription, but also additional fluids administered as vectors of various treatments, blood products, or line flush infusions. IV-MFT should be differentiated from fluid boluses and resuscitation fluids that are administered to correct a relative or true fluid deficit, or from replacement fluids that are administered to correct abnormal fluid losses, even if this might be challenging as they are often administered simultaneously. IV-MFT is a standard of care for many hospitalized children in both acute and critical care settings (i.e. emergency department, pediatric wards, surgical wards or intermediate (high dependency) care units and pediatric intensive care units (PICU)). Despite this, maintenance fluid prescribing practices vary considerably [2] and guidelines are scarce [3]. Historically, IV-MFT prescriptions (fluid volume calculation formulas and solution composition) were based on Holliday and Segar's work [4]. Since then, the use of these guidelines has been associated with potentially severe complications such as hyponatremia, fluid overload and hyperchloremic acidosis, due to inappropriate fluid composition and/or infusion rates/volumes [3, 5–7]. Several established practices are currently questioned. First, the ideal fluid tonicity, i.e. the osmotic pressure gradient of the fluid which is determined by the concentration of osmoactive or non-penetrating solutes, mainly sodium [8]. Second, the chloride content and balanced nature of the fluid (i.e. balanced or buffered solutions are produced after the replacement of part of the chloride anions by organic anions to align to the plasma chloride levels, which may impact on acid–base equilibrium). Finally, the volume of fluid administered, especially in situations where patients are at risk of increased anti-diuretic hormone (ADH) secretion and free water excretion impairment [7]. Over the past decade, several pediatric societies have developed guidelines and recommendations surrounding IV-MFT, but their impact has been limited by a lack of dissemination, a lack of recent systematic reviews and because some important

questions remained unanswered [3, 9, 10]. In 2020, the Metabolism, Endocrine and Nutrition (MEN) section of the European Society of Pediatric and Neonatal Intensive care (ESPNIC) formed a working group to develop European guidelines on IV-MFT. These guidelines aim to provide evidence-based recommendations around the indications for IV-MFT, the tonicity of IV-MFT, the electrolyte or glucose content and the volume of IV-MFT administered to children from term to 18 years of age.

Method

To generate these evidence-based guidelines, we followed the Scottish Intercollegiate Guidelines Network (SIGN) 50 methodology [11, 12] and results are presented in line with the EQUATOR PRISMA checklist for systematic reviews [13] and the AGREE guideline reporting checklist [14]. The systematic review was registered on PROSPERO on December 15, 2020, when the research protocol was finalized by the working group (CRD42020218847) [15].

Selection of members

In September 2020, under ESPNIC, three project leaders (DB, LT and FVV) formed a working group of members within the MEN section. This group comprised medical doctors, nurses, pharmacists and dieticians, and was created following a call for interested candidates. Selection by the project leaders was based on expertise in the methods and experience in the field of pediatric acute and intensive care, metabolism, and research. This work group also included an academic librarian specialized in systematic reviews, a systematic review methodologist, an epidemiologist and a biostatistician specialized in meta-analyses. There was no industry input into the guidelines development. No member of the working group received honoraria for any role in the process and all members have declared any potential conflicts of interest.

Take-home message

A systematic review was conducted to produce guidelines on intravenous maintenance fluid therapy in acutely and critically ill children. Sixteen recommendations were produced, which suggest favouring isotonic balanced glucose-containing fluids designed for children, and to infuse them in lower amounts than Holliday and Segar's formula.

Question development

The content and wording of the clinical questions was agreed at the first online meeting. All questions were structured in the Population, Intervention, Control, and Outcome(s) (PICO) format as follows:

Population: acute and critically ill children aged term to 18 years. Critically ill children are those presenting with severe organ failure(s) or requiring pediatric intensive care admission; acutely ill children are those presenting with an acute non-critical condition and requiring in hospital care (e.g. admitted to the emergency department, to pediatric wards, intermediate or high dependency units, or post-surgery). Preterm babies (< 37 weeks gestational age) and the intra-operative setting were outside the scope of the guidelines.

The agreed questions were as follows:

PICO1—Indication: Does IV-MFT versus other hydration therapies (none, oral or enteral route) impact on clinical outcomes?

PICO2—Tonicity: Do isotonic solutions versus hypotonic solutions (as IV-MFT) impact on clinical outcomes?

PICO3—Balanced fluids: Do balanced solutions versus non-balanced solutions (as IV-MFT) impact on clinical outcomes?

PICO4—Composition: Does the composition of IV-MFT in terms of glucose, electrolytes (P, Mg, Ca, K), vitamins and trace elements impact on clinical outcomes?

PICO5—Amounts: Does the use of a restrictive IV-MFT volume versus the standard Holliday and Segar calculated volume impact on clinical outcomes?

Outcomes: Standard outcomes (i.e. mortality and length of hospital or PICU stay) were selected. PICO specific outcomes were further identified: hypo or hyper-natremia for PICO 2; hyper-chloremia and acidosis for PICO 3; hypo or hyper -glycemia, -kalemia, -phosphoremia and -magnesemia for PICO 4; fluid balance for PICO 5. However, the preliminary search revealed a large inconsistency in outcome reporting among studies and among PICOs, with discrepancy between outcome definition, presentation, and time of assessment. Consequently, all reported outcomes in reviewed studies were extracted and later included in meta-analysis whenever possible.

Each member of the working group was allocated to a sub-group dedicated to one of the five PICO questions. Allocation of the members to these subgroups was decided by the project leaders according to each member's preferences and expertise, ensuring a balanced distribution by countries, between professional disciplines, between junior and senior clinicians and between researchers. In each of the five subgroups, group leaders were allocated based on their methodological experience in conducting previous systematic reviews and guideline development.

Literature search and inclusion criteria

After an initial scoping search, each group identified MESH terms for their PICO questions. Subsequently, the medical librarian undertook the literature search on five databases (Pubmed/Medline; Web of Science; Scopus; Cochrane; Embase) for each PICO question. The inclusion criteria for papers were as follows: (1) all papers published until November 2020; (2) written in English, French, Spanish or German with an English abstract; (3) inclusion of critically ill or acutely ill (in the hospital setting) children aged from 37 weeks' gestational age (GA) to 18 years of age; (4) study designs were randomized controlled trials, cohort studies, before and after studies and case/control studies. To ensure an exhaustive search, literature reviews and editorials were sought and their reference lists checked, but they were not included in the data extraction. Animal studies, case studies, conference abstracts and letters were excluded. The search equations for each PICO question are presented in Supplementary Material 1.

After the removal of duplicates, the librarian uploaded the paper abstract for each PICO question, into the review online software Rayyan [Rayyan Systems Inc. Cambridge, Mass, USA], which access was shared with all the members of the working group.

Selection of relevant studies

Using Rayyan software, each PICO group was responsible for screening for relevance, by title and abstract, the articles for their PICO search, as per the inclusion criteria. At least, two group members, blinded to each other, performed this screening, to reduce subjectivity. In the case of disagreement, differences in decision were resolved via a discussion. If it could not be resolved, a third member was involved. Once all relevant papers were agreed, the full text papers were retrieved by the librarian and shared with each PICO group. A similar screening process was applied to full text manuscripts (double blind screening,) based on inclusion/exclusion criteria, until a final list of papers was agreed for data extraction.

Data extraction and assessment of methodological quality

Once papers were agreed for inclusion for each PICO, papers were independently analyzed by two group members (excluding any authors of the paper). Each member extracted key data and summarized the main findings in a standardized data extraction form, according to the study design. Concurrently the same two reviewers assessed the risk of bias according to the Cochrane risk-of-bias tool for randomized trials [16] and to the Newcastle–Ottawa Quality Assessment Form for cohort studies [17].

In case of disagreement, differences in assessment were resolved via discussion, involving the group leader(s) if required.

Data analysis

When appropriate, data were combined statistically in a meta-analysis. To be combined the data had to meet the following criteria: (1) more than one study; (2) the combined studies were of one study design either randomized trials or observational studies; (3) the population and the intervention were sufficiently similar; (4) the outcomes were the same, or for continuous outcome variables, data on the distribution of the variable was available; (5) the risk of bias was not considered critical according to the SIGN grading system. If two or more groups of patients in a same study were independent, we analyzed each sample as an independent study. Two biostatisticians (AB, JJP) conducted the meta-analyses, but did not participate in development of the recommendations or the voting process.

To compare experimental and control groups of randomised controlled trials (RCTs), we calculated the effect sizes and their 95% confidence intervals using the mean difference for quantitative endpoints and odds ratio for qualitative endpoints, weighted by the inverse of the variance. The analyses were performed using a random effects model. The heterogeneity of outcomes was determined using chi-squared and Higgins I^2 tests: a p-value < 0.05 or an $I^2 \geq 50\%$ indicated significant heterogeneity. If the heterogeneity was significant and the conditions for the validity of the analysis were verified, a sensitivity analysis was performed to assess the robustness of the results, excluding the most influential studies. The publication bias was explored for meta-analyses with four or more included studies using the funnel plots.

A p value less than 0.05 was considered significant; all p values were two-tailed. Meta-analyses were performed using Review Manager software (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Consensus methodology, grading of the recommendations and voting rounds

Two online consensus meetings took place in October and November 2021. At these meetings, each group presented their conclusions based on the results from the systematic review and the meta-analyses. A first draft of recommendations was proposed to the whole study team. The wording of the recommendations was discussed with the study team and reworded if required. The classification of the grades of recommendation (A–D, Good Clinical Practice) was undertaken according to the SIGN grading system [11] (supplemental material 2). After

those meetings, the recommendations, the supporting rationales, and the recording of the meetings were made available online to the whole team before the online voting. Every member of the study team attended the meetings or watched the meeting recordings and read the proposed rational before voting.

In December 2021, all the PICO recommendations were combined in an online survey (survey Monkey, Inc. (Palo Alto, CA)) for the members to vote, the intention being to gain consensus using a modified Delphi method [18]. Members were required to indicate "agreement", "partial agreement with a suggested minor wording change" or "disagreement, with free comments" for each recommendation.

Consensus was defined as "strong consensus" ($>95\%$), as "consensus" ($75–95\%$) and "no consensus" ($<75\%$) agreement. In the case of less than 95% agreement during the first online voting, each PICO group was asked to modify the wording of the recommendation according to members suggestions or, if they chose to make no amendment, to provide an explanation. A second and final online voting round took place in January 2022 to attempt to reach strong consensus on the set of recommendations. Members were required to indicate "agreement" or "disagreement", with explanations and proposal.

Results

A total of 18,399 abstracts were screened (Fig. 1 PRISMA flow chart). Subsequently 56 publications from 1969 to 2021 were included [19–74] for data extraction, which included 11,689 patients in both acute and critical care, medical and surgical care settings and used in the development of 16 recommendations (Table 1).

Overall, the level of evidence was low [11] with most studies graded 1 or lower with a serious risk of bias (Table 2 and supplemental files 3–6).

Furthermore, the data were only suitable to combine in a meta-analysis (Figs. 2–5) for some outcomes in four of the PICO questions (PICO 4 on composition did not allow for any meta-analysis). However, outcomes varied significantly between studies and limited the scope of the meta-analysis. All forest plots are available in Supplement files 3, 4, 5 and 6 with the respective heterogeneity assessment and relative risks.

Table 2 provides the list of included studies and their main characteristics; Table 3 summarizes for each PICO the profile of the patients recruited in these studies.

For PICO 1 on indications for IV-MFT, a meta-analysis included 1668 children. It showed no significant difference in length of stay between enteral and parenteral hydration (mean difference $= 9.09$, 95% CI [-1.24–19.43], $p = 0.08$) (Fig. 2) but a trend towards a reduction

in length of hospital stay in the enteral group [23, 24, 27, 28].

For PICO 2 on isotonic IV-MFT solutions, a meta-analysis of 17 RCTs (involving 3356 patients) assessing the risk of developing hyponatremia showed that isotonic solutions significantly reduced this risk compared with hypotonic fluids, with an odds ratio of 0.41 (95% CI [0.26–0.67], $p = 0.0003$), although the heterogeneity was high between studies [31–34, 36–40, 42, 45, 46] (Fig. 3).

In PICO 3 on balanced IV-MFT solutions, the length of acute care or PICU stay were slightly but significantly decreased in children receiving balanced solutions in a meta-analysis of 5 studies, including 283 patients (mean difference: −0.20 days; 95% CI [−0.33; −0.08], $p = 0.001$ [57, 58, 61–63] (Fig. 4).

For PICO 4, the data did not allow the conduct of any meta-analysis.

In PICO 5 on the amount of IV-MFT, a restrictive strategy was significantly associated with a lower change in plasma sodium (mean difference = 1.95; 95% CI [0.29; 3.62], $p = 0.02$) after 12 h or more of treatment, in a meta-analysis pooling 167 patients in six subgroups in three RCTs, including patients in the PICU [71, 73, 74] (Fig. 5).

Figure 6 provides a short answer to each PiCO question.

The grading of the 16 recommendations was heterogenous (ranging from good clinical practice and expert opinion to Grade A), according to the SIGN grading [11] and the quality of the meta-analysis (Table 1). After the 2-round voting process, strong consensus (>95% agreement) was reached for 11/16 (69%) and consensus (90% < agreement < 95%) for 5/16 (31%) of the recommendations.

A long rationale supporting each recommendation is provided for each PICO question in supplemental files 7–11. This details the underlying background and pathophysiology of the PICO question, summarizes current European practice [2], discusses available recommendations in adults or other pediatric settings, provides further details of our literature search, data extraction and analysis of the data, analyzes the volume of evidence, its applicability, generalizability, consistency and clinical impact of the recommendations and finally provides the recommendation.

Discussion
Summary of findings
These ESPNIC evidence-based recommendations provide guidance for clinicians using IV-MFT in children both in acute hospital and intensive care settings. They are based on a comprehensive literature search, including literature up to November 2020.

We were able to propose 16 recommendations corresponding to our questions with a high level of consensus, and to provide an extensive rationale to support each of them, available in supplemental material. Unfortunately, the general level of evidence remains low, both in terms of quantity and quality. Few well conducted and low risk of bias RCTs were available. Furthermore, the study populations, settings and interventions were heterogeneous and, in many cases, made it difficult to pool and to
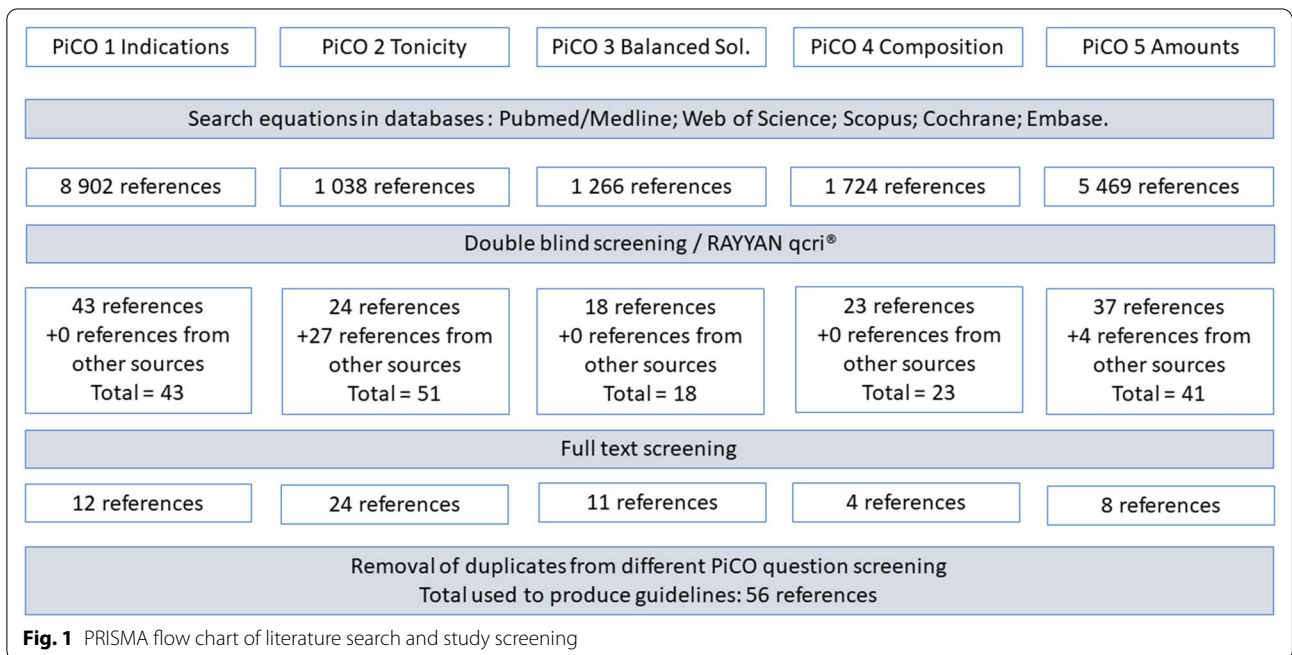

Fig. 1 PRISMA flow chart of literature search and study screening

Table 1 Intravenous maintenance fluid therapy (IV-MFT) recommendations, level of evidence according to SIGN grading, and consensus within the expert group

Recommendations	Level of evidence	Consensus
PiCO 1: IV-MFT indications		
In acutely ill children, the enteral or oral route for the delivery of maintenance fluid therapy should be considered, if tolerated, to reduce the failure rate of hydration access and costs	C	Strong consensus
In critically ill children with improving hemodynamic state, the enteral or oral route for the delivery of maintenance fluid therapy should be considered, if tolerated, to reduce length of stay in term neonates	GCP	Strong consensus
PiCO 2: use of isotonic fluids		
In acutely and critically ill children, isotonic maintenance fluid should be used to reduce the risk of hyponatremia	A	Strong consensus
PiCO 3: use of balanced solutions		
In critically ill children, balanced solutions should be favoured when prescribing intravenous maintenance fluid therapy to slightly reduce length of stay	B	Strong consensus
In acutely ill children, balanced solutions should be used when prescribing intravenous maintenance fluid therapy to slightly reduce length of stay	A	Strong consensus
In acutely and critically ill children, lactate buffer solution should not be considered in the case of severe liver dysfunction to avoid lactic acidosis	D	Consensus
PiCO 4: IV-MFT fluid composition (Ca, Mg, P, Micronutrients, Glucose)		
In acutely and critically ill children, glucose provision in intravenous maintenance fluid therapy should be considered in sufficient amount and guided by blood glucose monitoring (at least daily) to prevent hypoglycaemia	GCP	Consensus
In critically ill children, glucose provision in intravenous maintenance fluid therapy should not be excessive and guided by blood glucose monitoring (at least daily) to prevent hyperglycaemia	B	Consensus
In acutely and critically ill children, there is insufficient evidence to recommend routine supplementation of magnesium, calcium and phosphate in intravenous maintenance fluid therapy	GCP	Strong consensus
In acutely and critically ill children, an appropriate amount of potassium should be considered and added to intravenous maintenance fluid therapy, based on the child's clinical status and regular potassium level monitoring to avoid hypokalemia	GCP	Consensus
In acutely and critically ill children, there is insufficient evidence to recommend routine supplementation of vitamins and trace elements in intravenous maintenance fluid therapy, in the absence of signs of deficiency	GCP	Strong consensus
PiCO 5: volume of IV-MFT administered		
In acutely and critically ill children, in order to prevent fluid creep and reduce fluid intake, the total daily amount of maintenance fluid therapy should be considered including: IV fluids, blood products, all IV medications (both infusions and bolus drugs), arterial and venous line flush solutions and enteral intake, but does not include replacement fluids and massive transfusion	D	Strong consensus
In acutely and critically ill children, avoidance of fluid overload and cumulative positive fluid balance should be considered, to avoid prolonged mechanical ventilation and length of stay	D	Strong consensus
In acutely and critically ill children, who are at risk of increased endogenous secretion of ADH, restriction of total intravenous maintenance fluid therapy volume (calculated by Holliday and Segar formula) should be considered to some extent, to avoid a decrease in natremia but the amount and duration of this restriction is uncertain	C	Strong consensus
In acutely and critically ill children who are at risk of increased endogenous secretion of ADH, restricting maintenance fluid therapy volume to between 65–80% of the volume calculated by the Holliday and Segar formula should be considered to avoid fluid overload In children at greater risk of oedematous states, e.g., heart failure, renal failure or hepatic failure, restricting maintenance fluid therapy volume to between 50% to 60% of the volume calculated with the Holiday and Segar formula should be considered to avoid fluid overload	GCP	Strong consensus
Whilst receiving intravenous maintenance fluid therapy, re-assessment of acutely and critically ill children should be considered at least daily in terms of fluid balance and clinical status and regularly regarding electrolytes, especially sodium level	D	Consensus

ADH anti-diuretic hormone; *GCP* good clinical practice; *IV-MFT* intravenous maintenance fluid therapy; Consensus (expert votes): 90% < agreement < 95%; Strong consensus: > 95% agreement

Long rationales are available for each recommendation in supplemental materials 7–11

compare results. Thus, even with a strong consensus, the majority of the recommendations 12/16 (75%) might be considered as weak (C or under) as they are based on a low level of evidence.

Consistency with other guidelines and recent publications
Our recommendations are consistent with the 2018 American Academic of Pediatrics clinical practice IV-MFT guidelines regarding the use of isotonic fluids [3]. Indeed, the American Academic of Pediatrics

guidelines strongly recommended the use of isotonic fluids in children between 28 days to 18 years of age in acute or intensive care settings. However, our guidelines extend beyond the American guidelines as they also make recommendations on the indications for IV-MFT, on the composition of IV-MFT, and on the amount of IV-MFT that should be prescribed. In 2021, Leung and colleagues [75] published a consensus statement on IV-MFT in hospitalized children, based on a review of the literature (2000–2019). Their recommendations are similar to ours regarding prioritization of the enteral route, the use of isotonic fluids, the reduced amount of fluids administered and the type of monitoring. With the exception of isotonic fluids (strong recommendation with high quality of evidence), recommendations were all consensus based on low-quality evidence and expert opinion. The use of balanced fluids was not addressed.

Our study protocol included literature until November 2020 only, we used the same search equations and inclusion criteria to extract recent IV-MFT studies (December 2020–June 2022) to ensure the consistency of their findings with our guidelines. Twenty-one new studies (and 3 ongoing trials) were identified and are summarized in supplemental digital content 12. Their findings are globally consistent with our recommendations, especially regarding the use of isotonic fluids, reduced infusion volumes and the use of the enteral route when possible. The impact of isotonic fluids has now been studied in specific sub-groups of children such as newborns and patients with diabetic keto acidosis. Balanced solutions are currently being studied, and we have identified three ongoing RCTs comparing them to non-balanced solutions which may help revising our guidelines or adapting their level of evidence in the future.

Implications for practice

The reporting of key outcomes was inconsistent within studies, which prevented us from conducting other meta-analyses. For example, the impact of isotonic and/or balanced solutions on Na and Cl plasma levels was presented as absolute values in some papers, or changes over time, or absolute difference in others. Improving the standardization of outcome reporting in future trials is essential to allow pooling of the data. In the future, our expert group aims to conduct an international Delphi study to gain expert consensus and develop a core outcome set to be reported in future studies on IV-MFT in children. Despite this, these guidelines highlight several important points that must be considered in daily practice when prescribing IV-MFT for children. First, the intravenous route for hydration is not required in every clinical situation. Second, isotonic IV-MFT should be preferred over hypo or hypertonic solutions. Third, balanced fluids should be the standard IV-MFT solution used in children. Fourth, the IV fluid composition is important, and glucose and plasma electrolyte monitoring is essential. Finally, the harm of excessive fluids and volume overload is highlighted, and the daily calculation of fluid balance is essential for any child receiving IV-MFT.

Future implementation challenges

As per its definition, IV-MFT needs to be differentiated from IV replacement therapy, which aims to compensate for abnormal losses (e.g. skin losses in case of major wounds or burns, intestinal losses in case of severe enteropathy, losses through drains, etc.). However, IV-MFT and replacement fluids may be administered through one single IV fluid prescription which then needs to combine both IV-MFT recommendations (in terms of amounts and composition) and adapt to the rate of loss and composition of fluid losses. The implementation of these recommendations into clinical practice may be challenged by the lack of availability of ready-to-use solutions adapted for children in some European countries. A recent survey by Morice et al. [2] reported some centers having to reconstitute isotonic glucose IV-MFT solutions within clinical care units. The use of ready-to-use IV-MFT is beneficial to avoid reconstitution errors, physico-chemical stability issues and microbiological contaminations. Furthermore, products designed for adults do not usually provide glucose and, therefore, do not meet the requirements of younger children. Perioperative maintenance fluids designed as per Sümpelmann et al. recommendations [10] (Glucose 1–2.5%) may not provide sufficient amounts of glucose if used outside the perioperative setting. Isotonic balanced solutions, providing some glucose (4 to 10%) and limited amounts of potassium (+/- 4 mmol/L), would meet most children's requirements in terms of IV-MFT. Solutions such as these can be found in certain countries in various amounts (250, 500 and 1000 mL bags) and have an osmolarity compatible with peripheral infusion. Nevertheless, such solutions are inconsistently available through Europe. Availability of ready-to-use IV-MFT solutions that are tailored to childrens needs would help facilitate the implementation of these new ESPNIC recommendations.

Limitations

The main limitation of these evidence-based recommendations is the general paucity of evidence and the low level of evidence around some of the questions. We have included all studies published until 2021 due to the paucity of studies available, but most (80.0%) were published

Table 2 Summary table of studies included to produce recommendations and their SIGN level of evidence

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/ patients	SIGN level of evidence
Mackenzie et al. (1991)	PICO 1 IV vs enteral hydration with electrolyte solutions	RCT Single centre Australia	104 dehydrated acutely ill children with gastroenteritis	No difference	Serious risk	High	1−
Nager et al. (2002)	PICO 1 IV vs enteral hydration with electrolyte solutions	RCT Single Centre United states of America (USA)	90 dehydrated acutely ill children with gastroenteritis	Higher costs in IV group	Serious risk	High	1−
Sharifi et al. (1985)	PICO 1 IV rehydration vs enteral rehydration	RCT Single Centre Iran	470 dehydrated acutely ill children with gastroenteritis	Less hyponatremia, acidosis hypokalaemia, diarrhoea, and higher weight gain in enteral group	Serious risk	High	1−
Spandorfer et al. (2005)	PICO 1 IV rehydration vs enteral rehydration	RCT Single Centre USA	73 dehydrated acutely ill children with gastroenteritis	No difference	Serious risk	Moderate	1−
Rao et al. (2020)	PICO 1 IV hydration vs enteral feeding	RCT Single Centre India	186 Critically ill term neonates on inotropes	No difference	Low risk	High	1++
Oakley et al. (2013)	PICO 1 IV vs enteral hydration or enteral feeds	RCT Multicentre Australia and New Zealand	759 acutely ill bronchiolitis children	No difference	Serious risk	High	1−
Oakley et al. (2017)	PICO 1 IV vs enteral hydration or enteral feeds	RCT Multicentre Australia and New Zealand	759 acutely ill bronchiolitis children	Higher costs in IV group	Serious risk	High	1−
Duke et al. (2002)	PICO 1 100% 0,45%NaCl-G5 IV, vs 60% breast milk	RCT Multicentre Papua New Guinea	357 acutely ill children with meningitis	Improved outcomes in IV hydration group	Serious risk	Moderate	1−
Saeidi et al. (2009)	PICO 1 Breast milk + IV hydration, vs breast milk	RCT Single Centre Iran	100 term neonates requiring phototherapy for hyper-bilirubinemia	Bilirubin levels decreased faster in the IV group	Serious risk	Moderate	1−
Wilson et al. (1990)	PICO 1 IV vs no IV hydration	RCT Single Centre United Kingdom	50 children undergoing tonsillectomy	No difference	Serious risk	High	1−
Easa et al. (2013)	PICO 1 EN feeds with supplemental IV hydration, vs EN feeds or EN hydration	RCT Single Centre Iraq	64 term neonates requiring phototherapy for hyper-bilirubinemia	No difference	Serious risk	Moderate	1−
Szabo et al. (2015)	PICO 1 NPO + low IV hydration, Vs NPO + high IV hydration, Vs PO + low IV hydration, Vs PO + high IV hydration	Retrospective cohort study Single Centre USA	201 acutely and critically ill children with pancreatitis	Improved outcomes in the PO + high IV hydration group	Good quality	Moderate	2+

Table 2 (continued)

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/ patients	SIGN level of evidence
McNab et al. (2015)	PICO 2 Isotonic (Plasmalyte-G5%®) vs Hypotonic ((G5%-NaCl 0,45%)	RCT Single Centre Australia	641 acutely ill children	Lower risk of hyponatremia in isotonic group	Serious risk	Moderate	1−
Lehtiranta et al. (2021)	PICO 2 Isotonic (Plasmalyte-G5%®) vs Hypotonic (G5%-NaCl 80 mmol/L)	RCT Single Centre Finland	614 acutely ill children	No significant difference in natremia	Serious risk	Moderate	1−
Coulthard et al. (2012)	PICO 2 and PICO 3 and PICO 5 Hartmann-G5% full maintenance vs 0.45NaCl-G5%, 2/3 of Holliday and Segar formula	RCT Single Centre Australia	82 critically ill children after neurosurgery	smaller postoperative fall in plasma sodium in Hartmann-G5% group No difference in Cl and HCO3 plasma levels No data support the effect of rate/amount due to mixed intervention	Serious risk	Low	1−
Almeida et al. (2015)	PICO 2 Isotonic (0.9%NaCl) vs hypotonic (0.45%NaCl) IV-MFT	RCT Single Centre Portugal	233 critically ill children	Lower risk of hypernatremia with 0.9% saline than hyponatremia with 0.45%	Serious risk	Moderate	1−
Bagri et al. (2019)	PICO 2 Isotonic (0.9%NaCl) vs hypotonic (0.45%NaCl) IV-MFT	RCT Single Centre India	150 acutely ill children	lower serum osmolarity at 48 h in the hypotonic group	Serious risk	High	1−
Castilla et al. (2019)	PICO 2 Isotonic (0.9%NaCl) vs hypotonic (0.30%NaCl) IV-MFT	RCT Single Centre Spain	130 critically ill children after surgery	Lower risk of hyponatremia in isotonic group	Serious risk	High	1−
Choong et al. (2011)	PICO 2 Isotonic (0.9%NaCl) vs hypotonic (0.45%NaCl) IV-MFT	RCT Single Centre Canada	258 acutely and critically ill children after surgery	Lower risk of hyponatremia in isotonic group	Low risk	High	1++
Flores et al. (2016)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%) vs Hypotonic (G5%- NaCl 0,3%)	RCT Single Centre Mexico	163 acutely ill children	Lower risk of hyponatremia in isotonic group	Low risk	Moderate	1+
Friedman et al. (2015)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre Canada	110 acutely ill children with acute respiratory diagnosis	No significant differences	Low risk	High	1+
Kannan et al. (2010)	PICO 2 & PICO 5 Isotonic (G5%-NaCl 0.9%) vs Hypotonic (G5%- NaCl 0.18%) vs Hypotonic (G5%- NaCl 0.18%%) lower infusion rate	RCT Single Centre India	167 acutely ill children	Less hyponatremia in isotonic group Less hyponatremia in the restrictive group	Moderate risk (serious)	High (moderate)	1+ (1−)

Table 2 (continued)

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/ patients	SIGN level of evidence
Kumar et al. (2020)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre India	168 acutely ill children	No difference	Moderate risk	Moderate	1—
Montanana et al. (2008)	PICO 2 Isotonic (NaCl 140 mmol/L) vs Hypotonic (20–100 mmol/L Na)	RCT Single Centre Spain	122 critically ill children	Increased risk of hyponatremia in hypotonic group	Serious risk	High	1—
Pemde et al. (2015)	PICO 2 Isotonic (NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre India	92 acutely ill children with central nervous system infection	Less Hyponatremia in the isotonic group	Serious risk	Low	1—
Ramanathan et al. (2016)	PICO 2 Isotonic (NaCl 0,9%) vs Hypotonic (NaCl 0,18%)	RCT Single Centre India	119 acutely ill children with pneumonia	Increased risk of hyponatremia in hypotonic group	Serious risk	Moderate	1—
Rey et al. (2011)	PICO 2 Isotonic (NaCl 156 mmol/L) vs Hypotonic (50–70 mmol/L Na)	RCT Multicentre Spain	125 critically ill children	Increased risk of hyponatremia in hypotonic group	Serious risk	Low	1—
Saba et al. (2011)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre Canada	37 acutely ill children requiring IV-MFT	No difference	Serious risk	Moderate	1—
Torres et al. (2019)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre Argentina	294 acutely and critically ill children requiring IV-MFT	Increased risk of hyponatremia in hypotonic group	Serious risk	Low	1—
Jorro Baron et al. (2013)	PICO 2 Isotonic (NaCl 154 mmol/L) vs Hypotonic (77 mmol/L Na)	RCT Single Centre Argentina	63 critically ill children	Higher Na Plasma levels in isotonic group	Serious risk	High	1—
Tuzun et al. (2020)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre Turkey	108 critically ill term neonates	Lower plasma Na Change in isotonic group	Serious risk	Low	1—
Velasco et al. (2018)	PICO 2 Isotonic (NaCl 154 mmol/L) vs Hypotonic (51–77 mmol/L Na)	Retrospective cohort Single Centre Spain	111 critically ill children	Less hyponatremia risk in isotonic group	Good quality	High	2—
Da Silva Vadalao et al. (2015)	PICO 2 Isotonic (NaCl 0,9%) vs Hypotonic (NaCl 0,18%)	RCT Single Centre Brazil	50 acutely ill children after appendicectomy	No difference	Critical risk	Low	1—
Carandang et al. (2013)	PICO 2 Isotonic (any type) vs Hypotonic (any type)	Retrospective cohort Single Centre USA	1048 acutely ill children	Increased risk of hyponatremia in the hypotonic group	Poor quality	Low	2—
Golshekan et al. (2016)	PICO 2 Isotonic (G5%-NaCl 0,9%) vs Hypotonic (G5%- NaCl 0,45%)	RCT Single Centre Iran	75 acutely ill children	Increased risk of hyponatremia in the hypotonic group	Critical risk	Low	1—

Table 2 (continued)

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/patients	SIGN level of evidence
Karageorgos et al. (2018)	PICO 2 Isotonic (NaCl 0,9%) vs Hypotonic (Na 0.45%, 0.675% or 0.225%)	Retrospective cohort Multicentre USA	472 acutely ill children	Increased risk of hyponatremia in the hypotonic group	Poor quality	Moderate	2+
Lima et al. (2019)	PICO 3 Plasma-Lyte A® vs NaCl0.9%	RCT Single Centre Brazil	53 acute and critically ill children after brain tumour surgery	Higher chloremia in the NaCl group, and lower natremia in the balanced group	Serious risk	High	1−
Naseem et al. (2020)	PICO 3 Ringer Lactate vs NaCl 0.9%	RCT Single Centre India	70 acutely ill children with dehydration and gastroenteritis	Faster resolution of metabolic acidosis occurs with Ringer lactate	Moderate risk	Moderate	1−
Mahajan et al. (2012)	PICO 3 Ringer Lactate vs NaCl 0.9%	RCT Single Centre India	22 acutely ill children with dehydration and gastroenteritis	No difference	Serious risk	Low	1−
Kartha et al. (2017)	PICO 3 Ringer Lactate vs NaCl 0.9%	RCT Single Centre India	68 acutely ill children with dehydration and gastroenteritis	Clinical and pH improvement increased in the Ringer lactate group	Low risk	Moderate	1+
Gutman et al. (1969)	PICO 3 Ringer Lactate vs Cholera designed replacement solution (45 mmol/L acetate)	RCT Single Centre Taiwan	27 acutely ill children with dehydration and gastroenteritis (cholera)	Faster normalisation of HCO$_3$ in the cholera buffer enriched solution	Serious risk	Moderate	1−
Farrell et al. (2020)	PICO 3 Ringer Lactate vs NaCl 0.9%	Retrospective cohort Multicentre USA	1581 acutely ill children with pancreatitis	Shorter length of stay and lower costs in the Ringer lactate group	Fair quality	Moderate	2−
Yung et al. (2017)	PICO 3 Ringer Lactate vs NaCl 0.9%	RCT Single Centre Australia	77 acute and critically ill children with moderate and severe diabetic ketoacidosis	No difference	Low risk	Moderate	1++
Williams et al. (2020)	PICO 3 Plama-Lyte A® vs NaCl 0.9%	RCT Single Centre India	66 acutely and critically ill children with moderate and severe diabetic ketoacidosis	No difference	Low risk	Moderate	1++
Balamuth et al. (2019)	PICO 3 Ringer Lactate vs NaCl 0.9%	RCT Single Centre USA	50 acutely ill children with septic shock	No difference (pilot study)	Serious risk	Low	1−
Bulfon et al. (2019)	PICO 3 0.9% NaCl, 0,45% NaCl Vs Ringer lactate	Retrospective cohort Multicentre Canada	543 critically ill children	Lower risk of Hyperchloremic metabolic acidosis in the ringer lactate group	Good quality	High	2++
Martinez Carapeto et al. (2018)	PICO 4 G3.3% vs G5% MV-MFT	RCT Single Centre Spain	130 critically ill children after surgery	No difference	Serious risk	Moderate	1−

Table 2 (continued)

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/patients	SIGN level of evidence
De Betue et al. (2012)	PICO 4 Glucose infusion: 2.5 mg/kg/min vs 5 mg/kg/min	RCT Single Centre The Netherlands	11 critically ill children after cardiac surgery	Lower glycemia in the 2.5 mg group, without hypoglycemia	Low risk	High	1+
Verbruggen et al. (2011)	PICO 4 Glucose infusion: 2.5 mg/kg/min vs 5 mg/kg/min	RCT Single Centre The Netherlands	8 critically ill children after craniosynostosis surgery	Higher hyperglycemia risk in the 5 mg group	Low risk	High	1+
Lex et al. (2014)	PICO 4 G10% vs G5% MV-MFT	Case control study Single Centre Hungary	596 critically ill children after cardiac surgery	Hospital length of stay was longer in the 10% group	Fair quality	Moderate	2−
Diaz et al. (2018)	PICO 5 100% (standard) vs 50% (pre-emptive) of Holliday Segar formula	Case control study Single Centre Chile	76 critically ill children with sepsis or ARDS	Fluid overload, ventilation duration, length of stay were significantly lower in pre-emptive group	Poor quality	Moderate	2−
Ingelse et al. (2019)	PICO 5 85% (standard) vs < 70% (conservative) of Holliday Segar formula	RCT Single Centre The Netherlands	23 critically ill children respiratory infection on mechanical ventilation	No difference	Critical Risk	High	1−
Yung et al. (2009)	PICO 5 100% (standard) vs < 2/3 (conservative) of Holliday Segar formula sub studies based on fluid type: A. Normal saline 0.9% B. 4% Dextrose – 0.18% saline	RCT Single Centre Australia	50 critically ill children	No difference	Serious risk	Moderate	1−
Raksha et al. (2017)	PICO 5 0.18% saline in 5%G at 2/3 standard rate vs 0.9% saline in 5%G at standard IV maintenance rate	RCT Single Centre India	240 critically ill children	Less hyponatremia and shorter length of ICU stay in isotonic group No data support the effect of rate/amount due to mixed intervention	Serious risk	Low	1−
Neville et al. (2010)	PICO 5 100% (standard) vs < 50% (conservative) of Holliday Segar formula sub studies based on fluid type: A. 5% dextrose + normal saline 0.9% B. 5% dextrose + half normal saline 0.45%	RCT Single Centre Australia	62 acutely ill children after surgery	No difference	Serious risk	Moderate	1−

Table 2 (continued)

Study: author and year of publication	Study examined	Study design settings and location	Patient population	Summary of results	Risk of bias	Applicability to our question/ patients	SIGN level of evidence
Singhi et al. (1995)	PICO 5 Standard rate (100% Holliday Segar formula) vs Restrictive rate (65% of standard, liberalization after 24 h with an increase of 10 ml/kg/8 h) Sub studies based on patient status at inclusion: A. Patients without hyponatremia B. Patients with hyponatremia	RCT Single Centre India	50 acutely ill children with meningitis	No difference	Serious risk	High	1—

EN enteral nutrition; *IV* intravenous; *IV-MFT* intravenous maintenance fluid therapy; *NPO* nil per oral; *PO* per os; *RCT* randomised controlled trial
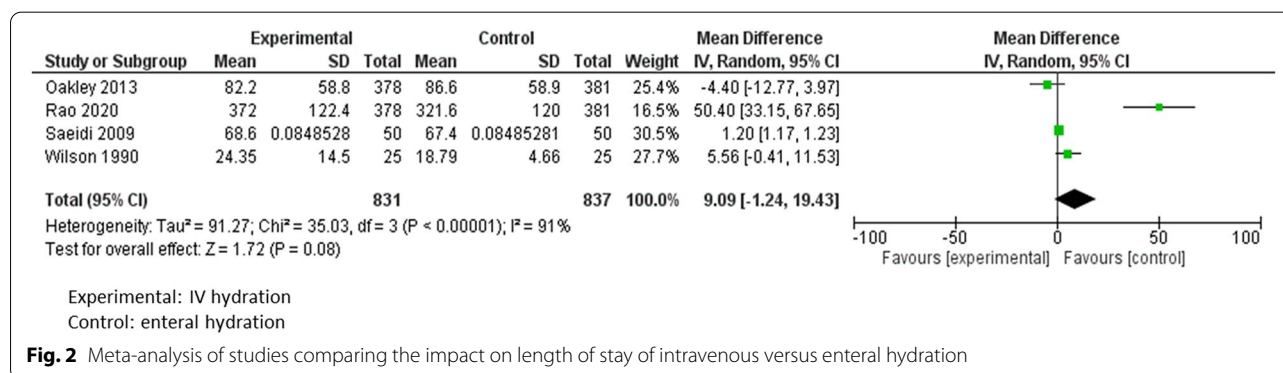
Fig. 2 Meta-analysis of studies comparing the impact on length of stay of intravenous versus enteral hydration

in the last decade, which reduces the bias from studies published within a large time period. Our definition of acute and critical illness may slightly differ from the one used in some studies as PICU admission policies vary within institutions. For most of the recommendations, apart from PICO 1, sparse evidence prevented us from translating this to specific pediatric populations or specific clinical situations; sub populations should be further studied in future trials to secure extrapolation of these guidelines to specific groups of patients and for different age ranges. Apart from the trials conducted on IV-MFT during phototherapy, term neonates were rarely analyzed as a specific group or a subgroup in most of the studies, and extrapolation of the results to this specific population should be considered with caution. Cardiac patients were included in some of the study populations and recommendations for PICO 2 and 5 are likely to apply to this specific population. Some studies assessed both IV-MFT and replacement or bolus fluid therapy, as these

treatments were administered simultaneously or consequently over the study period. Consequently, this may have introduced a bias in the interpretation of the results, even if the results were consistent with other studies focusing on IV-MFT. However, a consistent fluid strategy considering resuscitation, replacement and maintenance fluid therapy seems reasonable. Furthermore, due to inconsistencies among the interventions (fluids and volumes used) and outcomes, meta-analyses were not possible to conduct for many questions and heterogeneity between studies may have resulted in some bias. Finally, in these evidence-based recommendations, the PICO questions and consensus voting only reflects the view of our ESPNIC expert group. Service users (acute and critically ill children) and their parents were not involved in the design of the project. Despite these limitations, this is the most up to date and extensive review of IV-MFT in children both in acute and critical care settings.

Table 3 Characteristics of the patients recruited in the included studies

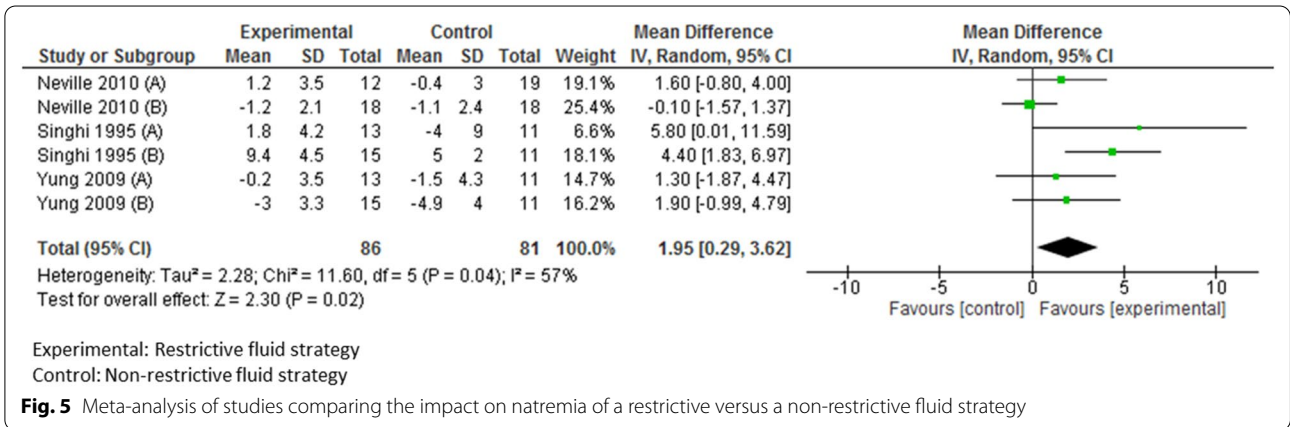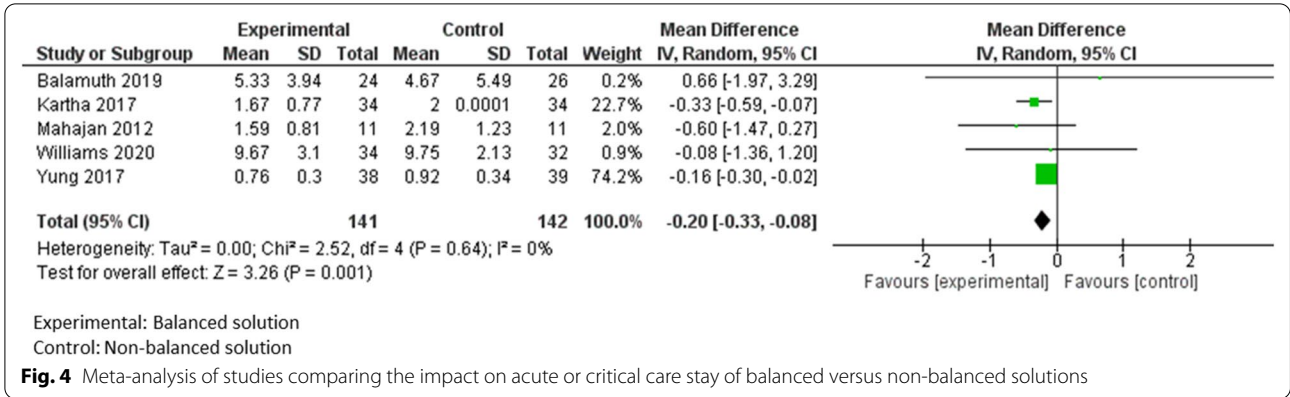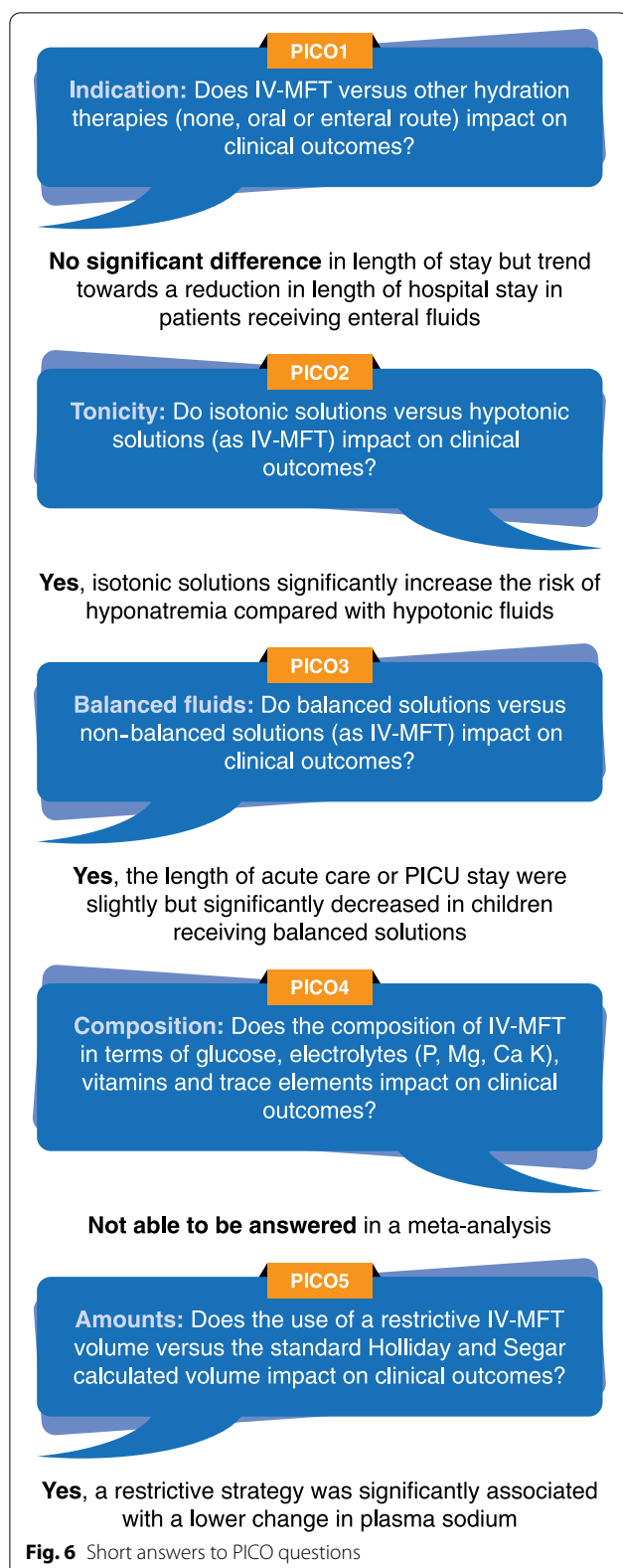|	Acutely ill children	Critically ill children	No distinction possible between acute and critically ill children
PICO 1	11 studies Total: 2268 patients Gastroenteritis $n = 737$ Bronchiolitis $n = 759$ Meningitis $n = 357$ Newborns with hyperbilirubinemia $n = 164$ Post tonsillectomy $n = 50$ Pancreatitis $n = 201$	1 study Total: 186 term newborns	0
PICO 2	14 studies Total: 3444 patients Respiratory failure $n = 229$ Surgery $n = 229$ Central nervous system infection $n = 92$ Various diagnosis $n = 2894$	10 studies Total: 1692 patients Surgery $n = 207$ Neurosurgery $n = 82$ Term neonates $n = 108$ Various diagnosis $n = 1295$	1 study Total: 294 patients Various diagnosis
PICO 3	7 studies Total: 1849 patients Gastroenteritis $n = 187$ Pancreatitis $n = 1581$ Sepsis $n = 50$ DKA $n = 31$	3 studies Total: 660 patients DKA $n = 35$ Neurosurgery $n = 82$ Various diagnosis $n = 543$	2 studies Total: 130 patients Neurosurgery $n = 53$ DKA $n = 77$
PICO 4	0	4 studies Total: 745 patients Post-surgery $n = 130$ Post cardiac surgery $n = 607$ Post craniosynostosis $n = 8$	0
PICO 5	3 studies Total: 279 patients Meningitis $n = 50$ Post-surgery $n = 62$ Various diagnosis $n = 167$	5 studies Total: 471 patients Neurosurgery $n = 82$ Respiratory failure $n = 23$ Various diagnosis $n = 366$	0

DKA diabetic keto acidosis
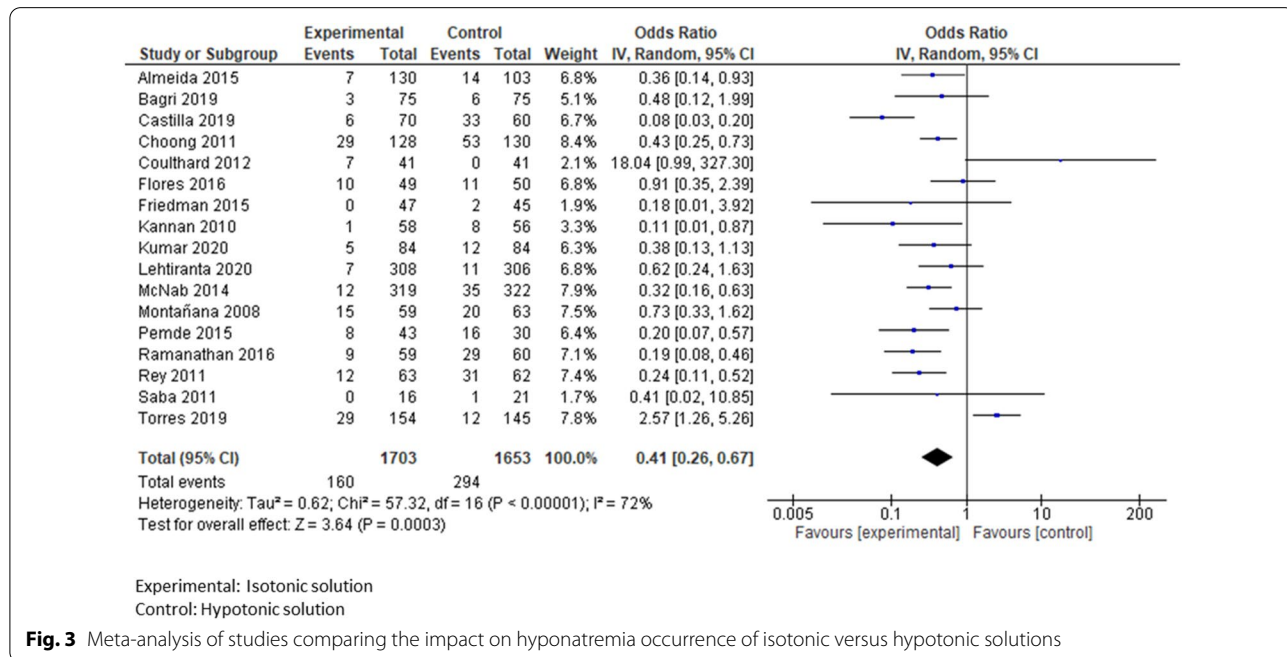
Fig. 3 Meta-analysis of studies comparing the impact on hyponatremia occurrence of isotonic versus hypotonic solutions

Fig. 4 Meta-analysis of studies comparing the impact on acute or critical care stay of balanced versus non-balanced solutions

Fig. 5 Meta-analysis of studies comparing the impact on natremia of a restrictive versus a non-restrictive fluid strategy

Conclusions

These evidence-based recommendations provide a 'best-available-evidence' guide for both pediatric and intensive care clinicians around the prescription of IV-MFT. Due to a paucity of robust evidence, the evidence level for most of the recommendations is low, even when strong consensus was reached among the expert group. Thus, many recommendations are based on expert opinion. This review clearly identifies the urgent need and gaps for future research in this field. Each of our PICO questions deserves further robust research, and new RCTs should be conducted specifically to clarify the impact of the use of isotonic solutions or balanced solutions in various age groups (term neonates, infants and older children) and a variety of clinical conditions. The lack of evidence regarding optimal electrolyte compositions (K, P, Mg, Ca) of IV-MFT is striking and so is the need for micronutrient additions in IVMFT. Consistent reporting of relevant outcome is mandatory to enable future metanalysis. ESPNIC intends to update these guidelines every 5 years, following the same methodology. In the future, our expert group also aims to produce tools to help implement these guidelines into clinical practice and promote auditing and monitoring of their implementation.

PICO1

Indication: Does IV-MFT versus other hydration therapies (none, oral or enteral route) impact on clinical outcomes?

No significant difference in length of stay but trend towards a reduction in length of hospital stay in patients receiving enteral fluids

PICO2

Tonicity: Do isotonic solutions versus hypotonic solutions (as IV-MFT) impact on clinical outcomes?

Yes, isotonic solutions significantly increase the risk of hyponatremia compared with hypotonic fluids

PICO3

Balanced fluids: Do balanced solutions versus non-balanced solutions (as IV-MFT) impact on clinical outcomes?

Yes, the length of acute care or PICU stay were slightly but significantly decreased in children receiving balanced solutions

PICO4

Composition: Does the composition of IV-MFT in terms of glucose, electrolytes (P, Mg, Ca K), vitamins and trace elements impact on clinical outcomes?

Not able to be answered in a meta-analysis

PICO5

Amounts: Does the use of a restrictive IV-MFT volume versus the standard Holliday and Segar calculated volume impact on clinical outcomes?

Yes, a restrictive strategy was significantly associated with a lower change in plasma sodium

Fig. 6 Short answers to PICO questions

Author details
[1] Pediatric Intensive Care, Medical School, Université Caen Normandie, CHU de Caen, Caen, France. [2] Pediatric Intensive Care Unit Alder Hey Children's Hospital, Faculty of Health, Social Care and Medicine, Edge Hill University, Liverpool, Ormskirk, UK. [3] Department of Biostatistics, CHU de Caen, 14000 Caen, France. [4] Department of Nutrition and Dietetics, Geneva School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Geneva, Switzerland. [5] Bureau d'Echange des Savoirs pour des praTiques Exemplaires de Soins (BEST): A JBI Centre of Excellence, Lausanne, Switzerland. [6] Pediatric Intensive Care, HUDERF, Brussels, Belgium. [7] Pediatric Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands. [8] University Hospital Southampton NHS Foundation Trust, Southampton, UK. [9] Pediatric Intensive Care, Pediatric Department, College of Medicine, King Saud University, Riyadh, Saudi Arabia. [10] Pediatric Intensive Care, Assistance Publique Hopitaux de Marseille, Marseille, France. [11] Pediatric Intensive Care, Bambino Gesù Children's Hospital, Rome, Italy. [12] Pediatric Intensive Care, S. Orsola-Malpighi University Hospital, Bologna, Italy. [13] Pediatric Intensive Care, Hospices Civils de Lyon, Lyon, France. [14] Pediatric Intensive Care, Medical School, University Hospital, University of Crete, Heraklion, Greece. [15] Moi Teaching and Referral Hospital, Eldoret, Kenya. [16] Department of Paediatrics, Division of Paediatric Critical Care Medicine, Beatrix Children's Hospital, Critical Care, Anaesthesiology, Peri-Operative and Emergency Medicine (CAPE), University of Groningen, Groningen, the Netherlands. [17] Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland. [18] Pediatric Intensive Care, Gregorio Marañón General University Hospital, Madrid, Spain. [19] Pediatric Intensive Care, Alder Hey Childrens Hospital, Liverpool, UK. [20] Pediatric Intensive Care, University Hospital of Geneva, Geneva, Switzerland. [21] Department of Paediatric Anaesthesiology and Intensive Therapy, Medical University of Warsaw, Warsaw, Poland. [22] Pediatric Intensive Care, Virgen de la Arrixaca Hospital, Murcia, Spain. [23] Pediatric Intensive Care, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [24] Department of Pediatric Nephrology, CHU de Nantes, Nantes, France. [25] Pediatric Intensive Care, Departament of Pediatrics, Faculdade de Medicina, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, Universidade de Lisboa, Lisbon, Portugal. [26] Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland. [27] Pediatric Intensive Care, Dr. Burhan Nalbantoglu State Hospital, Nicosia, North Cyprus, Cyprus. [28] Pediatric Intensive Care, Aglaia Kyriakou Children's Hospital, Athens, Greece. [29] Department of Biostatistics, CHU de Caen, Université Caen Normandie, INSERM U1311 DYNAMICURE, 14000 Caen, France. [30] Department of Pharmacy, CHU de Caen, Caen, France. [31] Service de Réanimation Pédiatrique, Hôpital Femme Mère Enfant, 59 Boulevard Pinel, 69500 Bron, France.

Declarations

Conflicts of interest
LRB and FVV declare consultant fees received from Baxter. IG received consultant fees from BBraun medical. Other authors declare no conflicting interest.

Ethical approval
Not applicable.

Informed consent
Not applicable.

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