CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics
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Clinical Practice Guideline: Maintenance Intravenous Fluids in Children

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abstract

Maintenance intravenous fluids (IVFs) are used to provide critical supportive care for children who are acutely ill. IVFs are required if sufficient fluids cannot be provided by using enteral administration for reasons such as gastrointestinal illness, respiratory compromise, neurologic impairment, a perioperative state, or being moribund from an acute or chronic illness. Despite the common use of maintenance IVFs, there is high variability in fluid prescribing practices and a lack of guidelines for fluid composition administration and electrolyte monitoring. The administration of hypotonic IVFs has been the standard in pediatrics. Concerns have been raised that this approach results in a high incidence of hyponatremia and that isotonic IVFs could prevent the development of hyponatremia. Our goal in this guideline is to provide an evidence-based approach for choosing the tonicity of maintenance IVFs in most patients from 28 days to 18 years of age who require maintenance IVFs. This guideline applies to children in surgical (postoperative) and medical acute-care settings, including critical care and the general inpatient ward. Patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; and adolescents older than 18 years old are excluded. We specifically address the tonicity of maintenance IVFs in children.

The Key Action Statement of the subcommittee is as follows:

1A: The American Academy of Pediatrics recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong)

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To cite: Feld LG, Neuspiel DR, Foster BA, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics*. 2018;142(6):e20183083

INTRODUCTION

Maintenance intravenous fluids (IVFs) are used to provide critical supportive care for children who are acutely ill. IVFs are required if sufficient fluids cannot be provided by using enteral administration for reasons such as gastrointestinal illness, respiratory compromise, neurologic impairment, a perioperative state, or being moribund from an acute or chronic illness. For the purposes of this document, specifying appropriate maintenance IVFs includes the composition of IVF needed to preserve a child's extracellular volume while simultaneously minimizing the risk of developing volume depletion, fluid overload, or electrolyte disturbances, such as hyponatremia or hypernatremia. Because maintenance IVFs may have both potential benefits and harms, they should only be administered when clinically indicated. The administration of hypotonic IVF has been the standard in pediatrics. Concerns have been raised that this approach results in a high incidence of hyponatremia and that isotonic IVF could prevent the development of hyponatremia. Guidelines for maintenance IVF therapy in children have primarily been opinion based, and evidence-based consensus guidelines are lacking.

OBJECTIVE

Despite the common use of maintenance IVFs, there is high variability in fluid prescribing practices and a lack of guidelines for fluid composition and electrolyte monitoring.[1–4] Our goal in this guideline is to provide an evidence-based approach for choosing the tonicity of maintenance IVFs in most patients from 28 days to 18 years of age who require maintenance IVFs. These recommendations do not apply to patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; or adolescents older than 18 years old.

BACKGROUND

Phases of Fluid Therapy

Recent literature has emerged in which researchers describe the context-dependent use of IVFs, which should be prescribed, ordered, dosed, and delivered like any other drug.[5–7] Four distinct physiology-driven time periods exist for children requiring IVFs. The resuscitative phase is the acute presentation window, when IVFs are needed to restore adequate tissue perfusion and prevent or mitigate end-organ injury. The titration phase is the time when IVFs are transitioned from boluses to maintenance; this is a critical window to determine what intravascular repletion has been achieved and the trajectory of fluid gains versus losses in children who are acutely ill. The maintenance phase accounts for fluids administered during the previous 2 stabilization phases and is a time when fluids should be supplied to achieve a precise homeostatic balance between needs and losses. Finally, the convalescent phase reflects the period when exogenous fluid administration is stopped, and the patient returns to intrinsic fluid regulation. The dose of fluid during these 4 phases of fluid therapy needs to be adjusted on the basis of the unique physiologic needs of each patient, and a specific protocoled dose is not able to be applied to all patients.[8,9]

A variety of IVFs are commercially available for use in infants and children. These solutions principally vary by their specific electrolyte composition, the addition of a buffer, and whether they contain glucose (Table 1).[10] The buffer in plasma is bicarbonate, but buffers in commercially available solutions include various concentrations of lactate, acetate, and gluconate. Multiple balanced salt solutions can be compared with normal saline (0.9% saline), which has the same sodium concentration as plasma but has a supraphysiologic chloride concentration.

Effect of Dextrose on Tonicity

Tonicity is used to describe the net vector of force on cells relative to a semipermeable membrane when in solution. Physiologic relevance occurs with tonicity studied in vivo (eg, as IVF is infused intravascularly). Infused isotonic fluids do not result in osmotic shifts; the cells stay the same size. Cellular expansion occurs during immersion in hypotonic fluids as free water, in higher relative abundance in the extracellular environment, and crosses the semipermeable membrane. The converse happens in hypertonic fluid immersion: free water shifts out of the cells, leading to cellular contraction. A distinct but related concept is the concept of osmolality. Osmolality is measured as osmoles of solute per kilogram of solvent. Serum osmolality can be estimated by the following formula:

$$2 \times \mathrm{Na}(\mathrm{mEq}/L) + \mathrm{BUN}\ (\mathrm{mg/dL})/2.8 + \mathrm{glucose}\ (\mathrm{mg/dL})/18$$

Osmolality is distinct from tonicity (effective osmolality) in that tonicity relates to both the effect on a cell of a fluid (dependent on the selective permeability of the membrane) and the osmolality of the fluid. In the plasma, urea affects osmolality but not tonicity because urea moves freely across cell membranes with no effect on tonicity. The tonicity of IVF is primarily affected by the sodium and potassium concentration.

Dextrose (D-glucose) can be added to IVFs (Table 1). Although dextrose affects the osmolarity of IVFs, it is not a significant contributor to the plasma osmotic pressure or tonicity

TABLE 1 Composition of Commonly Used Maintenance IVFs

Fluid	Glucose, g/dL	Sodium	Chloride	Potassium, mEq/L	Calcium	Magnesium	Buffer	Osmolarity,[a] mOsm/L
Human plasma	0.07–0.11	135–145	95–105	3.5–5.3	4.4–5.2	1.6–2.4	23–30 bicarbonate	308[b]
Hypotonic solutions								
D_5 0.2% NaCl	5	34	34	0	0	0	0	78
D_5 0.45% NaCl	5	77	77	0	0	0	0	154
Isotonic and/or near-isotonic solutions								
D_5 0.9% NaCl	5	154	154	0	0	0	0	308
D_5 lactated Ringer	5	130	109	4	3	0	28 lactate	273
PlasmaLyte[c,d]	0	140	98	5	0	3	27 acetate and 23 gluconate	294

[a] The osmolarity calculation excludes the dextrose in the solution because dextrose is rapidly metabolized on infusion.

[b] The osmolality for plasma is 275–295 mOsm/kg.

[c] Multiple electrolytes injection, type 1 *United States Pharmacopeia*, is the generic name for PlasmaLyte.

[d] PlasmaLyte with 5% dextrose is not available in the United States from Baxter Healthcare Corporation in Deerfield, Illinois.

in the absence of uncontrolled diabetes because it is rapidly metabolized after entering the blood stream. Thus, although dextrose will affect the osmolarity of solutions, for patients in whom maintenance IVFs are needed, the dextrose component generally is not believed to affect the tonicity of solutions.

Historical Maintenance IVF Practice and Hyponatremia

Hyponatremia (serum sodium concentration <135 mEq/L) is the most common electrolyte abnormality in patients who are hospitalized, affecting approximately 15% to 30% of children and adults.[11,12] Patients who are acutely ill frequently have disease states associated with arginine vasopressin (AVP) excess that can impair free-water excretion and place the patient at risk for developing hyponatremia when a source of electrolyte-free water is supplied, as in hypotonic fluids.[10] Nonosmotic stimuli of AVP release include pain, nausea, stress, a postoperative state, hypovolemia, medications, and pulmonary and central nervous system (CNS) disorders, including common childhood conditions such as pneumonia and meningitis.[13–15] These conditions can lead to the syndrome of inappropriate antidiuresis (SIAD) or SIAD-like states, which lead to water retention followed by a physiologic natriuresis in which fluid balance is maintained at the expense of plasma sodium.

Children have historically been administered hypotonic maintenance IVFs.[3,4] This practice is based on theoretical calculations from the 1950s.[16] The water requirement was based on the energy expenditure of healthy children, with 1 mL of fluid provided for each kilocalorie (kcal) expended, or 1500 mL/m^2 per day. The resting energy expenditure in healthy children is vastly different in those with an acute disease and/or illness or after surgery. When using calorimetric methods, energy expenditure in these patients is closer to the basal metabolic rate proposed by Talbot,[17] which averages 50 to 60 kcal/kg per day.[18] The electrolyte concentration of IVFs was estimated to reflect the composition of human and cow milk. The final composition consisted of 3 mEq of sodium and 2 mEq of potassium per 100 kcal metabolized.[16]

Most hyponatremia in patients who are hospitalized is hospital acquired and related to the administration of hypotonic IVFs in the setting of elevated AVP concentrations.[10,11] Studies in which researchers evaluated hospital-acquired hyponatremia have revealed a relationship with the administration of hypotonic IVFs.[11,19,20] The most serious complication of hospital-acquired hyponatremia is hyponatremic encephalopathy, which is a medical emergency that can be fatal or lead to irreversible brain injury if inadequately treated.[21–24] The reports of hospital-acquired hyponatremic encephalopathy have occurred primarily in otherwise healthy children who were receiving hypotonic IVFs, in many cases after minor surgical procedures.[21,23] Patients with hospital-acquired hyponatremia are at particular risk for hyponatremic encephalopathy, which usually develops acutely in less than 48 hours, leaving little time for the brain to adapt. Children are at particularly high risk of developing symptomatic hyponatremia because of their larger brain/skull size ratio.[24] Symptoms of hyponatremia can be nonspecific, including fussiness, headache, nausea, vomiting, confusion, lethargy, and muscle cramps, making prompt diagnosis difficult.

After reports of severe hyponatremia and associated neurologic injury were reported in 1992, a significant debate emerged regarding the appropriateness of administering hypotonic maintenance IVFs to children.[21] In 2003, it was

recommended that isotonic fluids be administered to children who are acutely ill and require maintenance IVFs to prevent the development of hyponatremia.[24] Since then, the Institute for Safe Medical Practices of both the United States[25] and Canada[26] released reports on deaths from severe hyponatremia in patients who were hospitalized and received hypotonic IVFs. The United Kingdom released a national safety alert reporting 4 deaths and 1 near miss from hospital-acquired hyponatremia,[27] and 50 cases of serious injury or child death from hypotonic IVFs were reported in the international literature.[22]

After the recognition of hospital-acquired hyponatremia in patients receiving hypotonic IVFs and recommendations for avoiding them,[24] the use of 0.2% saline has declined with an increase in the use of 0.45% and 0.9% saline.[3,28] There have been concerns raised about the safety of the proposed use of isotonic maintenance IVFs in children who are acutely ill for the prevention of hospital-acquired hyponatremia.[18] Some believe that this approach could lead to complications such as hypernatremia, fluid overload with edema and hypertension, and hyperchloremic acidosis.[29] In the past 15 years, there have been a multitude of clinical trials and systematic reviews in which researchers have attempted to address this debate.[30–35] Authors of textbooks and review articles in the United States continue to recommend hypotonic fluids.[36–38] Conversely, the National Clinical Guideline Centre in the United Kingdom published evidence-based guidelines for IVF therapy in children younger than 16 years old and recommended isotonic IVFs.[34]

METHODS

In April 2016, the American Academy of Pediatrics (AAP) convened a multidisciplinary subcommittee composed of primary care clinicians and experts in the fields of general pediatrics, hospital medicine, emergency medicine, critical care medicine, nephrology, anesthesiology, surgery, and quality improvement. The subcommittee also included a guideline methodologist and/or informatician and an epidemiologist who were skilled in systematic reviews. All panel members declared potential conflicts on the basis of the AAP policy on conflicts of interest and voluntary disclosure. Subcommittee members repeated this process annually and on publication of the guideline. All potential conflicts of interest are listed at the end of this document. The project was funded by the AAP.

The subcommittee initiated its literature review by combining the search strategies in 7 recent systematic reviews of clinical trials of maintenance IVFs in children and adolescents, which consisted of 11 clinical trials involving 1139 patients.[9,33,34,39–42] The subcommittee then used this combined search strategy to discover 7 additional clinical trials of maintenance IVFs involving 1316 children and adolescents (ages 28 days to 18 years) published since 2013 (the last year included in the previous 6 systematic reviews) in the PubMed, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Library databases. All articles that were initially identified were back searched for other relevant publications. Studies published as of March 15, 2016, were included. Three independent reviewers from the subcommittee then critically appraised the full text of each identified article (n = 17) using a structured data collection form that was based on published guidelines for evaluating medical literature.[43,44] These reviews were integrated into an evidence table by the subcommittee epidemiologist (Supplemental Table 3). Forest plots for all included randomized controlled trials (RCTs) in which researchers used random-effects models and Mantel-Haenzel (M-H) statistics with the outcome of hyponatremia are shown in Supplemental Figs 2–4.

To appraise the methodology of the included studies, a risk-of-bias assessment was completed by using the *Cochrane Handbook* risk of bias assessment framework.[45] Using this framework, raters placed a value of low, high, or unclear risk of bias for each article in the areas of selection bias (both random-sequence generation and allocation concealment), performance bias, detection bias, attrition bias, and reporting bias. Two authors independently reviewed each study identified in the systematic review and made an independent judgment. Differences in assessment were resolved via discussion.

The resulting systematic review was used to develop the guideline recommendations by following the Policy Statement from the AAP Steering Committee on Quality Improvement and Management, "Classifying Recommendations for Clinical Practice Guidelines."[46] Decisions and the strength of recommendations were based on a systematic grading of the quality of evidence from the updated literature review by the subcommittee with guidance by the epidemiologist. Expert consensus was used when definitive data were not available. If committee members disagreed with the consensus, they were encouraged to voice their concerns until full agreement was reached. Full agreement was reached on the clinical recommendations below.

Clinical recommendations were entered into Bridge-Wiz 2.1 for AAP software (Building Recommendations in a Developers Guideline Editor), an interactive software tool that is used to lead guideline development

TABLE 2 Key Action Statement 1A

Aggregate Evidence Quality	Grade A
Benefits	More physiologic fluid, less hyponatremia
Risks, harm, cost	Potential harms of hypernatremia, fluid overload, hypertension, hyperchloremic metabolic acidosis, and acute kidney injury have not been found to be of increased risk with isotonic maintenance fluids.
Benefit-harm assessment	Decreased risk of hyponatremia
Intentional vagueness	None
Role of patient preferences	None
Exclusions	Patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are <28 d old or in the NICU; or adolescents >18 y old
Strength	Strong recommendation
Key references	9·33·39–42

teams through a series of questions that are intended to create clear, transparent, and actionable Key Action Statements.[47] The committee was actively involved while the software was used and solicited the inputs of this program, which included strength of evidence and balance of benefits versus harms, and chose which sentences recommended by the program to use as part of the guideline. Bridge-Wiz also integrates the quality of available evidence and a benefit-harm assessment into the final determination of the strength of each recommendation per the guidance in Fig 1.

Before formal approval by the AAP, this guideline underwent a comprehensive review by stakeholders, including AAP councils, committees, and sections; selected outside stakeholder organizations; and individuals who were identified by the subcommittee as experts in the field. All comments were reviewed by the subcommittee and incorporated into the final guideline when appropriate.

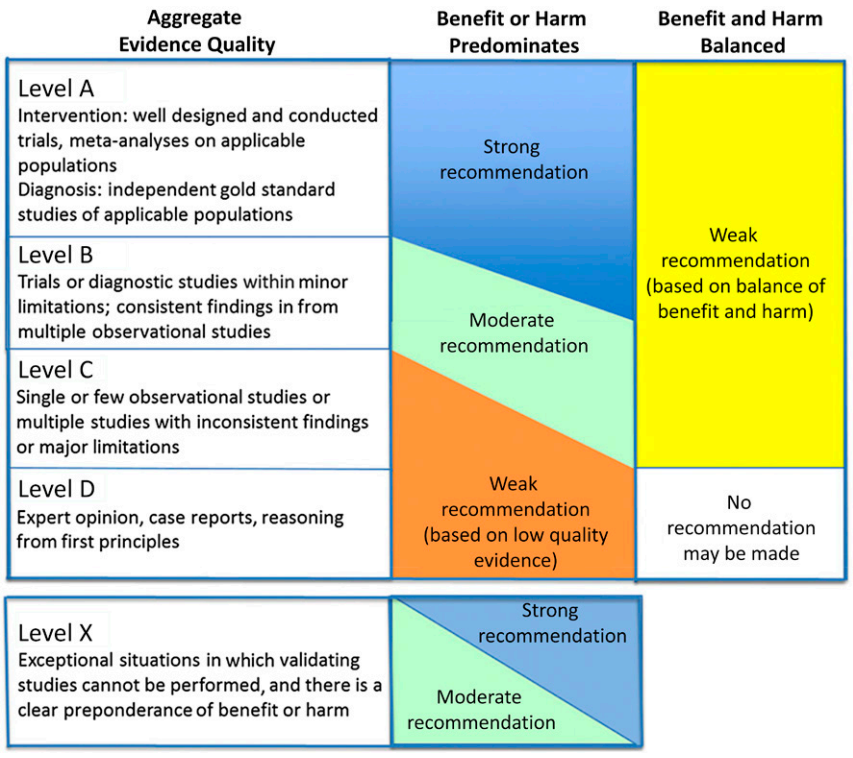

FIGURE 1
AAP rating of evidence and recommendations.

On the basis of the reviewed literature, this guideline applies to children 28 days to 18 years of age in surgical (postoperative) and medical acute-care settings, including critical care and the general inpatient ward. This guideline DOES NOT apply to children with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; or adolescents older than 18 years old because the majority of the researchers in the prospective studies reviewed in this guideline excluded these subsets of patients or did not include patients with these specific high-risk diagnoses.

RESULTS

Key Action Statement

The Key Action Statement is as follows:

1. Composition of Maintenance IVFs

1A: The AAP recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride (KCl) and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong; Table 2).

Isotonic Solutions Versus Hypotonic Solutions

Isotonic fluid has a sodium concentration similar to plasma (135–144 mEq/L). Plasma is approximately 93% aqueous and 7% anhydrous with a sodium concentration in the aqueous phase of plasma of 154 mEq/L and osmolarity of 308 mOsm/L, similar to that of 0.9% sodium chloride (NaCl). Conversely, hypotonic fluid has a sodium concentration lower than that of the aqueous phase of plasma. In the studies evaluated in the formulation of these guidelines, there is some heterogeneity in both the isotonic and hypotonic fluids used. The sodium concentration of isotonic fluids ranged from 131 to 154 mEq/L. Hartmann solution (sodium concentration 131 mEq/L; osmolality 279 mOsm/L) was used in only 46 patients.[48,49] PlasmaLyte (sodium concentration 140 mEq/L; osmolarity 294 mOsm/L) was used in 346 patients.[35] Researchers in the majority of the studies used either 0.9% NaCl (sodium concentration 154 mEq/L; osmolarity 308 mOsm/L) or a fluid of equivalent tonicity. Hypotonic fluids ranged from 30 to 100 mEq/L.[33] Lactated Ringer solution (sodium concentration 130 mEq/L; osmolarity 273 mOsm/L), a slightly hypotonic solution, was not involved in any of the clinical trials. For the purposes of this guideline, isotonic solutions have a sodium concentration similar to PlasmaLyte, or 0.9% NaCl. Recommendations are not made regarding the safety of lactated Ringer solution. Researchers in the majority of studies added dextrose (2.5%–5%) to the intravenous (IV) solution.

The search revealed 17 randomized clinical trials[20,31,32,35,48–60] that met the search criteria, including a total 2455 patients (2313 patients had primary outcome data for analysis in Supplemental Figs 2–4), to help evaluate the question of whether isotonic or hypotonic fluids should be used in children who are hospitalized. Sixteen of the studies revealed that isotonic fluids were superior to hypotonic fluids in preventing hyponatremia. There have also been 7 systematic reviews over the past 11 years in which researchers have synthesized various combinations of the above RCTs.[9,33,34,39–42] The number needed to treat with isotonic fluids to prevent hyponatremia (sodium <135 mEq/L) was 7.5 across all included studies and 27.8 for moderate hyponatremia (sodium <130 mEq/L).

Study appraisal for risk of bias (Supplemental Table 4) revealed the reviewed studies in total to be methodologically sound. Most types of bias were found to be of low risk in all but 2 studies. There was 1 study with 2 bias types of potentially high risk and 11 studies with 1 or more unclear bias areas.

Inclusion and Exclusion Criteria: Rationale for Specific Subgroups

Age

The specific age groups from which data are available from randomized clinical trials range from 1 day (1 trial) to 18 years. Given this broad age range, we specifically evaluated whether there was variability in the outcomes by age, particularly for the lower age range. McNab et al[33] examined this question in their systematic review and found 100 children studied at younger than 1 year of age, 243 children studied between the ages of 1 and 5 years, and 465 children studied at older than 5 years of age. They showed a significant benefit of isotonic IVFs in each age group stratum. There have been 7 additional studies in which researchers have also included children younger than 1 year old, although there are not specific outcome data reported for this age group.[31,32,35,50,51,55,58]

Surgical (Postoperative Patients)

Surgical or postoperative patients have been specifically studied in 7 studies[20,48,49,51,54,56,57] that included 529 patients. McNab[30] showed a pooled risk ratio of 0.48 (95% confidence interval [CI], 0.38–0.60) for the outcome of hyponatremia in favor of isotonic fluids.

Medical (Nonsurgical Patients)

Medical patients are defined here as children who are hospitalized in an acute-care setting with no indication for a surgical operation and no immediate history of a surgical operation. For these patients, there are 4 randomized clinical trials[32,52,55,58] in which researchers enrolled only medical patients and 6 randomized clinical trials[50,51,53,56,57,59] in which researchers enrolled both medical and surgical patients. Some of the mixed studies in which researchers looked at both medical and surgical patients include outcomes for only medical patients, whereas most include combined outcomes for both groups.

Varying Acuity (ICU Versus General Ward)

There are 6 randomized clinical trials[31,49,50,53,56,59] in which researchers enrolled only ICU patients, and all but one[50] revealed a significant difference favoring isotonic IVFs for the prevention of hyponatremia. Researchers in 8 randomized clinical trials enrolled exclusively patients in a general ward setting,[32,51,52,54,55,57,58,60] and those in all but 2[32,57] found a significant reduction in hyponatremia among those receiving isotonic IVFs. McNab et al[35] enrolled patients in both the ICU and general surgical ward, and they were at similar risk for developing hyponatremia.

Exclusion of Specific Populations Not Studied

Patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease,

cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who were younger than 28 days old or in the NICU (researchers in the majority of prospective studies reviewed in this guideline excluded this subset of patients); and adolescents older than 18 years old were excluded. Patients with congenital or acquired heart disease have been either explicitly excluded from every study listed previously or were not described, so no conclusions may be drawn related to this specific population. Similarly, patients with known liver or renal disease or adrenal insufficiency have also been excluded from most of the studies listed, limiting any conclusions for these patients as well. Neurosurgical patients and those with traumatic brain injury were excluded from most studies. Oncology patients have been included in some of the randomized trials, but no specific subanalysis for them has been completed, and data are not available separately to conduct one. Many patients receiving chemotherapy receive high volumes of fluids to prevent renal injury, and there are reports of clinically significant hyponatremia, which is possibly associated with the fluid type.[61] Further study is needed to evaluate the fluid type, rate, and risk of renal injury and hyponatremia for this population. The committee did not specifically review literature for those with the following care needs: patients with significant renal concentrating defects, such as nephrogenic diabetes insipidus, and patients with voluminous diarrhea or severe burns who may have significant ongoing free-water losses.

Complications

Hyponatremia

The reviewed studies revealed the relative risk of developing mild and moderate hyponatremia (defined as a serum sodium concentration <135 mEq/L and <130 mEq/L, respectively) to be >2 and >5, respectively. The risk related to hyponatremia persisted regardless of age, medical versus surgical status, and intensive care versus general pediatric ward setting. These data strongly reveal an increased risk of hyponatremia when children receive hypotonic versus isotonic IVFs. This association is reinforced by the observations that increased hyponatremia occurs in (1) children with normal sodium at baseline (hospital-acquired hyponatremia) and (2) children who have a low sodium concentration at baseline (hospital-aggravated hyponatremia). This association has been found when using both 0.2% saline (sodium 34 mEq/L) and 0.45% saline (sodium 77 mEq/L). The risk for hyponatremia with hypotonic fluids persisted in the subgroup of patients who received fluids at a restricted rate.[49,54,58,59] A sensitivity analysis in which the Shamim et al[58] study was excluded given the anomalous number of events in both arms revealed no change in the overall estimated relative risk (0.43; 95% CI, 0.35–0.53) compared with that of all the studies included (0.46; 95% CI, 0.37–0.57; Supplemental Fig 2). In the clinical trials in which researchers assessed the possible mechanism for this finding, elevated antidiuretic hormone (ADH) concentration was found to play a putative role.[54]

There is heterogeneity in the design of the above studies in the types of patients enrolled, IVF rate and type, frequency of plasma sodium monitoring, and study duration. Despite this heterogeneity, the increased risk of hyponatremia with hypotonic IVFs is consistent. Some may argue that mild hyponatremia (plasma sodium 130–134 mEq/L) and moderate hyponatremia (plasma sodium 125–129 mEq/L) may not be clinically significant or constitute harm. However, the studies in which researchers evaluated moderate hyponatremia revealed benefits of isotonic versus hypotonic IVFs (Supplemental Figs 2 and 4). Furthermore, hypotonic solutions have been associated with a larger decrease in serum sodium. Also, the true effects of hypotonic IVFs may have been underestimated because many of the studies also included rigorous monitoring of sodium, during which patients were removed from the study if mild hyponatremia developed. Numerous studies of adults have revealed that mild and asymptomatic hyponatremia is associated with deleterious consequences, is an independent risk factor for mortality,[62,63] and leads to increased length of hospitalization and increases in costs of hospitalization.[64,65] Thus, the subcommittee believes that hyponatremia is an appropriate indicator of potential harm.

Hypernatremia

One of the concerns when providing a higher level of sodium in IVFs is the development of hypernatremia (serum sodium >145 mEq/L). This was evaluated in the most recently published systematic review.[33] Those authors identified that there was no evidence of an increased risk of hypernatremia associated with the administration of isotonic fluids, although the quality of evidence was judged to be low, primarily given the low incidence of hypernatremia in the studies included. To be clear, there was not evidence of no risk; the risk is unclear from the meta-analysis results. The estimated risk ratio from that meta-analysis was 1.24 (95% CI, 0.65–2.38), drawn from 9 studies with 937 patients, although 3 studies had no events and did not contribute to the estimate. Researchers in 2 large studies published since the meta-analysis did not find evidence of an increased risk of hypernatremia with isotonic IVFs. In the study by Friedman et al,[32] there was 1 patient in each randomized group (N = 110)

who developed hypernatremia, and in the study by McNab et al,[35] the incidence of hypernatremia was 4% in the isotonic IVF group and 6% in the hypotonic IVF group, with no significant difference noted between the 2 groups (N = 641 with data for analysis). The available data among the meta-analysis discussed above and subsequent large RCTs were unable to be used to demonstrate an increased risk of hypernatremia associated with the use of isotonic IVFs.

Acidosis

A hyperchloremic metabolic acidosis has been associated with 0.9% NaCl when it is used as a resuscitation fluid. Researchers in the majority of studies reviewed in this series did not specifically evaluate the development of acidosis or report on it as a complication. Researchers in 4 studies involving 496 patients evaluated the effect of IVF composition on acid and/or base status,[31,49,54,58] and the majority were not able to demonstrate that 0.9% NaCl resulted in acidosis. Two studies in which researchers compared 0.9% NaCl to 0.45% NaCl involving 357 children found no effect on the development of acidosis based on the change in total carbon dioxide (Tco_2), a measure of plasma bicarbonate, with a low Tco_2 being a surrogate marker for acidosis rather than a low pH.[31,54] Researchers in 1 study compared Hartman solution, which has a base equivalent to 0.45% NaCl, involving 79 patients and found no effect on the development of acidosis based on a change in Tco_2.[49] Researchers in 1 study involving 60 patients compared 0.9% NaCl to 0.18% NaCl and demonstrated a decrease in pH from 7.36 to 7.32 in the 0.9% NaCl group compared with an increase in pH from 7.36 to 7.38 in the 0.18% NaCl group (P = .01), but the effect on Tco_2 was not reported.[58]

Fluid Overload

Children receiving IVFs are at risk for fluid accumulation leading to a positive fluid balance or volume overload. A combination of excessive fluid and sodium can synergistically increase retained volume, a condition that is exacerbated in children with chronic comorbidities (such as systolic cardiac dysfunction [congestive heart failure (CHF)], cirrhotic hepatic failure, chronic kidney disease, and hepatorenal syndrome) and metabolic disturbances (such as hyperaldosteronism and long-term steroid use). Researchers in recent literature, most notably in the critically ill population (adults and children), have attempted to delineate the causative and outcome associations with significant positive fluid accumulation, termed "fluid overload."[66] In the non-ICU population, researchers in only a handful of studies mention an association between fluid tonicity and volume overload (or "weight gain").[20,59,60] Choong et al[20] reported on "overhydration" as estimated by using total weight gain, finding no significant difference between isotonic and hypotonic IVF administration. In the meta-analyses that encompass 12 different RCTs and more than 750 children, neither weight nor net fluid balance is discussed. Increasing scrutiny is being given to fluid management in the critically ill population.[33] To determine any association in patients who are noncritically ill, more evidence is required.

Specific Groups That May Be at Higher Risk for Developing Hyponatremia

Researchers in the RCTs reviewed for this statement excluded many groups of patients who are at particularly high risk for hyponatremia, such as those with congenital or acquired heart disease, liver disease, renal failure or dysfunction, or adrenal insufficiency; neurosurgical patients; and patients taking medication known to impair free-water excretion, such as desmopressin. Data on the efficacy of isotonic fluids to prevent hyponatremia and the potential complications related to isotonic fluids in these patients are lacking. Further studies in which researchers evaluate optimal fluid management in these groups of patients are necessary. Patients with edematous states, such as CHF, cirrhosis, and nephrotic syndrome, have an impaired ability to excrete both free water and sodium and are at risk for both volume overload and hyponatremia. Administering isotonic saline at typical maintenance rates will likely be excessive and risk volume overload, and IVFs should be restricted with close monitoring. Renal diseases can have multiple effects on sodium and water homeostasis; patients with glomerulonephritis may avidly reabsorb sodium, whereas those with tubulopathies may have obligatory urinary sodium losses. Patients with renal failure have a relative inability to excrete free water because of the reduced glomerular filtration rate and simultaneously are unable to produce maximally concentrated urine. Patients with adrenal insufficiency can have renal salt wasting and an impaired ability to excrete free water. Patients with CNS disorders can have multiple conditions that impair water excretion, including SIAD and cerebral salt wasting. Patients receiving certain medications are at particularly high risk for developing hyponatremia, such as desmopressin administered perioperatively for Von Willebrand disease, antiepileptic medications (such as carbamazepine), and chemotherapeutic agents (such as IV cyclophosphamide and vincristine). Isotonic IVFs may be the preferred fluid composition for these disease states, but care is needed in dosing the quantity of fluids, and close

monitoring of both the volume status and electrolytes is required.

Limitations

The subcommittee's recommendation to use isotonic fluids when maintenance IVFs are required does not mean that there are no indications for administering hypotonic fluids or that isotonic fluids will be safe in all patients. Patients with significant renal concentrating defects, such as nephrogenic diabetes insipidus, could develop hypernatremia if they are administered isotonic fluids. Patients with voluminous diarrhea or severe burns may require a hypotonic fluid to keep up with ongoing free-water losses. Hypotonic fluids may also be required to correct hypernatremia. However, for the vast majority of patients, isotonic fluids are the most appropriate maintenance IVF and are the least likely to result in a disorder in serum sodium.

CONCLUSIONS

For the past 60 years, the prescription for maintenance IVFs for infants and children has been a hypotonic fluid. These recommendations were made on theoretical grounds and were not based on clinical trials. Despite this accepted dogma, over the past decade and longer, there have been increasing reports of the deleterious effect of hyponatremia in the acute care setting with the use of the prevailing hypotonic maintenance solutions. Using an evidence-based approach, recommendations for optimal sodium composition of maintenance IVFs are provided to prevent hyponatremia and acute or permanent neurologic impairment related to it. Recommendations are not made regarding the use of an isotonic buffered crystalloid solution versus saline, the optimal rate of fluid therapy, or the need for providing potassium in maintenance fluids. The use of this guideline differentiates the applicability to 2 subgroups of children: (1) The guideline applies to surgical (postoperative) medical patients in a critical care setting and the general inpatient ward. (2) The guideline does not apply to patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; or adolescents older than 18 years of age (Supplemental Fig 5).

This guideline is intended for use primarily by clinicians providing acute care for children and adolescents who require maintenance IVFs. It may be of interest to parents and payers, but it is not intended to be used for reimbursement or to determine insurance coverage. This guideline is not intended to be the sole source of guidance in the use of maintenance IVFs but rather is intended to assist clinicians by providing a framework for clinical decision-making.

The Key Action Statement is as follows:

1A: The AAP recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate KCl and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong).

BIOCHEMICAL LABORATORY MONITORING

Although the frequency for biochemical laboratory monitoring was not specifically addressed in the 17 RCTs included in the meta-analysis, researchers in most of the studies obtained serial plasma sodium values, with the first plasma sodium being measured between 6 hours and 12 hours. The incidence of hyponatremia in patients receiving isotonic fluids ranged from 0% to 23%, whereas that of hypotonic fluids ranged from 5% to 100%. This large variability was likely related to the different study designs. Many patients who were hospitalized and received isotonic IVFs will be at risk for hyponatremia if they are receiving IV medications containing free water or are consuming additional free water via the enteral route. For these reasons, clinicians should be aware that even patients receiving isotonic maintenance IVFs are at sufficient risk for developing hyponatremia. If an electrolyte abnormality is discovered, this could provide useful information to adjust maintenance fluid therapy. If patients receiving isotonic maintenance IVFs develop hyponatremia, they should be evaluated to determine if they are receiving other sources of free water or if they may have SIAD and/or an adrenal insufficiency. If hypernatremia develops (plasma sodium >144 mEq/L), patients should be evaluated for renal dysfunction or extrarenal free-water losses.

In patients at high risk for developing electrolyte abnormalities, such as those who have undergone major surgery, those in the ICU, or those with large gastrointestinal losses or receiving diuretics, frequent laboratory monitoring may be necessary. If neurologic symptoms that could be consistent with hyponatremic encephalopathy are present, such as unexplained nausea, vomiting, headache, confusion, or lethargy, electrolytes should be measured.

FUTURE QUALITY-IMPROVEMENT QUESTIONS

Future questions are as follows:

1. How frequently is plasma sodium concentration abnormal, and

is this abnormality clinically significant?

2. Will the widespread use of isotonic maintenance IVFs in the acute-care setting significantly reduce or eliminate hyponatremia- and hyponatremia-related neurologic events?
3. Will the widespread use of 0.9% saline for maintenance IVFs in the acute care setting increase clinically significant metabolic acidosis?
4. Are isotonic-balanced solutions superior to 0.9% saline for the maintenance IVF in the acute-care setting?
5. How frequently should clinicians monitor the serum sodium concentrations when a patient is receiving maintenance IVFs and for patients who are at high risk of sodium abnormalities?

SUBCOMMITTEE ON FLUID AND ELECTROLYTE THERAPY

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ADH: antidiuretic hormone
AVP: arginine vasopressin
CHF: congestive heart failure
CI: confidence interval
CNS: central nervous system
IV: intravenous
IVF: intravenous fluid
kcal: kilocalorie
KCl: potassium chloride
M-H: Mantel-Haenzel
NaCl: sodium chloride
RCT: randomized controlled trial
SIAD: syndrome of inappropriate antidiuresis
T_{CO_2}: total carbon dioxide

DOI: https://doi.org/10.1542/peds.2018-3083

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-3083 originally published online November 26, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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