Clinical Practice Guideline:
Maintenance Intravenous Fluids in Children

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Michael L. Moritz, MD, FAAP
Matthew D. Garber, MD, FHM, FAAP
On behalf of the AAP Subcommittee on Fluid and Electrolyte Therapy
Sahar N. Rooholamini, MD, MPH, FAAP
On behalf of the AAP Section on Hospital Medicine Listserv Live
January 31, 2019
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- James J. Fehr, MD, FAAP – Society for Pediatric Anesthesia
- Clare Hawkins, MD – American Academy of Family Physicians
- Ron L. Kaplan, MD, FAAP – Pediatric Emergency Medicine
- Echo V. Rowe, MD, FAAP – Pediatric Anesthesiology and Pain Medicine
- Muhammad Waseem, MD, MS, FAAP, FACEP – American College of Emergency Physicians
- Michael L. Moritz, MD, FAAP – Pediatric Nephrology
Topics for Discussion

- Definitions
- Objective
- Background
- Methods
- Results
- Standardization of Fluids in Inpatient Setting
- Conclusions and Limitations
- Questions
DEFINITIONS
Maintenance Intravenous Fluids (IVFs)

- The appropriate composition and quantity of IVFs 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.
Tonicity of IVFs

- Tonicity represents the concentration of effective osmoles (Na+, K+, Ca++, Mg++) which are impermeable across the cell membrane and can affect the transcellular movement of water.

- Urea and dextrose are ineffective osmoles as urea is permeable across the cell membrane and dextrose is metabolized.

- Isotonic fluids have a total electrolyte composition similar to the aqueous phase of plasma (154 mEq/L).

- Hypotonic fluids have a total electrolyte composition < the aqueous phase of plasma.
# TABLE 1 Composition of Commonly Used Maintenance IVFs

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Glucose, g/dL</th>
<th>Sodium</th>
<th>Chloride</th>
<th>Potassium, mEq/L</th>
<th>Calcium</th>
<th>Magnesium</th>
<th>Buffer</th>
<th>Osmolarity, mOsm/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasma</td>
<td>0.07–0.11</td>
<td>135–145</td>
<td>95–105</td>
<td>3.5–5.3</td>
<td>4.4–5.2</td>
<td>1.6–2.4</td>
<td>23–30 bicarbonate</td>
<td>308b</td>
</tr>
<tr>
<td>Hypotonic solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₅ 0.2% NaCl</td>
<td>5</td>
<td>34</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>78</td>
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<tr>
<td>D₅ 0.45% NaCl</td>
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<td>77</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>154</td>
</tr>
<tr>
<td>Isotonic and/or near-isotonic solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₅ 0.9% NaCl</td>
<td>5</td>
<td>154</td>
<td>154</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>308</td>
</tr>
<tr>
<td>D₅ lactated Ringer</td>
<td>5</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>28 lactate 273</td>
<td></td>
</tr>
<tr>
<td>PlasmaLyte&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>0</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>27 acetate and 23 gluconate</td>
<td></td>
</tr>
</tbody>
</table>

Objective

To provide an evidence-based approach for choosing the tonicity of IVFs in most patients from 28 days to 18 years of age who require maintenance IVFs.
Guideline Recommendations Do Not Address

- Deficit therapy
- Rate of maintenance IVF
- Potassium concentration of IVF
- Balanced solutions vs saline solutions
- Treatment of electrolyte abnormalities
- Electrolyte monitoring
This GUIDELINE DOES NOT APPLY TO CHILDREN WITH THE FOLLOWING HIGH RISK DIAGNOSES

- Neurological disorders
- Congenital or acquired cardiac disease
- Hepatic disease
- Cancer
- Renal dysfunction
- Diabetes insipidus
- Voluminous watery diarrhea
- Severe burns
Background

- Hyponatremia affects up to 30% of hospitalized children and adults.
- Patients who are acutely ill frequently have disease states associated with arginine vasopressin (AVP) excess that can impair free-water excretion and place patients at risk for developing hyponatremia when a source of electrolyte-free water is supplied, as in hypotonic fluids.
Nonosmotic States of AVP Excess

Hemodynamic stimuli
- Volume depletion
- Hypotension
- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Adrenal insufficiency

Nonhemodynamic stimuli
- Pain and stress
- Nausea and vomiting
- Hypoxemia and hypercapnia
- Hypoglycemia
- Medications
- Perioperative state
- Inflammation
- Cancer
- Pulmonary disease
- CNS disease

Syndrome of Inappropriate Antidiuresis: Diagnostic Criteria

- Hyponatremia with hypoosmolality
- Urine osmolality less than maximally dilute
  - >100 mOsm/kg/H2O
- Urine sodium excretion increases with salt loading or water loading
- Hypouricemia and ↑ FEurate
- Normal effective circulating volume
  - No edema-forming states
  - Normal blood pressure
- Normal renal function
- Normal adrenal function
- Normal thyroid function
Historical Approach to Maintenance IVF

- For over 60 years hypotonic fluids have been the standard.
- Water requirement based on 1 mL for each kcal – 1500 mL/m²/day or Holliday-Segar formula 100/50/20 ml/kg/d rule. (*Pediatrics*. 1957)
- Electrolyte concentration reflected composition of human and cow milk.
  - 3 mEq of Na and 2 mEq K per 100 kcal metabolized (Holliday and Segar) or 30 mEq/L and 20 mEq/L, respectively.
Hyponatremic Encephalopathy

- Numerous reports of hospital-acquired hyponatremic encephalopathy including death and permanent neurologic impairment in otherwise healthy children receiving hypotonic maintenance IVF.

- Non-specific presenting symptoms: headache, nausea, vomiting, confusion, lethargy, muscle cramps, fussiness, followed by seizure, coma, respiratory arrest.

- Usually develops within 48 hours of starting maintenance IVF.
Isotonic Fluids for Maintenance IVFs

- Since 2003, there has been emerging literature (US, UK, Canada) suggesting that isotonic fluids given as maintenance IVFs prevent hyponatremia.
- In 2015, the National Clinical Guideline Centre in the UK recommended isotonic IVFs in children <16 years of age.
- No prior US or AAP clinical guidelines recommending composition maintenance IVF therapy.
Methods

- Literature review through 3/15/2016 identified 17 clinical trials.
- Evidence table was done by the epidemiologist.
- Forest plots (using random effect models and Mantel-Haenzel statistics).
- Risk bias assessment (Cochrane Handbook) using low, high, or unclear risk of bias in areas of selection bias, performance bias, detection bias, attrition bias, and reporting bias.
Methods

- Guideline followed the policy statement by the AAP Steering Committee on Quality Improvement and Management.
- Systematic grading of the quality of evidence was used.
- Full agreement on the clinical recommendation by the committee members.
- BRIDGE-Wiz software was used for guideline development to achieve actionable Key Action Statements.
- Guideline was reviewed by stakeholders
  - AAP councils, committees, sections, selected outside stakeholder organizations, and identified outside experts.
  - All comments were reviewed and incorporated as deemed appropriate.
RESULTS – Recommendation

- KEY ACTION STATEMENT

  - The AAP 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
RESULTS
Isotonic (131-154 mEq/L) vs Hypotonic Solutions (30-100 mEq/L)

- 17 randomized controlled trials (RCTs) with 2,455 patients
  - 16 of 17 revealed isotonic was superior to hypotonic solutions.

- 7 systemic reviews analyzed the 17 RCTs
  - Number to treat with isotonic fluids to prevent hyponatremia (<135 mEq/L) was 7.5 across all studies and 27.8 for moderate hyponatremia (<130 mEq/L).

- Study appraisal for risk of bias
  - Bias was low risk except in 2 studies.
All Hypotonic Fluids vs Isotonic for Sodium <135 mEq/L

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Isotonic</th>
<th>Risk Ratio</th>
<th>Hypotonic</th>
<th>Risk Ratio</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<td>Almeida 2015</td>
<td>7</td>
<td>130</td>
<td>14</td>
<td>103</td>
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<td>Brazel 1996</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Choong 2011</td>
<td>26</td>
<td>106</td>
<td>47</td>
<td>112</td>
</tr>
<tr>
<td>Coulthard 2012</td>
<td>0</td>
<td>39</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Flores-Robles 2015</td>
<td>1</td>
<td>52</td>
<td>21</td>
<td>99</td>
</tr>
<tr>
<td>Friedman 2015</td>
<td>0</td>
<td>47</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>Jorro Barón 2013</td>
<td>4</td>
<td>31</td>
<td>5</td>
<td>32</td>
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<tr>
<td>Kannan 2010</td>
<td>5</td>
<td>58</td>
<td>18</td>
<td>109</td>
</tr>
<tr>
<td>McNab 2014</td>
<td>12</td>
<td>319</td>
<td>35</td>
<td>322</td>
</tr>
<tr>
<td>Montanana 2008</td>
<td>3</td>
<td>59</td>
<td>13</td>
<td>63</td>
</tr>
<tr>
<td>Neville 2010</td>
<td>6</td>
<td>62</td>
<td>19</td>
<td>62</td>
</tr>
<tr>
<td>Ramanathan 2016</td>
<td>9</td>
<td>59</td>
<td>29</td>
<td>60</td>
</tr>
<tr>
<td>Rey 2011</td>
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<td>45</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Saba 2011</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Shamin 2014</td>
<td>16</td>
<td>30</td>
<td>25</td>
<td>30</td>
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<td>Valadao 2015</td>
<td>5</td>
<td>23</td>
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<td>27</td>
</tr>
<tr>
<td>Yung 2009</td>
<td>3</td>
<td>29</td>
<td>7</td>
<td>32</td>
</tr>
</tbody>
</table>

Total (95% CI) | 1110 | 1203 | 100.0% | 0.46 (0.37–0.57) |

SUPPLEMENTAL FIGURE 2
Forest plot of all included RCTs using a random-effects model and M-H statistics with the outcome of hyponatremia (sodium <135 mEq/L). df, degrees of freedom.

Hypotonic Fluid (>70 mEq/L) vs Isotonic for Sodium <135 mEq/L

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Isotonic</th>
<th>Hypotonic</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida 2015</td>
<td>7/130</td>
<td>14/103</td>
<td>0.40 (0.17–0.95)</td>
</tr>
<tr>
<td>Choong 2011</td>
<td>26/106</td>
<td>47/112</td>
<td>0.58 (0.39–0.87)</td>
</tr>
<tr>
<td>Coulthard 2012</td>
<td>0/39</td>
<td>7/40</td>
<td>0.07 (0.00–1.16)</td>
</tr>
<tr>
<td>Flores-Robles 2015</td>
<td>1/52</td>
<td>11/50</td>
<td>0.09 (0.01–0.65)</td>
</tr>
<tr>
<td>Friedman 2015</td>
<td>0/47</td>
<td>2/45</td>
<td>0.19 (0.01–3.89)</td>
</tr>
<tr>
<td>Jorro Barón 2013</td>
<td>4/31</td>
<td>5/32</td>
<td>0.83 (0.24–2.79)</td>
</tr>
<tr>
<td>McNab 2014</td>
<td>12/319</td>
<td>35/322</td>
<td>0.35 (0.18–0.65)</td>
</tr>
<tr>
<td>Neville 2010</td>
<td>6/62</td>
<td>19/62</td>
<td>0.32 (0.14–0.74)</td>
</tr>
<tr>
<td>Saba 2011</td>
<td>1/16</td>
<td>1/21</td>
<td>1.31 (0.09–19.42)</td>
</tr>
</tbody>
</table>

Total (95% CI) 802/787 100.0% 0.43 (0.30–0.61)

Heterogeneity: τ² = 0.05; χ² = 9.75, df = 8 (P = .28); I² = 18%
Test for overall effect: z = 4.67 (P < .00001)

SUPPLEMENTAL FIGURE 3
Forest plot of all included RCTs with moderately hypotonic fluids (>70 mEq/L) compared with isotonic fluids. Random-effects model and M-H statistics with the outcome of hyponatremia (sodium <135 mEq/L) are shown. df, degrees of freedom.

All Hypotonic vs Isotonic for Sodium <130 mEq/L

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Isotonic</th>
<th>Hypotonic</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida 2015</td>
<td>0</td>
<td>130</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Brazel 1996</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>7.6%</td>
<td>0.15 (0.01–2.26)</td>
</tr>
<tr>
<td>Choong 2011</td>
<td>1</td>
<td>106</td>
<td>7</td>
<td>11.8%</td>
<td>0.15 (0.02–1.21)</td>
</tr>
<tr>
<td>Coulthard 2012</td>
<td>0</td>
<td>39</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Flores-Robles 2015</td>
<td>0</td>
<td>52</td>
<td>0</td>
<td>99</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Friedman 2015</td>
<td>0</td>
<td>47</td>
<td>0</td>
<td>45</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Jorro Barón 2013</td>
<td>0</td>
<td>31</td>
<td>1</td>
<td>32</td>
<td>2.6%</td>
</tr>
<tr>
<td>Kannan 2010</td>
<td>1</td>
<td>58</td>
<td>10</td>
<td>109</td>
<td>12.1%</td>
</tr>
<tr>
<td>McNab 2014</td>
<td>2</td>
<td>319</td>
<td>2</td>
<td>322</td>
<td>3.5%</td>
</tr>
<tr>
<td>Montanana 2008</td>
<td>0</td>
<td>59</td>
<td>4</td>
<td>63</td>
<td>7.6%</td>
</tr>
<tr>
<td>Neville 2010</td>
<td>0</td>
<td>62</td>
<td>0</td>
<td>62</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Ramanathan 2016</td>
<td>1</td>
<td>59</td>
<td>8</td>
<td>60</td>
<td>13.8%</td>
</tr>
<tr>
<td>Rey 2011</td>
<td>1</td>
<td>45</td>
<td>3</td>
<td>39</td>
<td>5.6%</td>
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<tr>
<td>Saba 2011</td>
<td>0</td>
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<td>0</td>
<td>21</td>
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<tr>
<td>Shamin 2014</td>
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<td>30</td>
<td>36.5%</td>
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<tr>
<td>Valadão 2015</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>27</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total (95% CI) 1081 1171 100.0% 0.31 (0.19–0.50)

Total events 16 60
Heterogeneity: $\chi^2 = 5.80$, df = 8 ($P = .67$); $I^2 = 0$

Test for overall effect: $z = 4.76$ ($P < .000001$)

SUPPLEMENTAL FIGURE 4
Forest plot of all included RCTs using a random-effects model and M-H statistics with the outcome of moderate hyponatremia (sodium <130 mEq/L). df, degrees of freedom.

## Supplemental Table 4: Study Appraisal for Risk of Bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Performance</th>
<th>Detection</th>
<th>Attrition</th>
<th>Reporting</th>
<th>Other</th>
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<tr>
<td>Almeida et al.</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
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<tr>
<td>Brazen and McPhee</td>
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<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>Choong et al.</td>
<td>Low</td>
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<td>Low</td>
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</tr>
<tr>
<td>Coultward et al.</td>
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<td>Low</td>
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<tr>
<td>Flores Robles and Cuello García</td>
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<td>Low</td>
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<td>Low</td>
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<td>Friedman et al.</td>
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<td>Yung and Keeley</td>
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</table>

Isotonic Fluids Superior in All Ages and Settings

- **Age:** 8 RCTs, <1 year of age; McNab showed significant benefit for isotonic fluids for all age groups (<1; 1–5; >5 years of age).
- **PostOp Patients:** 7 RCTs; McNab showed pooled risk ratio of 0.48 favoring isotonic fluids.
- **Medical Wards:** 8 RCTs with 6 showing significant reductions of hyponatremia with isotonic fluids.
- **Intensive Care Unit (ICU):** 6 RCTs with 5 showing significant isotonic fluid preference.
Hyponatremia

- Hyponatremia: Relative risk for mild and moderate hyponatremia were >2 and >5, respectively
  - Regardless of age, medical vs surgical status, location of care (wards, ICU)
  - Increased risk of hyponatremia in children with normal or low serum sodium at baseline using 0.2% or 0.45% saline

- Despite some heterogeneity of study design, increased risk of low serum sodium with hypotonic fluid administration

- Hyponatremia is an appropriate indicator of potential harm
Hypernatremia

- Hypernatremia (>145 mEq/L): No evidence of increased risk with isotonic fluid although there was not evidence of no risk—estimated risk ratio of 1.24 from meta-analysis of 9 RCTs.
  - 2 large RCTs after the meta-analysis—no increased risk for hypernatremia.
  - McNab—incidence in isotonic was 4% and 6% in hypotonic group.
Hyperchloremic Acidosis

- Hyperchloremic Acidosis: Most studies did not evaluate, although 4 studies, with 496 patients, did not demonstrate an adverse effect of isotonic fluids.
Fluid Overload

- Fluid Overload: 12 RCTs did not address this issue.
  - Choong found no fluid overload based on weight gain.

- More evidence will be required.
SUPPLEMENTAL FIGURE 5
Algorithm used to describe the selection of maintenance IVFs in children who are acutely ill.

Available at http://pediatrics.aappublications.org/content/142/6/e20183083.supplemental
Implementation Tools (Similar to SOHM Project – Standardization of Fluids in Inpatient Setting)

GLOBAL AIM is to improve patient safety by ensuring patients are on appropriate maintenance IVFs.

- Key Driver Diagram: [https://downloads.aap.org/DOCCSA/IVF_Key_Driver_Diagram.pdf](https://downloads.aap.org/DOCCSA/IVF_Key_Driver_Diagram.pdf)
- Quality Improvement Metric: [https://downloads.aap.org/DOCCSA/IVF_QI_Metric.pdf](https://downloads.aap.org/DOCCSA/IVF_QI_Metric.pdf)
- Order Set: [https://downloads.aap.org/DOCCSA/Maintenance_IV_Fluids_Plan_MOCKUP.pdf](https://downloads.aap.org/DOCCSA/Maintenance_IV_Fluids_Plan_MOCKUP.pdf)
Global Aim: Improve patient safety by ensuring patients are on appropriate maintenance IVFs.

Specific Aim: Increase/sustain use of isotonic maintenance IVFs (as a proportion of total maintenance IVF use in appropriate patients) to >= 80% by <date>.

Outcomes (Primary Drivers):
- Isotonic IVFs are more readily available for clinical use than hypotonic fluids.
- Providers understand the evidence supporting safety of isotonic fluids (including exclusion criteria) and apply this evidence to their clinical work.
- Areas for improved clinical practice are continuously identified and addressed.

Interventions (Secondary Drivers):
- Isotonic IVFs are preferentially stocked in automated dispensing cabinets.
- Clinical pathways and decision support with IVF orders are updated with guidance on exclusion criteria and fluid tonicity choice.
- Education through Listserv Live and PCO webinars.
- Participating sites receive real-time data feedback on their adherence to using isotonic fluids.
Quality Improvement Metric

Inclusion Criteria:
- 28 days to 18 years old requiring maintenance IVFs

Exclusion Criteria:
- No neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, severe burns, patients in the neonatal intensive care unit

Overall Aim:
- Increase the percentage of patients on maintenance IVFs who receive isotonic maintenance IVFs to at least 80%

Metric:
- Percent receiving isotonic/all eligible patients
Limitations

- The 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.

- SEE GUIDELINE FOR DETAILS

- LABORATORY MONITORING BASED ON CLINICAL ASSESSMENT – RECEIVING ADDITIONAL FLUIDS, HIGH RISK CHILDREN (MAJOR SURGERY, ICU, LARGE RENAL AND EXTRA RENAL LOSSES, NEUROLOGICAL SYMPTOMS, ETC.)
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