Pediatric Grand Rounds: IV Fluid Therapy in Pediatrics

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Disclosure:
- I have no relationships with commercial companies to disclose

Objectives:
- At the end of this presentation the participant will be able to:
  1. Describe the historical basis for prescription of IV fluids
  2. Understand the pathophysiology of hyponatremia in the hospitalized child
  3. Prescribe appropriate IV fluids to a hospitalized child

Outline:
- Explore current IV fluid prescribing practice
- Review the historical basis for current practice
- Outline our current understanding of physiology
- Evaluation of the clinical evidence
- Synthesis of the clinical evidence
- Reconcile history, physiology and clinical evidence for practice

TIPS
1. Standard texting rates only (worst case US $0.20)
2. Capitalization doesn't matter, but spaces and spelling do
Case #1:
A patient is admitted to your service due to pneumonia. The patient is tachypneic, has significant retractions and is requiring face mask O2. Therefore, the decision is made to make the child NPO. Which maintenance fluid would you normally choose if the patient is a:
- 13 y/o girl
- 6 m/o boy
A. 0.2%NaCl  B. 0.45%NaCl  C. 0.9%NaCl  D. LR

Fluid prescribing:
Per the textbook (Nelson’s)
- Water requirements:
  - 100mL/kg for first 10kg
  - 50mL/kg for 11-20kg
  - 20mL/kg for every kg above 20 until 2400mL maximum total daily requirement
- Translates via dividing by 24hrs into 4-2-1 rule for hourly prescription of water needs

Electrolyte requirements
Per the textbook:
- Na: 2-4mEq/100kcal/day
- K: 1-3mEq/100kcal/day
- Using Holliday-Segar:
  - Na: 2-4mEq/100mL water/day
  - K: 1-3mEq/100mL water/day

Example of H-S in action:
- 12kg child:
  - Water needs: 100mL/kg*10kg + 50mL/kg*2kg = 1100mL
  - Na needs (2-4mEq): 1100mL*3mEq/100mL = 33mEq
  - K needs (1-3mEq): 1100mL*2mEq/100mL = 22mEq
  - Water per hour:
    - 1100/24 = 45.8mL/hr (44mL/hr by 4-2-1 rule)
    - Na: 0.45%NaCl = 77mEq/L * 1.1L = 84.7mEq/day
    - K: 20mEq/L * 1.1L = 22mEq/day
  - Therefore, child should receive D5 ½ NS with 20mEq KCl (or even D5 ¼ NS)
How did we get here

- A series of experiments by pioneers in pediatric clinical research
- Clinical experience and knowledge emphasized
- Tradition has carried us forward

How did we get here...

James Gamble, M.D.


Daniel Darrow, M.D.

- Developed regimen for rehydration
  - 20mL/kg isotonic saline IV
  - Deficit therapy plus maintenance delivered via hypodermoclysis, oral and IV combined
  - 1st day: hypodermoclysis
  - 2nd day: with D5 and orally

“When one of the students asked what was the treatment for scarlet fever, the doctor replied: "The treatment of scarlet fever depends on what is the matter with the patient."

Darrow D C. Bull NY Acad Med 1948.

Dr. Darrow’s Work

- Maintenance derived from estimates of urinary and insensible losses
- Insensible loss scaled to metabolic rate (100-150mL/100kcal/day)

| Table IV
| SOLUTION USED FOR DIARRHEA |
|-----------------|-------------------|
| Concentration per Liter |
| NaCl            | 4.5 g              |
| KCl             | 27 g               |
| NaHCO₃          | 4.6 g              |
| Cl               | 110 mEq/L          |
| HCO₃            | 10 mEq/L           |

Allan M. Butler, M.D. & Nathan Talbot, M.D.

- Provided a basic step towards standardization by defining safe upper and lower limits for water and electrolyte intake
- Scaled to surface area instead of metabolic rate
- Encouraged use of fluids with both intracellular and extracellular replacement


Malcolm Holliday & William Segar

- Water needs:
  - Insensible loss + urinary loss
  - Correlated energy expenditure to weight using prior data
  - Since water needs are function of energy expenditure, linked weight and water needs

Random urine osmolarity calculated from patients receiving IV fluids for at least 12 hrs.

Loss of water is a function of energy expenditure.

For estimate of insensible losses, used average from all ages of 50mL/100kcal.

Water & Energy Relationship

Proof of error at the time

Water & Energy Relationship

Water & Energy Relationship

Water & Energy Relationship

Water & Energy Relationship

Water & Energy Relationship
Since H & S 1957

- Decreased awareness of IV fluid therapy due to sharp decline in severe dehydration and advent of oral rehydration
- Arieff et al 1992:
  - Retrospective review of 16 cases of otherwise healthy children who died or suffered severe neurologic damage from hyponatremia
  - Retrospective cohort showed incidence of 0.34% of severe (<128mEq/L) hyponatremia and 8.4% mortality in those affected
  - Hypotonic fluids identified as potential cause

Flurry of studies and warnings:

Systematic review by Choong et al 2006:

- Tonicity is primarily a water regulation driven process
- Volume is primarily a sodium regulation issue
- Vasopressin (ADH) is primary modulator of water regulation
Vasopressin (ADH)

- Synthesized in paraventricular and supraoptic nuclei of hypothalamus
- Transported to posterior pituitary and stored
- Classic stimuli for release are osmotic and volume/pressure (at least 8% volume loss)
- Plasma osmolality maintained at a tight 285-295 mOsm/kg
- 1% change in osmolality → ADH release

Vasopressin action on kidney


Hyponatremia:

- Need two things:
  - Source of free water
  - Stimulus for holding onto that water (ADH)
  - Hypertonic urinary losses (rare)

Source of free water? commonly used IV fluids:

<table>
<thead>
<tr>
<th>Intravenous Fluid</th>
<th>Sodium mEq/L</th>
<th>Osmolality mOsm/kg</th>
<th>% Electrolyte-Free Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5 in Water</td>
<td>0</td>
<td>252</td>
<td>100</td>
</tr>
<tr>
<td>D5 with 0.2% NaCl in water</td>
<td>34</td>
<td>321</td>
<td>78</td>
</tr>
<tr>
<td>D5 with 0.45% NaCl in water</td>
<td>77</td>
<td>406</td>
<td>50</td>
</tr>
<tr>
<td>Lactated Ringer's</td>
<td>130</td>
<td>273</td>
<td>16</td>
</tr>
<tr>
<td>5% Dextrose Lactated Ringer's</td>
<td>130</td>
<td>525</td>
<td>16</td>
</tr>
<tr>
<td>D5 with 0.9% NaCl in water</td>
<td>154</td>
<td>560</td>
<td>0</td>
</tr>
</tbody>
</table>

Non-osmotic ADH release

- Hypovolemia/hypotension
- Non-hemodynamic:
  - Pulmonary: asthma, pneumonia, COPD, acute respiratory failure
  - Cancer
  - Nausea, pain, emesis, stress
  - Post-operative state
  - Cortisol deficiency
  - Marathon runners?

Mechanism for non-osmotic release

- Increase in vasopressin after IL-6 injection (human & rat) or LPS challenge
- Children with diagnosed SIADH after neurotrauma showed high correlation of ADH and IL-6 (r=0.96)

Mechanism for non-osmotic release


What we know:
- ADH is primary mechanism of water regulation
- Putative mechanism for non-osmotic stimulus of ADH in hospitalized patients
- Hospitalized patients have:
  - Multiple stimuli for non-osmotic ADH secretion
  - Potential source of free water in IV fluids
- Hypotonic fluids associated with hyponatremia related neurologic injury and death
- So what are we doing?

Current Practice:
- Survey of pediatric residents in 2009

How to address the question of which IV fluids are safe in hospitalized children?

Systematic review question:
- In hospitalized children age 1 month-18 years assessed to be euvoletic, does hypotonic saline vs. isotonic saline at maintenance rates confer an increased risk of developing hyponatremia defined as a serum sodium<135mmol/L?
Systematic Review Protocol:

Included Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Subject characteristics</th>
<th>Interventions compared (all with D unless noted)</th>
<th>Outcome data (Na&lt;135mmol/L)</th>
<th>Hypernatremia (Na&gt;145mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coulthard 2012</td>
<td>n=79, 4-14 years</td>
<td>PICU, surgical (spinal or craniotomy)</td>
<td>Hartmann’s vs. 0.45% saline</td>
<td>0/39 (0%) in isotonic; 7/40 (18%) in hypotonic</td>
</tr>
<tr>
<td>Rey 2011</td>
<td>n=84, 2-10 years</td>
<td>PICU, mixed surgical (45%) and medical</td>
<td>156mmol/L vs 50-70mmol/L</td>
<td>8/45 (17.8%) in isotonic; 19/39 (48.7%) in hypotonic</td>
</tr>
<tr>
<td>Yung 2009</td>
<td>n=61, 30 days - 18 years</td>
<td>PICU, mixed surgical and medical</td>
<td>0.9% saline vs. 0.18% saline</td>
<td>3/29 (10.3%) in isotonic; 7/32 (21.9%) in hypotonic</td>
</tr>
<tr>
<td>Montanana 2008</td>
<td>n=122, 29 days - 18 years</td>
<td>PICU, surgical thoracic, cardiac, abdominal, CNS</td>
<td>Na140mEq/L, K15mEq/L</td>
<td>3/59 (5.1%) in isotonic; 13/63 (20.6%) in hypotonic</td>
</tr>
<tr>
<td>Saba 2011</td>
<td>n=37, 3 months - 18 years</td>
<td>Floor, mixed surgical (67%) and medical</td>
<td>0.9% saline vs. 0.45% saline</td>
<td>1/16 (6%) in isotonic; 1/21 (5%) in hypotonic</td>
</tr>
</tbody>
</table>

Quick Primer on Meta-analysis

- Pools risk estimates from across studies to generate overall estimate of risk
- Like a sharp knife
- Caveats
  - Cannot improve quality of individual studies and must therefore assess and include with care
  - Must assess for heterogeneity of results (I² from 0-100%)

Assessment of quality of studies:
Results:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Translating into number needed to treat (harm):</th>
<th>Conclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.26 (95% CI: 3.85-9.09)</td>
<td>Translating into number needed to treat (harm):</td>
</tr>
<tr>
<td></td>
<td>If you treat 5 patients with hypotonic fluids, 1</td>
<td>5.26 (95% CI: 3.85-9.09)</td>
</tr>
<tr>
<td></td>
<td>will develop a serum Na&lt;135.</td>
<td>Unable to assess risk for significant hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Hypotonic fluids including 1/2NS carry risk of harm</td>
<td>Hypotonic fluids including 1/2NS carry risk of harm</td>
</tr>
<tr>
<td></td>
<td>used at maintenance rates in euvolemic patients</td>
<td>used at maintenance rates in euvolemic patients</td>
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</tbody>
</table>

Comparison of at least ½ NS with isotonic fluids:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Holliday 2007:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>recognized need for less water but argued that isotonic fluids not the answer</td>
</tr>
<tr>
<td></td>
<td>need to be better clinicians and assess volume status better</td>
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Alternate hypotheses:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Counter:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Neville 2010: subjects receiving hypotonic fluids at ½ maintenance had similar risk of hyponatremia as those receiving at maintenance</td>
</tr>
<tr>
<td></td>
<td>Yung 2009: fluid type but not rate (2/3 maintenance) was predictor of hyponatremia</td>
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</table>

Potential dangers of isotonic fluids

<table>
<thead>
<tr>
<th>Fluid overload:</th>
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<tbody>
<tr>
<td>Heart failure, liver failure, renal failure</td>
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<table>
<thead>
<tr>
<th>Hypernatremia:</th>
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</thead>
<tbody>
<tr>
<td>Especially in diabetes insipidus</td>
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</table>

<table>
<thead>
<tr>
<th>Hyperchloremic metabolic acidosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concern primarily with 0.9% NaCl; documented case series; seen primarily with resuscitation-level volumes, not maintenance</td>
</tr>
</tbody>
</table>

Case #2:

<table>
<thead>
<tr>
<th>A patient is admitted to your service due to a clinical presentation and initial LP findings concerning for meningitis. The patient is irritable and mildly somnolent, and has been unable to take PO. Which maintenance fluid would you normally choose if the patient is a:</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 m/o M</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Case #2</td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>Case #2</td>
</tr>
</tbody>
</table>
Where from here?

- Recommendation of AAP statement on IV fluids in pediatrics to raise awareness of problem and forge potential consensus
- Recommendation of not using any IV fluids routinely and definitely not ½ NS as routine maintenance
- Further questions include:
  - Why aren’t hypotonic oral rehydration fluids problematic?
  - Possible non-ADH induced anti-diuresis as possible pathway
  - Better defining best treatment of SIAD/SIADH

Thanks:

- Vanessa Hill & Dina Tom – collaborators
- Michelle Arandes – letting me muck around
- Holliday, Segar and all the old dudes – their invaluable contributions and observations
- Erin & Atticus Foster – support and humor

Questions?

Treatment of hyponatremia:

- Based on neurologic symptoms, not a pure numbers game
- If clinically stable, fluid restriction before hypertonic saline if Na>120
- If symptomatic (altered, seizures) 3% saline to correct quickly 2-4mmol/L and until symptomatic improvement
- Total correction of deficit should be done over 48hrs
  - Total body water (TBW) x (desired SNa – actual SNa)
  - 0.6*20kg x (140-125) = 180 mEq