RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]


2. Hypertext link to PDF of full article http://www.ncbi.nlm.nih.gov/pubmed/27131100

3. First date published study available to readers 05/10/16

4. PubMed ID 27131100

5. Nominated By Jim Stevermer Other:

6. Institutional Affiliation of Nominator University of Missouri Other:

7. Date Nominated 05/01/16

8. Identified Through Other Other: TOC

9. PURLS Editor Reviewing Nominated Potential PURL Kate Rowland Other:

10. Nomination Decision Date 05/26/16

11. Potential PURL Review Form (PPRF) Type RCT

12. Other comments, materials or discussion

13. Assigned Potential PURL Reviewer Other Other: UPMC

14. Reviewer Affiliation Other Other: UPMC

15. Date Review Due 06/06/16

16. Abstract IMPORTANCE:
Gastroenteritis is a common pediatric illness. Electrolyte maintenance solution is recommended to treat and prevent dehydration. Its advantage in minimally dehydrated children is unproven.

OBJECTIVE:
To determine if oral hydration with dilute apple juice/preferred fluids is noninferior to electrolyte
maintenance solution in children with mild gastroenteritis.

DESIGN, SETTING, AND PARTICIPANTS:
Randomized, single-blind noninferiority trial conducted between the months of October and April during the years 2010 to 2015 in a tertiary care pediatric emergency department in Toronto, Ontario, Canada. Study participants were children aged 6 to 60 months with gastroenteritis and minimal dehydration.

INTERVENTIONS:
Participants were randomly assigned to receive color-matched half-strength apple juice/preferred fluids (n=323) or apple-flavored electrolyte maintenance solution (n=324). Oral rehydration therapy followed institutional protocols. After discharge, the half-strength apple juice/preferred fluids group was administered fluids as desired; the electrolyte maintenance solution group replaced losses with electrolyte maintenance solution.

MAIN OUTCOMES AND MEASURES:
The primary outcome was a composite of treatment failure defined by any of the following occurring within 7 days of enrollment: intravenous rehydration, hospitalization, subsequent unscheduled physician encounter, protracted symptoms, crossover, and 3% or more weight loss or significant dehydration at in-person follow-up. Secondary outcomes included intravenous rehydration, hospitalization, and frequency of diarrhea and vomiting. The noninferiority margin was defined as a difference between groups of 7.5% for the primary outcome and was assessed with a 1-sided α=.025. If noninferiority was established, a 1-sided test for superiority was conducted.

RESULTS:
Among 647 randomized children (mean age, 28.3 months; 331 boys [51.1%]; 441 [68.2%] without evidence of dehydration), 644 (99.5%) completed follow-up. Children who were administered dilute apple juice experienced treatment failure less often than those given electrolyte maintenance solution (16.7% vs 25.0%; difference, -8.3%; 97.5% CI, -∞ to -2.0%; P < .001 for inferiority and P = .006 for superiority). Fewer children administered apple juice/preferred fluids received intravenous rehydration (2.5% vs 9.0%; difference, -6.5%; 99% CI, -11.6% to -1.8%). Hospitalization rates and diarrhea and vomiting frequency were not significantly different between groups.

CONCLUSIONS AND RELEVANCE:
Among children with mild gastroenteritis and minimal dehydration, initial oral hydration with dilute apple juice followed by their preferred fluids, compared with electrolyte maintenance solution, resulted in fewer treatment failures. In many high-income countries, the use of dilute apple juice and preferred fluids as desired may be an appropriate alternative to electrolyte maintenance fluids in children with mild gastroenteritis and minimal dehydration.

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?
Among 647 randomized children (mean age, 28.3 [SD, 15.9] months; 331 boys [51.1%]; 441 [68.2%] without clinical evidence of dehydration), 644 (99.5%) completed follow-up. Children who were administered dilute apple juice experienced treatment failure less often than those given electrolyte maintenance solution (16.7% vs 25.0%; difference, -8.3%; 97.5% CI, -∞ to -2.0%; P < .001 for inferiority and P = .006 for superiority). Fewer children administered apple juice/preferred fluids received intravenous rehydration (2.5% vs 9.0%; difference, -6.5%; 99% CI, -11.6% to -1.8%). Hospitalization rates and diarrhea and vomiting frequency were not significantly different between groups.

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?
Eligible children were aged 6 months to 60 months who presented with the following: 3 or more episodes of vomiting or diarrhea in the preceding 24 hours; less than 96 hours of symptoms; weight of 8 kg (17.7 lb) or higher; and minimal dehydration. Dehydration was quantified using the 4-item, 8-point Clinical Dehydration Scale. Children with Clinical Dehydration Scale scores lower than 5 and capillary refill of less than 2 seconds were classified as having minimal dehydration. Children were excluded if they had a history of chronic gastrointestinal disease (eg, inflammatory bowel disease, celiac disease) or other diseases (eg, diabetes mellitus, inborn errors of metabolism) that complicated the clinical picture; prematurity with corrected postnatal age of less than 30 weeks; bilious vomiting, hematemesis, hematochezia, or clinical concern for acute abdomen; or a need for immediate intravenous rehydration.
3. Intervention(s) being investigated?

Half strength apple juice/preferred fluid. All participants received 2 L of their assigned solution for use in the ED and at home following discharge. Children received 5-mL aliquots of the assigned fluid every 2 to 5 minutes. Those who vomited received oral ondansetron. All children underwent ED physician evaluation; treatment decisions were at the discretion of the responsible physician. If oral consumption or hydration status were unsatisfactory, the physician could continue oral rehydration with the same or alternate (ie, crossover) solution or administer intravenous hydration.

4. Comparison treatment(s), placebo, or nothing?

Electrolyte maintenance solution. All participants received 2 L of their assigned solution for use in the ED and at home following discharge.

5. Length of follow up? Note specified end points e.g. death, cure, etc.

Caregivers were telephoned daily by a research nurse who was blinded to treatment assignment until the child had been asymptomatic for 24 hours. Standardized criteria were used to guide recommendations (eg, eAppendix 4 in Supplement 1). A registered letter was sent to families not contacted after 5 telephone attempts. Caregivers were provided a diary in which to record key details such as follow-up health care clinician visits and diarrhea and vomiting frequency. These were returned at the final in-person reassessment or by mail. Data verification for ED revisits, hospitalization, and adverse events was obtained from 2 provincial registries, the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which includes hospital discharge diagnoses from all hospitals in the province, and the National Ambulatory Care Reporting System (NACRS), which includes ED visit diagnoses.

6. What outcome measures are used? List all that assess effectiveness.

The primary outcome of treatment failure was a composite measure defined by any of the following occurring within 7 days of enrollment: (1) hospitalization or intravenous rehydration; (2) subsequent unscheduled physician encounter in an office, urgent care, or ED setting for the same episode of vomiting or diarrhea (ie, “episode” terminates when symptom-free for 24 hours); (3) protracted symptoms (ie, ≥3 episodes of vomiting or diarrhea within a 24-hour period occurring >7 days after enrollment); (4) physician request to administer a solution representing treatment allocation crossover at the index visit; or (5) a 3% or greater weight loss or Clinical Dehydration Scale score of 5 or higher at in-person follow-up. Secondary outcomes identified a priori were (1) intravenous rehydration at the index visit or a subsequent visit within 7 days of enrollment; (2) hospitalization at the index visit or a subsequent visit; (3) frequency of diarrhea and vomiting; and (4) percentage weight change at the 72- to 84-hour reassessment. Planned exploratory outcomes included serum sodium, potassium, bicarbonate, urea, and creatinine among children receiving intravenous rehydration at a revisit; time to return to a 75% “normal” diet; and caregiver satisfaction with the discharge instructions provided and the ease of implementation, evaluated at first in-person follow-up visit.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

In the intention-to-treat analysis, which encompassed all events occurring at the index visit and during follow-up, the treatment failure rate was 16.7% (54/323; 95% CI, 12.8%–21.2%) in the apple juice/preferred fluids and 25.0% (81/324; 95% CI, 20.4%–30.1%) in the electrolyte maintenance solution group (difference, −8.3%; 97.5% CI, −19.0% to −2.0) (Table 2). These findings are consistent with noninferiority, with the upper bound of the 1-sided 97.5% CI for the difference in failure being less than the prespecified noninferiority margin of 7.5%. The P value for the null hypothesis of inferiority was P < .001.
Testing for superiority yielded a $P=0.006$.

8. What are the adverse effects of intervention compared with no intervention?

9. Study addresses an appropriate and clearly focused question - select one

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments: We hypothesized that allowing children to drink dilute apple juice followed by their preferred fluids would not result in an increased frequency of treatment failure compared with electrolyte maintenance solution use.

10. Random allocation to comparison groups

Comments: Children were randomly assigned to receive half-strength apple juice/preferred fluids or electrolyte maintenance solution in a 1:1 ratio using computer-generated blocks of 8.

11. Concealed allocation to comparison groups

Comments: The study team was unaware of the block sizes. Research support pharmacy staff, who were not responsible for patient selection, enrollment, or treatment allocation, created and stored the randomization table, which they used to prepare the study solutions and randomization assignment instructions. The latter were inserted into identical, opaque, sealed envelopes that were consecutively numbered on the outside and stored in a locked cabinet. Color-matched, refrigerated study solutions were prepared in opaque, identical-appearing bottles (eAppendix 1 in Supplement 1).

12. Subjects and investigators kept “blind” to comparison group allocation

Comments: Baseline characteristics were not different between the groups (Table 1). The 225 children whose caregivers declined participation were less likely to receive ondansetron, but otherwise the groups were not significantly different (eTables 2 and 3 in Supplement 1).

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

Comments: Nonexperimental ED treatments were implemented according to accepted standards3,4,16 and institutional guidelines. Children received 5-mL aliquots of the assigned fluid every 2 to 5 minutes. Those who vomited received oral ondansetron.17,18 All children
the differences are a potential source of bias.

underwent ED physician evaluation; treatment decisions were at the discretion of the responsible physician. If oral consumption or hydration status were unsatisfactory, the physician could continue oral rehydration with the same or alternate (ie, crossover) solution or administer intravenous hydration.

15. Were all relevant outcomes measured in a standardized, valid, and reliable way?

- [ ] Well covered
- [x] Adequately addressed
- [ ] Poorly addressed
- [ ] Not applicable

Comments: In the statistic section of the methods

16. Are patient oriented outcomes included? If yes, what are they?

Yes, all the components of the primary outcome were patient oriented.

17. What percent dropped out, and were lost to follow up? Could this bias the results? How?

Of the 647 patients randomized, only 3 patients were lost to follow-up. This is unlikely a source of bias.

18. Was there an intention-to-treat analysis? If not, could this bias the results? How?

Analyses were undertaken by intention-to-treat principles. Continuous data are presented as means with standard deviations and medians with interquartile ranges (IQRs). The primary efficacy analysis evaluated noninferiority by calculating the 95% confidence interval for the difference in probability of failure (ie, apple juice/preferred fluids minus electrolyte maintenance solution). If the upper bound of the 95% CI for this difference was less than the inferiority margin (ie, +7.5%), inferiority could be rejected. If noninferiority was confirmed, a test for superiority would be conducted at the 1-sided α=.025 level, according to the recommendation of the Committee for Proprietary Medicinal Products.

19. If a multi-site study, are results comparable for all sites?

single site study at a tertiary care facility in Toronto, Ontario

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?

This study was supported by a grant provided by the Physician Services Incorporated Foundation (grant 10q1011). Dr Freedman holds the Alberta Children’s Hospital Foundation Professorship in Child Health and Wellness.

21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.

These findings apply to all parents, caregivers of children.

22. In what care settings might the findings apply, or not apply?

While this was studied in an ED setting, there may be extrapolation to an urgent care type setting as well.

23. To which clinicians or policy makers might the findings be relevant?

this would be relevant for all primary care providers of children, pediatricians, parents, teachers.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]
Fluid and electrolytes:

- for children with no or minimal signs of dehydration - home-based fluid management recommended
  - increase fluid intake to compensate for losses and prevent development of dehydration
  - if possible, replace fluid after each episode of diarrhea with commercially available oral rehydration solution (ORS)
  - 50-120 mL (2-4 fluid ounces) in children < 2 years old or < 10 kg (22 lbs)
  - 100-240 mL (4-8 fluid ounces) in children aged 2-10 years or > 10 kg (22 lbs)
- for children with acute or persistent vomiting, attempt small amounts (5 mL) of oral rehydration solution 5-10 minutes after vomiting ceases, and gradually advance as tolerated
  - avoid commercial juices and carbonated beverages
  - continue usual feeding
  - encourage caretakers to bring child to healthcare facility if signs of dehydration arise
- for children with mild or moderate dehydration - rapid fluid replacement with oral rehydration therapy at health facility recommended
  - provide 50-100 mL/kg ORS over first 4 hours - give frequently in small amounts (such as teaspoonful every 1-2 minutes or frequent small sips) and provide additional ORS to replace ongoing losses, if tolerated
  - considerations for oral rehydration therapy
  - World Health Organization (WHO) estimated amounts of ORS to give within first 4 hours is 75 mL/kg body weight
  - ORS may also be provided by age if weight unknown

Approximate Amount of ORS by Age in First 4 Hours:

<table>
<thead>
<tr>
<th>Age</th>
<th>ORS Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 months</td>
<td>200-400 mL</td>
</tr>
<tr>
<td>4-11 months</td>
<td>400-600 mL</td>
</tr>
<tr>
<td>12-23 months</td>
<td>600-800 mL</td>
</tr>
<tr>
<td>2-4 years</td>
<td>800-1,200 mL</td>
</tr>
<tr>
<td>5-14 years</td>
<td>1,200-2,200 mL</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>2,200-4,000 mL</td>
</tr>
</tbody>
</table>

Abbreviation: ORS, oral rehydration solution.

- oral rehydration therapy by mouth or nasogastric (NG) tube may have similar overall safety and efficacy as IV rehydration therapy for first-line treatment of dehydration due to acute gastroenteritis in children (level 2 [mid-level] evidence)
- reduced osmolarity ORS reduces unscheduled IV infusions and vomiting compared to conventional ORS in children hospitalized with diarrhea (level 1 [likely reliable] evidence)
- contraindications to oral rehydration therapy include impairment of airway protective reflexes, abdominal ileus, intussusception, or carbohydrate malabsorption
• continue with usual fluids (including milk feeds) during ORS administration if child is not vomiting
  o consider NG administration of ORS in child with normal mental status who is unable to drink or who vomits persistently with oral ORS
  o consider IV therapy in child with decreased consciousness or if unresponsive to oral or NG administration of ORS
  o start IV therapy immediately if child shows signs of severe dehydration or clinical deterioration
  o encourage home fluid management after dehydration corrected

2. DynaMed citation/access date
ORT is the mainstay of treatment

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Supportive treatment — The management of acute viral gastroenteritis is supportive. Fluid repletion and replacement of ongoing fluid losses are the goals of therapy, whether the child is managed at home, in the emergency department, or in the hospital.
Fluid repletion and maintenance — Initial therapy is directed toward correcting fluid deficit and electrolyte imbalance. Fluid repletion is based upon the degree of hypovolemia (dehydration) (table 1). Intravenous (IV) fluids should be administered if dehydration is severe or if the patient is unable to take oral solutions. (See "Clinical assessment and diagnosis of hypovolemia (dehydration) in children").
● Severe dehydration – Severe hypovolemia requires rapid isotonic fluid resuscitation, which is discussed separately. (See "Treatment of hypovolemia (dehydration) in children").
● Mild to moderate dehydration – Oral rehydration therapy is the preferred first-line treatment for fluid and electrolyte losses in children with mild to moderate dehydration from acute gastroenteritis. (See "Oral rehydration therapy", section on 'Clinical management'.)

4. UpToDate excerpts
Supportive treatment — The management of acute viral gastroenteritis is supportive. Fluid repletion and replacement of ongoing fluid losses are the goals of therapy, whether the child is managed at home, in the emergency department, or in the hospital.
Fluid repletion and maintenance — Initial therapy is directed toward correcting fluid deficit and electrolyte imbalance. Fluid repletion is based upon the degree of hypovolemia (dehydration) (table 1). Intravenous (IV) fluids should be administered if dehydration is severe or if the patient is unable to take oral solutions. (See "Clinical assessment and diagnosis of hypovolemia (dehydration) in children").
● Severe dehydration – Severe hypovolemia requires rapid isotonic fluid resuscitation, which is discussed separately. (See "Treatment of hypovolemia (dehydration) in children").
● Mild to moderate dehydration – Oral rehydration therapy is the preferred first-line treatment for fluid and electrolyte losses in children with mild to moderate dehydration from acute gastroenteritis. (See "Oral rehydration therapy", section on 'Clinical management'.)

5. UpToDate citation/access date
Always use Basow DS as editor & current year as publication year.
ORT and supportive treatment is the mainstay of therapy in resource rich countries

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp
8. PEPID citation/access data
9. PEPID content updating
1. Do you recommend that PEPID get updated on this topic?
   Yes, there is important evidence or recommendations that are missing
   No, this topic is current, accurate and up to date.
   If yes, which PEPID Topic, Title(s): 
   2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (Ed) that should be updated on the basis of the review?
   Yes, there is important evidence or recommendations that are missing
   No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s):  

10. Other excerpts  
(USPSTF; other guidelines; etc.)  
11. Citations for other excerpts  

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)  

ORT at home is the mainstay of treatment for mild gastroenteritis in children.

SECTION 4: Conclusions  
[to be completed by the Potential PURL Reviewer]  
[to be revised by the Pending PURL Reviewer as needed]  

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?  
Give one number on a scale of 1 to 7  
(1=extremely well; 4=neutral; 7=extremely poorly)  
☐ 1 ☒ 2 ☐ 3 ☐ 4 ☒ 5 ☒ 6 ☒ 7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?  

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians?  
Give one number on a scale of 1 to 7  
(1=extremely well; 4=neutral; 7=extremely poorly)  
☐ 1 ☒ 2 ☐ 3 ☐ 4 ☒ 5 ☒ 6 ☒ 7

Even though in an ED population, can be extrapolated to urgent care settings.

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.  

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?  
Give one number on a scale of 1 to 7  
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)  
☐ 1 ☒ 2 ☐ 3 ☐ 4 ☒ 5 ☒ 6 ☒ 7

Some FM physicians may already be doing this, particularly for cost reasons.

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.  

7. Applicability to a Family Medical Care Setting:  
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc),  
Give one number on a scale of 1 to 7  
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)  
☒ 1 ☐ 2 ☐ 3 ☐ 4 ☒ 5 ☒ 6 ☒ 7
such as prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. **Immediacy of Implementation:** Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

10. If you coded 4.9 as a 4, 5, 6, or 7, please explain why.

11. **Clinical meaningful outcomes or patient oriented outcomes:** Are the outcomes measured in the study clinically meaningful or patient oriented?

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?

**Criteria for a Pending PURL:**

- **Valid:** Strong internal scientific validity; the findings appears to be true.
- **Relevant:** Relevant to the practice of family medicine
- **Practice changing:** There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- **Applicability in medical setting:**
• Immediacy of implementation

14. Comments on your response in 4.13

This would validate what some FM physicians are already doing with evidence, in place of only expert opinion recommendations from the Peds organization.