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]

1. Citation	Freedman SB, Willan AR, Boutis K, Schuh S. Effect of Dilute Apple Juice and Preferred Fluids vs Electrolyte Maintenance Solution on Treatment Failure Among Children With Mild Gastroenteritis: A Randomized Clinical Trial. JAMA. 2016 May 10;315(18):1966-74.
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	
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.

17. Pending PURL Review Date

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 ofdehydration) (Figure 1), 323were randomizedto apple juice/preferred fluids therapy and 324 to electrolyte maintenance solution.
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Eligible chil- dren were aged 6 months to 60 months who presented with the following: 3 or more episodes of vomiting or diarrhea10 in the preceding 24 hours; less than 96 hours of symptoms; weight of 8 kg (17.7 lb) or higher; and minimal dehydration.4 Dehydration was quantified using the 4-item, 8-point Clini- cal Dehydration Scale.8,11-14 Children with Clinical Dehydra- tion Scale scores lower than 5 and capillary refill of less than 2 seconds15 were classified as having minimal dehydration. Chil- dren were excluded if they had a history of chronic gastroin- testinal disease (eg, inflammatory bowel disease, celiac dis- ease) or other diseases (eg, diabetes mellitus, inborn errors of metabolism) that complicated the clinical picture; prematu- rity with corrected postnatal age of less than 30 weeks; bil- ious vomiting, hematemesis, hematochezia, or clinical con- cern for acute abdomen; or a need for immediate intravenous rehydration

3. Intervention(s) being investigated?	half strength apple juice/preferred fluid. All par- ticipants 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.17,18 All children underwent ED physician evaluation; treatment de- cisions were at the discretion of the responsible physician. If oral consumption or hydration status were unsatisfactory, the phy- sician could continue oral rehydration with the same or alternate (ie, crossover) solution or administer intravenous hydration.
4. Comparison treatment(s), placebo, or nothing?	electrolyte maintainence solution All par- ticipants 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.	Caregiverswere telephoned daily by a research nursewhowas blindedtotreatmentassignmentuntilthechildhadbeenasymptomatic for 24 hours. Standardized criteriawere used to guide recommendations (eg, eAppendix 4 in Supplement 1). A registeredletterwas sent to familiesnot contactedafter 5 telephoneattempts. 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, andadverse eventswas obtainedfrom 2provincial registries, theCanadian Institute forHealth Information (CIHI) Discharge AbstractDatabase,whichincludes hospital discharge diagnoses fromall hospitals in the province,and theNationalAmbulatoryCareReportingSystem(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 definedbyanyof the following occurringwithin 7days 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 vomitingor diarrhea19 (ie, "episode" terminateswhensymptomfree for 24hours); (3) protractedsymptoms(ie, ≥3 episodes of vomiting or diarrheawithin 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 greaterweight loss or ClinicalDehydration Scale score of 5 or higher at in-person follow-up. Secondaryoutcomesidentified a prioriwere (1) intravenous rehydration at the indexvisitor a subsequent visitwithin 7days ofenrollment;(2)hospitalizationattheindexvisitorasubsequent visit; (3) frequencyofdiarrheaandvomiting;and(4) percentage weight change at the 72- to 84-hour reassessment.20-22 Planned exploratory outcomes included serumsodium, potassium, bicarbonate, urea, and creatinineamong childrenreceiving intravenousrehydration at a revisit; time toreturn toa 75%"normal" diet; and caregiver satisfactionwith the discharge instructions provided and the ease of implementation, evaluated at first inperson 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, −! to −2.0) (Table 2). These findings are consistentwith noninferiority,with the upper bound of the 1-sided 97.5%CI for the difference in failure being less than the prespecified noninferioritymargin of+7.5%. The P value for the null hypothesis of inferiority was P<.001.

Testing for superiority yielded a P=.006.

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

No other adverse eventswere reported or identified.

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

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: Children were randomly assigned to receive half-strength apple juice/preferred fluids or electrolyte maintenance solu- tion in a 1:1 ratio using computer-generated blocks of 8.

11. Concealed allocation to comparison groups

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

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

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: The study team was unaware of the block sizes. Research support pharmacy staff, who were not responsible for patient selec- tion, 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 enve- lopes 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. Comparison groups are similar at the start of the trial

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: Baseline characteristicswere 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 treat- ments 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 de- cisions 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 ☒ 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 medianswith 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.24
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 andWellness.
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]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts

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:

Age	ORS Volume
< 4 months	200-400 mL
4-11 months	400-600 mL
12-23 months	600-800 mL
2-4 years	800-1,200 mL
5-14 years	1,200-2,200 mL
≥ 15 years	2,200-4,000 mL

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
  - consider NG administration of ORS in child with normal mental status who is unable to drink or who vomits persistently with oral ORS
  - consider IV therapy in child with decreased consciousness or if unresponsive to oral or NG administration of ORS
  - start IV therapy immediately if child shows signs of severe dehydration or clinical deterioration
  - encourage home fluid management after dehydration corrected

2. DynaMed citation/access date

Title. Rotavirus gastroenteristis Author. Paritosh Prasad, MD In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 11/2/2015. Accessed 6/8/2016

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

ORT is the mainstay of treatment

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.

Title. Acute viral gastroenteritis in children in resource-rich countries: Management and preventionAuthor. David Matson In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: 4/25/16`. Accessed06/8/16

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

ORT and supportive treatment is the mainstay of therapy in resource rich countries

7. PEPID PCP excerpts

www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed

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 (EB) 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

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

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

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

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.

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

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 a 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 4, 5, 6, or 7, please explain why.

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

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.

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

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:

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

- 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.