RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

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

A. Citiation: Hooton TM, Vecchio M, Iroz A, Tack I, Dornic Q, Seksek I, Lotan Y. Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial. JAMA Intern Med. 2018 Nov 1;178(11):1509-1515. doi: 10.1001/jamainternmed.2018.4204. PubMed PMID: 30285042.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/?term=30285042
C. First date published study available to readers: 11/1/2018
D. PubMed ID: 30285042
E. Nominated By: Anne Mounsey
F. Institutional Affiliation of Nominator: UNC Chapel Hill
G. Date Nominated: 10/3/2018
H. Identified Through: JAMA
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 10/11/2018
K. Potential PURL Review Form (PPRF) Type: RCT
L. Assigned Potential PURL Reviewer: Scott Earwood
M. Reviewer Affiliation: Eisenhower Army Medical Center
A. Abstract: Increased hydration is often recommended as a preventive measure for women with recurrent cystitis, but supportive data are sparse.

OBJECTIVE:
To assess the efficacy of increased daily water intake on the frequency of recurrent cystitis in premenopausal women.

DESIGN, SETTING, AND PARTICIPANTS:
Randomized, open-label, controlled, 12-month trial at a clinical research center (years 2013-2016). Among 163 healthy women with recurrent cystitis (≥3 episodes in past year) drinking less than 1.5 L of fluid daily assessed for eligibility, 23 were excluded and 140 assigned to water or control group. Assessments of daily fluid intake, urinary hydration, and cystitis symptoms were performed at baseline, 6- and 12-month visits, and monthly telephone calls.

INTERVENTIONS:
Participants were randomly assigned to drink, in addition to their usual fluid intake, 1.5 L of water daily (water group) or no additional fluids (control group) for 12 months.

MAIN OUTCOMES AND MEASURES:
Primary outcome measure was frequency of recurrent cystitis over 12 months. Secondary outcomes were number of antimicrobial regimens used, mean time interval between cystitis episodes, and 24-hour urinary hydration measurements.

RESULTS:
The mean (SD) age of the 140 participants was 35.7 (8.4) years, and the mean (SD) number of cystitis episodes in the previous year was 3.3 (0.6). During the 12-month study period, the mean (SD) number of cystitis episodes was 1.7 (95% CI, 1.5-1.8) in the water group compared with 3.2 (95% CI, 3.0-3.4) in the control group, with a difference in means of 1.5 (95% CI, 1.2-1.8; P < .001). Overall, there were 327 cystitis episodes, 111 in the water group and 216 in the control group. The mean number of antimicrobial regimens used to treat cystitis episodes was 1.9 (95% CI, 1.7-2.2) and 3.6 (95% CI, 3.3-4.0), respectively, with a difference in means of 1.7 (95% CI, 1.3-2.1; P < .001). The mean time interval between cystitis episodes was 142.8 (95% CI, 127.4-160.1) and 84.4 (95% CI, 75.4-94.5) days, respectively, with a difference in means of 58.4 (95% CI, 39.4-77.4; P < .001). Between baseline and 12 months, participants in the water group, compared with those in the control group, had increased mean (SD) urine volume (1.4 [0.04] vs 0.1 [0.04] L; P < .001) and voids (2.4 [0.2] vs -0.1 [0.2]; P < .001) and decreased urine osmolality (-402.8 [19.6] vs -24.0 [19.5] mOsm/kg; P < .001).

CONCLUSIONS AND RELEVANCE:
Increased water intake is an effective antimicrobial-sparing strategy to prevent recurrent cystitis in premenopausal women at high risk for recurrence who drink low volumes of fluid daily.

B. Pending PURL Review Date**:** 5/6/2019

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

A. Number of patients starting each arm of the study?
70 people to water group and 70 people to control.

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Included pre-menopausal women at least 18 years old, in good health, absence of current UTI symptoms, reported at least 3 symptomatic episodes of cystitis in the past year resulting in a visit to a clinician (proven), at least one episode of which had to be cultured to confirm >100K CFU of bacteria in a voided midstream urine cultures and self-reported drinking less than 1.5 L of fluid daily.

Excluded out of the age group, current symptoms, history of pyelonephritis in past 12 months, interstitial cystitis, pregnant, lactating or planning to become pregnant in the following 12 months.

C. Intervention(s) being investigated?
Given 1.5 L additional of Avion water to water group. Assess efficacy of increased daily water intake on the frequency of recurrent cystitis in premenopausal women. Primary outcome was frequency of recurrent cystitis over 12 months.

D. Comparison treatment(s), placebo, or nothing?
Compared those who drank 1.5L of water daily in addition to their usual fluid intake or no additional fluids for 12 months

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
12 months

F. What outcome measures are used? List all that assess effectiveness.
Clinical UTI, culture proved UTI, causative bacteria, antibiotic use, median time to first cystitis, average time interval between episodes, self-reported fluid intake, self-reported number of voids/day, 6 and 12 month urine collection for volume and osmolality.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
   a. Cystitis 1.7 (95%CI, 1.5-1.8) in water group compared with 3.2 (95% CI, 3.0-3.4) in control with difference in means of 1.5 (95% CI, 1.2-1.8; P<0.001).
   b. 327 cystitis episodes, 111 in the water group compared to 216 in the control
   c. Mean number of antimicrobial regimen used to treat cystitis 1.9 (95% CI, 1.7–2.2) and 3.6 (95% CI, 3.3-4.0) with a difference in means of 1.7 (95% CI, 1.3-2.1; P<0.001)
   d. Mean time of interval between cystitis episodes 142.8 (95%CI, 127.4-160.1) and 84.4 (95% CI, 75.4-94.5) days, with a difference in means of 58.4 (95% CI, 39.4-77.4; P<0.001)
   e. had increased mean (SD) urine volume (1.4 [0.04] vs 0.1 [0.04] L; *P* < .001) and voids (2.4 [0.2] vs −0.1 [0.2]; *P* < .001) and decreased urine osmolality (−402.8 [19.6] vs −24.0 [19.5] mOsm/kg; *P* < .001).

H. What are the adverse effects of intervention compared with no intervention?
Headache by 12 women, GI symptoms reported by 8 in each group; no serious events occurred

I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments:

J. Random allocation to comparison groups:
(select one) Well covered

Comments:

K. Concealed allocation to comparison groups:
(select one) Well covered

Comments:

randomization prepared by independent statistician and concealed until allocation

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Adequately addressed

Comments: subjects and investigators were blinded until allocated.

M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments: similar in respects to age, BMI, sexual activity, no of cystitis in past 12 months, daily fluid intake, urine volume and number of voids

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Well covered
Comments: No

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

(select one) Adequately addressed
Comments:

P. Are patient oriented outcomes included? If yes, what are they? Yes, frequency of recurrent cystitis, number of antimicrobials used

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
16 or 15.7% in control and 23 or 22.8% in water group.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes; all 70 in each arm included

S. If a multi-site study, are results comparable for all sites?
It was multi-site but done from a single data base. The study was managed at one site; but the urine obtained at multi-sites, the majority affiliated with home unit.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
Yes, potential bias because the funding by Danone Research which sells bottled water, Evian that is included in this study. However, actual bias is unknown. Raises concern for bias. Not apparent bias in methodology but always a concern when intervention is funded by the company that funds the research. The actual bias is not discernible. Attempt was made to have independent researchers oversee the study. The collection of outcome conducted by organization outside the funding organization as was the data analysis.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
Pre-menopausal women who are not pregnant and without co-morbidities with low fluid intake per day with recurrent UTIs. May also apply to teenagers, post-menopausal, lactating patients and others with comorbidities who have low fluid intakes.

V. In what care settings might the finding apply, or not apply?
Primary care; urologic specialty care. Adherence was facilitated by delivery of free bottled water, as well as monthly follow-up calls. Because these are not a part of routine medical care, it is unknown if simple physician advice is sufficient to spur such behavioral change.

W. To which clinicians or policy makers might the finding be relevant?
Family medicine physicians, urology, OBGYN

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 up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on 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 date modified if given.} Accesses 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 date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

increased water intake may help prevent cystitis in premenopausal women with recurrent cystitis and who usually have low daily fluid intake (level 2 [mid-level] evidence)

B. DynaMed citation/
Recurrent Cystitis in Women. In: DynaMed Available at http://www.DynamicMedical.com. Last updated Oct 17, 2018. Accessed May 5, 2019.

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Cited this journal article; no articles cited

D. UpToDate excerpts
These findings support the long-held but previously unproven belief that increased fluid intake is beneficial for patients with recurrent cystitis, theoretically because it helps to dilute and clear bacteriuria.

E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: . Accessed

Hooton, Thomas. Recurrent Simple Cystitis in Women In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2019. Available at: http://www.uptodate.com. {Modified 29APR2019} Accessed May 05, 2019

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
Cites this article in the up to date article

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

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

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

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", 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?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Other, explain
Potentially practice changing if we consider that the study provides a specific amount of fluid to recommend that patients drink in addition to their usual amount. It does require that physicians assess baseline fluid intake to determine if it is low (<1.2 L). The emergence of solid evidence of benefit and absence of harm is likely to spur physicians to give these explicit recommendations when they would not otherwise have taken the time to do so.

If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

In the era of evidenced based medicine, this gives evidence to support conventional wisdom which may promote certain physicians to change their practice and allow them to make a more specific recommendation.

F. **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.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Other, explain

G. Please explain your answer to **G**.

Yes, but the intervention used—free bottled water delivered to the home, is not an available intervention.

H. **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? No

I. If **I** was coded "Other, explain or No", please explain why.

J. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

K. If **K** was coded "Other, explain or No", please explain why.

L. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. 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.

4. Applicability in medical setting.

5. Immediacy of implementation

M. Comments on your response for question M.
Study supports widely supported but unproven belief about increased water intake reducing recurrent urinary tract infections in women. This is potentially practice-changing in that it provides stronger evidence (and therefore motivation) for physicians to make a recommendation, and provides a specific amount of fluid to recommend to low-volume fluid drinking patients. (if total fluid is <1.2 L/day, increase by 1.7 L, mostly water). However, its applicability to those who already drink more than 1.2 L per day may be limited.