MetaAnalysis – Systematic Review
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. Citation: Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, Simon MS, Evans AT.


C. First date published study available to readers: 2/10/2017

D. PubMed ID: 28192108

E. Nominated By: Jim Stevermer

F. Institutional Affiliation of Nominator: University of Missouri

G. Date Nominated: 7/3/2017

H. Identified Through: Evidence Updates

I. PURLS Editor Reviewing Nominated Potential PURL: Dean Seehusen

J. Nomination Decision Date: 7/11/2017

K. Potential PURL Review Form (PPRF) Type: Systematic Review

L. Assigned Potential PURL Reviewer: Corey Lyon

M. Reviewer Affiliation: University of Colorado

A. Abstract: BACKGROUND & AIMS:
Systematic reviews have provided evidence for the efficacy of probiotics in preventing Clostridium difficile infection (CDI), but guidelines do not recommend probiotic use for prevention of CDI. We performed an updated systematic review to help guide clinical practice.

METHODS:
We searched MEDLINE, EMBASE, International Journal of Probiotics and Prebiotics, and The Cochrane Library databases for randomized controlled trials evaluating use of probiotics and CDI in hospitalized adults taking antibiotics. Two reviewers independently extracted data and assessed risk of bias and overall quality of the evidence. Primary and secondary outcomes were incidence of CDI and adverse events, respectively. Secondary analyses examined the effects of probiotic species, dose, timing, formulation, duration, and study quality.

RESULTS:
We analyzed data from 19 published studies, comprising 6261 subjects. The incidence of CDI in the probiotic cohort, 1.6% (54 of 3277), was lower than of controls, 3.9% (115 of 2984) (P < .001). The pooled relative risk of CDI in probiotic users was 0.42 (95% confidence interval, 0.30-0.57; I² = 0.0%). Meta-regression analysis demonstrated that probiotics were significantly more effective if given closer to the first antibiotic dose, with
a decrement in efficacy for every day of delay in starting probiotics \((P = .04)\); probiotics given within 2 days of antibiotic initiation produced a greater reduction of risk for CDI (relative risk, \(0.32\); 95% confidence interval, \(0.22-0.48\); \(I^2 = 0\%\)) than later administration (relative risk, \(0.70\); 95% confidence interval, \(0.40-1.23\); \(I^2 = 0\%\)) \((P = .02)\). There was no increased risk for adverse events among patients given probiotics. The overall quality of the evidence was high.

CONCLUSIONS:
In a systematic review with meta-regression analysis, we found evidence that administration of probiotics closer to the first dose of antibiotic reduces the risk of CDI by >50% in hospitalized adults. Future research should focus on optimal probiotic dose, species, and formulation. Systematic Review Registration: PROSPERO CRD42015016395.

B. Pending PURL Review Date: 8/23/2018

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

A. What types of studies are included in this review?
RCTs that utilize probiotics to prevent CDI in hospitalized adults receiving antibiotic therapy for any indication.

B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.
Does the administration of probiotics with antibiotics in hospitalized adults reduce the risk of CDI? Answer: “There is sufficient data to recommend higher doses of Lactobacillus or Lactobacillus in combination with another species, as either a drink or capsule, within 2 days of the first antibiotic dose for most hospitalized adults.”
Strengths: robust search and selection strategy, several conservative analytic strategies to handle missing data, appropriate handling of studies with high risk of bias.
Limitations: Only included non-pregnant, immunocompetent hospitalized adults without a prosthetic heart valve.

C. Study addresses an appropriate and clearly focused question. Well covered
Comments:

D. A description of the methodology used is included. Well covered
Comments:

E. The literature is sufficiently rigorous to identify all the relevant studies. Well covered
Comments:

F. Study quality is assessed and taken into account. Well covered
Comments:

G. There are enough similarities between selected studies to make combining them reasonable.
Well covered
Comments:
H. Are patient oriented outcomes included? If yes, what are they?
CDI is defined as diarrhea with confirmed microbiologic test for C. difficile. Thus, the
study includes an active infection with diarrhea (patient-oriented), not just microbiologic
tests.

I. Are adverse effects addressed? If so, how would they affect recommendations?
Yes, adverse events were captured across most (15/19) of the studies and show no
difference in adverse events.

J. Is funding a potential source of bias? If yes, what measures (if any) were taken to
ensure scientific integrity?
Two of the included studies had a funding source as a risk for bias.

K. To which patients might the findings apply? Include patients in the metaanalysis and
other patients to whom the findings may be generalized.
Hospitalized, non-pregnant, immunocompetent adult patients receiving an antibiotic.

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

M. To which clinicians or policy makers might the findings be relevant?
Hospital clinicians and hospital quality and safety boards.

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

A. DynaMed excerpts

  probiotic efficacy data for prevention of *C. difficile* diarrhea

  a. **probiotics reduce incidence of *C. difficile*-associated diarrhea in hospitalized patients** *(level 1
likely reliable) evidence)*

  i. based on 2 randomized trials

  ii. 135 hospital patients (mean age 74 years) taking antibiotics were randomized to probiotic yogurt
drink 100 g (97 mL containing *Lactobacillus casei*, *Lactobacillus bulgaricus* and *Streptococcus
thermophilus*) (Actimel) vs. sterile milkshake (Yazoo) twice daily starting within 48 hours of initial
antibiotics and continuing until 1 week after antibiotic course completed

  1. 22 patients (16%) lost to follow-up, similar rates in each group

  2. 113 patients (84%) followed up 4 weeks after finishing study drink and this group
analyzed by intention-to-treat

  3. comparing probiotic vs. placebo

  a. 12% vs. 34% developed diarrhea (NNT 5, 95% CI 3-15)

  b. 0% vs. 17% had diarrhea due to *C. difficile* (NNT 6, 95% CI 4-14)

  4. only 2 patients were positive for *C. difficile* toxin at baseline and neither developed
diarrhea

  5. Reference - BMJ 2007 Jul 14;335(7610):80 full-text, correction can be found in BMJ 2007
Jul 28;335(7612), editorial can be found in BMJ 2007 Jul 14;335(7610):54 full-text,
commentary can be found in BMJ 2007 Jul 28;335(7612):171 full-text, Evid Based Med
2008 Apr;13(2):46

  6. **DynaMed commentary** -- despite 16% loss to follow-up, absolute differences large enough
that dropouts would not change results. However, the control group had an

Updated 8/2017
extraordinarily high rate of *C. difficile* infection which may make probiotics appear more effective than in typical populations.

iii. 255 hospitalized adults randomized to probiotics 2 capsules daily vs. probiotics 1 capsule daily vs. placebo
   1. probiotic included 50 billion colony-forming units of *L. acidophilus* plus *L. casei*
   2. comparing probiotic 2 capsules vs. probiotic 1 capsule vs. placebo
      a. antibiotic-associated diarrhea in 15.5% (p ≤ 0.001, NNT 4) vs. 28.2% (p = 0.02, NNT 7) vs. 44.1%
      b. *C. difficile* diarrhea in 1.2% (p = 0.002, NNT 5) vs. 9.4% (p = 0.03, NNT 7) vs. 23.8%


b. probiotics along with strengthened infection control measures associated with reduced incidence of *C. difficile* infection in hospitalized patients (level 2 [mid-level] evidence)
   i. based on retrospective cohort study
      1. 44,835 adult patients receiving probiotics (combination of *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2) in single hospital were reviewed for incidence of *C. difficile* infection between 2005 and 2014
      2. probiotics were given within 12 hours of antibiotic treatment
      3. probiotic dose was 50 or 100 billion colony-forming units/day
   ii. strengthened infection control measures were also enacted, including patient isolation, environmental and equipment disinfection, hand hygiene, and monitoring of antibiotic use
   iii. incidence of *C. difficile* decreased from 18 cases per 10,000 patient days to mean 2.3 cases per 10,000 patient days
   iv. compared to other equivalent or nearby hospitals, probiotics plus strengthened infection control measures associated with lower rate of *C. difficile* infection (mean incidence 2.3 cases per 10,000 patient days vs. 7.5-12.8 cases per 10,000 patient days, no p value reported)
   v. Reference - *Clin Infect Dis* 2015 May 15;60 Suppl 2:S144, editorial can be found in *Clin Infect Dis* 2015 May 15;60 Suppl 2:S65
   vii. *DynaMed commentary* -- unclear from study decision if reduction in rate of *C. difficile* infection is due to probiotics or strengthened infection control measures

C. review of probiotic combination of *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 can be found in *Clin Infect Dis* 2015 May 15;60 Suppl 2:S135

B. adverse effects associated with probiotic use are likely rare but can be severe and are not well studied
   c. discussion of probiotic safety can be found in *Clin Infect Dis* 2015 May 15;60 Suppl 2:S129 and *Clin Infect Dis* 2008 Feb 1;46 Suppl 2:S104-11; discussion S144

C. *DynaMed* citation

D. Bottom line recommendation or summary of evidence from *DynaMed* (1-2 sentences)
   “insufficient data to recommend probiotics for primary prevention of CDI outside of clinical trials”

E. *UpToDate* excerpts
USE OF PROBIOTICS — The clinical role of probiotics for C. difficile–associated diarrhea (CDAD) treatment and prevention is an evolving area of study [48-59]. Probiotics vary in their capacity to resist gastric and bile acids, colonize the lower intestinal tract, and influence cytokine secretion [25,36,60]. Therefore, it is difficult to generalize findings observed with one probiotic species (eg, product, dose, duration) to other probiotic species or combinations.

Prevention of CDAD — We do not favor administration of adjunctive probiotics for routine treatment of CDAD. Thus far, no randomized trials have demonstrated benefit associated with routine probiotic administration for prevention of CDAD [61]; some meta-analyses suggest that use of probiotics may be beneficial for prevention of CDAD [62-68].

One randomized trial including more than 2900 adults with antibiotic exposure noted no risk reduction among those who received a multistrain preparation of Lactobacillus acidophilus and Bifidobacterium bifidum (relative risk [RR] 0.71; 95% CI 0.34-1.47) [69]. Another randomized trial including 477 hospitalized patients found no evidence of an effect of S. boulardii for prevention of CDAD; it was stopped early for futility [70].

In a meta-analysis including 20 randomized trials and more than 3800 patients, probiotics reduced the incidence of CDAD by 66 percent, corresponding to a pooled relative risk of 0.34 (95% CI 0.24-0.49) [62]. Similarly, in a systematic review including 19 randomized trials and more than 6200 patients, the pooled relative risk of CDAD in patients receiving probiotics was 0.42 (95% CI 0.30-0.57) [63]. In both of these analyses, the authors estimate that administration of probiotics to patients receiving antibiotics would prevent 23 to 144 cases per 1000 patients. However, the incidence of CDAD applied in this calculation is likely an overestimation, and true outcomes are likely to be variable dependent upon regional rates. (See "Clostridium difficile infection in adults: Epidemiology, microbiology, and pathophysiology").

The strain, dose, and duration of probiotic used in the above studies varied widely. In designing future studies of probiotics for CDAD, it will be important to consider the different probiotic strains used and standardized probiotic dosing. In the meantime, if probiotics are used for prevention of CDAD, treatment should consist only of regimens with demonstrated efficacy (table 1).

F. UpToDate citation. 

G. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences) “In patients receiving antibiotics who are felt to be at increased risk for CDAD, we suggest coadministration of probiotics for prevention of CDAD (Grade 2B). Factors for consideration include prolonged duration of antibiotic therapy, local incidence of CDAD, and individual patient characteristics.”
H. Other excerpts (USPSTF; other guidelines; etc.)
Infectious Disease Experts recommend “utilization of specific probiotics to prevent C. difficile overgrowth”

American College of Gastroenterology and the Society for Healthcare Epidemiology of America do not recommend probiotics for primary prevention of CDI.

I. Citations for other excerpts


A. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)
Guidelines are mixed about their recommendations for use of probiotics to prevent C. diff infection.

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? Yes

F. 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.
   Routine use of lactobacillus containing probiotics on hospitalized immunocompetent adults who are receiving antibiotics. Probiotics should be started within two days of the first antibiotic dose to maximize efficacy.

G. **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? Yes

H. Please explain your answer to G.
   Family physicians routinely care for adults in the hospital setting receiving antibiotic therapy.

I. **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

J. If I was coded “Other, explain or No”, please explain why.
   This can be implemented quickly. The set of four questions above having competing directions, making a single yes or no answer incorrect.

K. **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

L. If K was coded “Other, explain or No”, please explain why.

M. 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

N. Comments on your response for question M.