

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. Citation: Daniels L, Ünlü Ç, de Korte N, van Dieren S, Stockmann HB, Vrouwenraets BC, Consten EC, van der Hoeven JA, Eijsbouts QA, Faneyte IF, Bemelman WA, Dijkgraaf MG, Boermeester MA; Dutch Diverticular Disease (3D) Collaborative Study Group. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. *Br J Surg*. 2017 Jan;104(1):52-61. doi: 10.1002/bjs.10309. Epub 2016 Sep 30. PubMed PMID: 27686365.
- B. Link to PubMed abstract: <https://www.ncbi.nlm.nih.gov/pubmed/?term=27686365>
- C. First date published study available to readers: 9/30/2016
- D. PubMed ID: 27686365
- E. Nominated By: Jim Stevermer
- F. Institutional Affiliation of Nominator: University of Missouri
- G. Date Nominated: 12/16/2016
- H. Identified Through: Evidence Updates
- I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
- J. Nomination Decision Date: 12/21/2016
- K. Potential PURL Review Form (PPRF) Type: RCT
- L. Assigned Potential PURL Reviewer: Mary Alice Noel, Bob Marshall
- M. Reviewer Affiliation: Madigan Army Medical Center
- A. Abstract: BACKGROUND:

Antibiotics are advised in most guidelines on acute diverticulitis, despite a lack of evidence to support their routine use. This trial compared the effectiveness of a strategy with or without antibiotics for a first episode of uncomplicated acute diverticulitis.

METHODS:

Patients with CT-proven, primary, left-sided, uncomplicated, acute diverticulitis were included at 22 clinical sites in the Netherlands, and assigned randomly to an observational or antibiotic treatment strategy. The primary endpoint was time to recovery during 6 months of follow-up. Main secondary endpoints were readmission rate; complicated, ongoing and recurrent diverticulitis; sigmoid resection and mortality. Intention-to-treat and per-protocol analyses were done.

RESULTS:

A total of 528 patients were included. Median time to recovery was 14 (interquartile range [i.q.r.] 6-35) days for the observational and 12 (7-30) days for the antibiotic treatment strategy, with a hazard ratio for recovery of 0.91 (lower limit of 1-sided 95 percent CI 0.78; P = 0.151). No significant differences between the observation and antibiotic treatment groups were found for secondary endpoints: complicated diverticulitis (3.8 versus 2.6 per cent respectively; P = 0.377), ongoing diverticulitis (7.3 versus 4.1 per cent; P = 0.183), recurrent diverticulitis (3.4 versus 3.0 per cent; P = 0.494), sigmoid resection (3.8 versus 2.3 per cent; P = 0.323), readmission (17.6 versus 12.0 per cent; P = 0.148), adverse events (48.5 versus 54.5 per cent;

P = 0.221) and mortality (1.1 versus 0.4 per cent; P = 0.432). Hospital stay was significantly shorter in the observation group (2 versus 3 days; P = 0.006). Per-protocol analyses were concordant with the intention-to-treat analyses. Due to sample size, these results were interpretable for Hinchey 1a classification, but not for Hinchey 1b.

CONCLUSION:

Observational treatment without antibiotics did not prolong recovery and can be considered appropriate in patients with uncomplicated Hinchey class 1a diverticulitis. Registration number: NCT01111253 (<http://www.clinicaltrials.gov>).

B. Pending PURL Review Date: 10/4/2017

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

- A. Number of patients starting each arm of the study?
 - a. Observational – 262
 - b. Antibiotics - 266

- B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
 - a. Inclusion Criteria: L-sided mild acute diverticulitis; CT-confirmed diverticulitis (Hinchey stage 1a or 1b); informed consent
 - b. Exclusion Criteria: Previous imaging-confirmed diverticulitis; suspicion of colon cancer by imaging; inflammatory bowel disease; Hinchey's stage 2 or greater for diverticulitis; other disease with < 6 month life-expectancy; contraindication for using study antibiotics; pregnant or breastfeeding; ASA fitness grade > III; immunocompromised; clinical suspicion of sepsis; inability to read/fill in questionnaires; antibiotics use within 4 weeks of inclusion
 - c. Netherland patients, Average 57 years old, equal M/F, avg pain score of 6, most with Hinchey category 1a

- C. Intervention(s) being investigated?
 - a. Treatment with antibiotics (based on practice guidelines of the Dutch Antibiotic Policy Committee and the American Society of Colon and Rectal Surgeons (ASCRS)) vs. observation in setting of first episode of uncomplicated diverticulitis confirmed with CT

- D. Comparison treatment(s), placebo, or nothing?
 - a. nothing

- E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
 - a. 24 months (2/6 month f/u in clinic, phone call at 12 and 24 mos)

- F. What outcome measures are used? List all that assess effectiveness.
 - a. Primary: Time to recovery during 6 months post infection
 - b. Secondary: readmission rate, complication, ongoing diverticulitis or recurrence, sigmoid resection, mortality

- G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
- a. Hazard ratio for recovery: 0.91 (lower limit of 1-sided 95 percent CI 0.78; P = 0.151).
 - b. No significant differences between the observation and antibiotic treatment groups were found for secondary endpoints:
 - i. complicated diverticulitis (3.8 versus 2.6 per cent respectively; P = 0.377),
 - ii. ongoing diverticulitis (7.3 versus 4.1 per cent; P = 0.183),
 - iii. recurrent diverticulitis (3.4 versus 3.0 per cent; P = 0.494),
 - iv. sigmoid resection (3.8 versus 2.3 per cent; P = 0.323),
 - v. readmission (17.6 versus 12.0 per cent; P = 0.148),
 - vi. overall morbidity (48.5 versus 54.5 per cent; P = 0.221),
 - vii. antibiotic-related adverse events (0.4 versus 8.3 percent; P = 0.006), and
 - viii. mortality (1.1 versus 0.4 per cent; P = 0.432).
 - c. Hospital stay was significantly shorter in the observation group (2 versus 3 days; P = 0.006).
 - d. Within the Hinchey 1a subgroup, hazard ratio for recovery was 0.88 (lower limit of 1-sided 95 percent CI 0.75; P=0.081)
 - e. As this was a non-inferiority study, other statistics were not calculated
- H. What are the adverse effects of intervention compared with no intervention?
- a. Intervention: cost, adverse side effects, allergic reaction to antibiotics, microbial resistance
- 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:
- L. Subjects and investigators kept "blind" to comparison group allocation:
(select one) Well covered
Comments:
- M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments:
- 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: ASA fitness grade was higher in antibiotic group; possible bias as those patients

who received abx may have been sicker at baseline

- O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Well covered
Comments:
- P. Are patient oriented outcomes included? If yes, what are they? Yes, clinical time to recovery from diverticulitis
- Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
a. 2% in the observation group; 3.6% in antibiotic group;
b. Probably no bias due to intention to treat analysis
- R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
a. Yes
- S. If a multi-site study, are results comparable for all sites?
a. They mentioned in their limitations that there are some sites that had significantly more patients
- T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
a. Funding was by what appeared to be a national organization, not privatized drug company
- U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
a. Any patients with first-time diverticulitis
- V. In what care settings might the finding apply, or not apply?
a. Apply in primary care clinic, ER setting, inpatient medicine ward
- W. To which clinicians or policy makers might the finding be relevant?
a. All family physicians who treat patients and especially those who provide inpatient care; those who are concerned with antibiotic stewardship for policy-making

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 UpToDate® 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.} 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 date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed® excerpts

Antibiotics

Efficacy

- **antibiotic use may not improve outcomes in patients with uncomplicated left-sided diverticulitis ([level 2 \[mid-level\] evidence](#))**
 - based on Cochrane review of trials without blinding
 - systematic review of 3 randomized trials evaluating antibiotics in patients with uncomplicated left-sided diverticulitis
 - 1 trial compared antibiotics to control, and 2 trials assessed comparative efficacy
 - comparing IV antibiotics vs. IV fluids in 1 trial with 623 patients (summarized [below](#)), no significant differences for rates of
 - complications (abscess, perforation)
 - emergency surgery
 - recurrence
 - comparing duration of IV antibiotics, no differences in late complication (sigmoid inflammatory stricture) with [amoxicillin-clavulanate](#) for 24-48 hours vs. 7 days in 1 trial with 44 patients (summarized [below](#))
 - comparing different antibiotic regimens, no significant differences in rates of emergency surgery comparing [cefoxitin](#) vs. gentamicin plus clindamycin in 1 trial with 51 patients
 - Reference - [Cochrane Database Syst Rev 2012 Nov 14;\(11\):CD009092](#), commentary can be found in [Ann Emerg Med 2014 Jan;63\(1\):52](#)
 - **antibiotics may not reduce complications or recurrence of diverticulitis in patients with acute uncomplicated left-sided diverticulitis compared to observation alone ([level 2 \[mid-level\] evidence](#))**
 - based on randomized trial without blinding
 - 623 patients (mean age 57 years) with acute uncomplicated left-sided diverticulitis (computed tomography-verified) randomized to antibiotics vs. no antibiotics for ≥ 7 days and followed for 1 year
 - initial antibiotic treatment was IV (combination of second- or third-generation cephalosporin plus metronidazole, or carbapenem antibiotics, or [piperacillin-tazobactam](#)), and was followed by oral antibiotics (ciprofloxacin or [cefadroxil](#) with metronidazole)

- comparing antibiotics vs. no antibiotics
 - recurrent diverticulitis with readmission to hospital in 15.8 % vs. 16.2% (not significant)
 - complications in 1% vs. 1.9% (not significant)
 - sigmoid resections in 1.6% vs. 2.3% (not significant)
 - median hospital stay 3 days vs. 3 days (not significant)
 - Reference - [Br J Surg 2012 Apr;99\(4\):532](#)
- **insufficient evidence to support use of antibiotics for acute uncomplicated left-sided diverticulitis**
 - based on systematic review of low-to-moderate quality studies
 - systematic review of 2 randomized trials and 2 retrospective cohort studies evaluating antibiotics for acute uncomplicated left-sided diverticulitis with 508 patients
 - no randomized trials identified comparing antibiotics vs. observation in patients with uncomplicated diverticulitis
 - no significant differences between
 - oral vs. IV antibiotics in randomized trial with 79 patients
 - [cefoxitin](#) vs. gentamicin-clindamycin in randomized trial with 51 patients
 - antibiotics vs. observation in retrospective cohort study with 311 patients
 - antibiotics with vs. without anaerobe coverage in retrospective cohort study with 67 patients
 - Reference - [Br J Surg 2011 Jun;98\(6\):761](#)

B. DynaMed® citation/ Title. Author. In: DynaMed® [database online]. Available at: access date www.DynamicMedical.com Last Updated: . Accessed

C. Diverticulitis. Fedorowicz Z. In: DynaMed® [database online]. Available at: www.DynamicMedical.com Last Updated:21 Dec 2015 . Accessed: 03 Oct 2017.

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

Insufficient evidence to support use of antibiotics for acute uncomplicated left-sided diverticulitis.

E. UpToDate® excerpts

ARE ROUTINE ANTIBIOTICS NECESSARY FOR UNCOMPLICATED DIVERTICULITIS? —

Despite a lack of direct, high-quality evidence for their efficacy, antibiotics have been the unchallenged cornerstone of diverticulitis treatment. Some clinicians (primarily in Scandinavia), however, are treating acute uncomplicated diverticulitis without antibiotics based on results of two trials that demonstrated the safety and efficacy of that approach:

- A randomized trial performed in Sweden suggested that intravenous antibiotics may not be necessary for inpatients hospitalized with acute uncomplicated diverticulitis [42]. In this study, 623 patients with CT-confirmed left-sided diverticulitis were treated with or without antibiotics. Complication rates (1.9 versus 1.0 percent), hospital length of stay (three days in both groups), and recurrence rates (16 percent in both groups) were similar. Ten patients initially treated

without antibiotics subsequently received antibiotics due to increasing abdominal pain, fever, or increasing C-reactive protein (CRP).

- A second trial (DIABOLO) conducted in the Netherlands randomly assigned 528 patients with first-episode, CT-proven, left-sided, acute diverticulitis to observation or 10 days of antibiotics (Augmentin in most, [ciprofloxacin](#) plus [metronidazole](#) in rest) [43]. Patients with complicated diverticulitis, with the exception of a small (<5 cm) abscess, were excluded, as were those with one or more characteristics that would mandate inpatient treatment. The median times to recovery with (14 [interquartile range 6 to 35] days) or without antibiotics (12 [7 to 30] days) were similar. At six months, there were no significant differences in terms of complicated diverticulitis (3.8 percent observation versus 2.6 percent antibiotics), smoldering diverticulitis (7.3 versus 4.1 percent), recurrent diverticulitis (3.4 versus 3 percent), need for sigmoid resection (3.8 versus 2.3 percent), need for readmission (17.6 versus 12.0 percent), adverse events (48.5 versus 54.5 percent), and mortality (1.1 versus 0.4 percent).

A closer examination of the two trials, however, revealed that few, if any, patients met criteria for inpatient treatment as outlined above (see '[Criteria for inpatient treatment](#)' above). Thus, the results of these studies cannot necessarily be generalized to patients who are admitted for diverticulitis because of complications, severe disease (eg, immunocompromised patients, high fever, significant leukocytosis), or because they failed outpatient therapy. Neither are these results applicable to outpatient therapy of acute diverticulitis, as all participants in the Swedish study and 93 percent of patients in the Dutch study were admitted to the hospital and given intravenous fluids. It remains to be shown if outpatients, who lack access to intravenous hydration and on-demand clinical reassessment, can be safely treated without any antibiotics. According to a 2014 systematic review, routine antibiotics for uncomplicated diverticulitis were recommended by the American Society of Colon and Rectal Surgeons (ASCRS), the European Association for Endoscopic Surgery (EAES), and the World Society for Emergency Surgery (WSES), but not by the Association of Surgeons of the Netherlands (ASN) or the Danish Surgical Society (DSS) [25]. The American Gastroenterological Association (AGA) 2015 guidelines recommend selective, rather than routine, use of antibiotics for patients with acute uncomplicated diverticulitis [44,45].

F. UpToDate® citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author.

Acute colonic diverticulitis: Medical management. Pemberton J. In: UpToDate® [database online]. Available at: <http://www.uptodate.com>. Last updated: 18 July 2017. Accessed 03 Oct 2017.

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

UpToDate authors reviewed this study as well, and since patients were admitted to the hospital and received IVF despite not meeting inpatient criteria, they are concerned about how this study would apply to patients if they did not receive IVF. It did mention that the AGA recommend selective use of antibiotics for patients with acute uncomplicated diverticulitis.

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

See attachments for full articles, bottom line cited below

I. Citations for other excerpts

Stollman N, Smalley W, Hirano I, AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guidelines on the Management of Acute Diverticulitis. *Gastroenterology*. 2015 Dec;149(7):1944-9.

Shah SD, Cifu AS. Management of Acute Diverticulitis. *JAMA*. 2017 Jul 18;318(3):291-292.

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

The AGA suggests that antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis. (Conditional recommendation, low quality of evidence).

Overuse of antibiotics can cause significant harm in the form of adverse reactions and increased antibiotic resistance. The potential harms of withholding antibiotics for treatment of diverticulitis may include higher rates of complications and recurrences, although the systematic review reported a very low number of complications and found that treatment with broad-spectrum antibiotics did not reduce duration of symptoms in AUD.

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? 2
- B. If **A** was coded 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?
- 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?
2
- D. If **C** was coded 4, 5, 6, or 7, 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?

1 (definitely a change from current practice)

F. If **E** 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.

New practice recommendation: Considering observation instead of treatment of patients with antibiotics if they have CT-confirmed, first-time, uncomplicated, mild diverticulitis

Target population: patients who present with first-time left-sided uncomplicated mild diverticulitis

Expected benefit: decreased antibiotic usage associated with decreased antibiotic resistance and decreased adverse side-effects from antibiotic, decreased cost for patients for both hospitalization and medication cost.

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? 2

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

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? 1 (definitely could be immediately applied)

J. If **I** was coded 4, 5, 6, or 7, please explain why.

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?

1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL?

1 (definitely a pending PURL)

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.

In the age of microbial resistance and antibiotic stewardship, this change to practice not only could assist in decreasing antimicrobial resistance but also decrease hospital admission rates; while most of these patients may be evaluated in the ED, the suspicion for clinical mild diverticulitis would indicate that FM docs could release patients without further imaging or with outpatient imaging.