**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]**

1. Citiation: 1: Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, Wootton M,
Hood K, Phillips R, Melbye H, Llor C, Cals JWL, Naik G, Kirby N, Gal M, Riga E,
Francis NA. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD
Exacerbations. N Engl J Med. 2019 Jul 11;381(2):111-120. doi:
10.1056/NEJMoa1803185. PubMed PMID: 31291514.
2. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/31291514
3. First date published study available to readers: 7/11/2019
4. PubMed ID: 31291514
5. Nominated By: Anne Mounsey
6. Institutional Affiliation of Nominator: NC - UNC
7. Date Nominated: 7/11/2019
8. Identified Through: NEJM
9. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
10. Nomination Decision Date: 7/17/2019
11. Potential PURL Review Form (PPRF) Type: RCT
12. Assigned Potential PURL Reviewer: Corey Lyon
13. Reviewer Affiliation: CO – University of Colorado
14. Abstract: **BACKGROUND:
Point-of-care testing of C-reactive protein (CRP) may be a way to reduce unnecessary use of antibiotics without harming patients who have acute exacerbations of chronic obstructive pulmonary disease (COPD).

METHODS:
We performed a multicenter, open-label, randomized, controlled trial involving patients with a diagnosis of COPD in their primary care clinical record who consulted a clinician at 1 of 86 general medical practices in England and Wales for an acute exacerbation of COPD. The patients were assigned to receive usual care guided by CRP point-of-care testing (CRP-guided group) or usual care alone (usual-care group). The primary outcomes were patient-reported use of antibiotics for acute exacerbations of COPD within 4 weeks after randomization (to show superiority) and COPD-related health status at 2 weeks after randomization, as measured by the Clinical COPD Questionnaire, a 10-item scale with scores ranging from 0 (very good COPD health status) to 6 (extremely poor COPD health status) (to show noninferiority).

RESULTS:
A total of 653 patients underwent randomization. Fewer patients in the CRP-guided group reported antibiotic use than in the usual-care group (57.0% vs. 77.4%; adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.20 to 0.47). The adjusted mean difference in the total score on the Clinical COPD Questionnaire at 2 weeks was -0.19 points (two-sided 90% CI, -0.33 to -0.05) in favor of the CRP-guided group. The antibiotic prescribing decisions made by clinicians at the initial consultation were ascertained for all but 1 patient, and antibiotic prescriptions issued over the first 4 weeks of follow-up were ascertained for 96.9% of the patients. A lower percentage of patients in the CRP-guided group than in the usual-care group received an antibiotic prescription at the initial consultation (47.7% vs. 69.7%, for a difference of 22.0 percentage points; adjusted odds ratio, 0.31; 95% CI, 0.21 to 0.45) and during the first 4 weeks of follow-up (59.1% vs. 79.7%, for a difference of 20.6 percentage points; adjusted odds ratio, 0.30; 95% CI, 0.20 to 0.46). Two patients in the usual-care group died within 4 weeks after randomization from causes considered by the investigators to be unrelated to trial participation.

CONCLUSIONS:
CRP-guided prescribing of antibiotics for exacerbations of COPD in primary care clinics resulted in a lower percentage of patients who reported antibiotic use and who received antibiotic prescriptions from clinicians, with no evidence of harm. (Funded by the National Institute for Health Research Health Technology Assessment Program; PACE Current Controlled Trials number, ISRCTN24346473.).**
15. Pending PURL Review Date**:** 3/12/2020

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

1. Number of patients starting each arm of the study?

325 CRP guided group, 324 assigned to usual care

1. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)

Patients 40 or older with COPD diagnosis in their primary care clinical record and presenting with acute exacerbation of COPD based on the Anthonisen criteria in 86 primary care practices located in England or Wales. Patient could not be in the PACE trial or currently/recently on antibiotics (supplement 1 has all the inclusion/exclusion criteria). Recruited between Jan 2015- Feb 2017.

Anthonisen Criteria: Worsening dyspnea, increased sputum purulence or increased in sputum volume. Severity: Severe - Type 1: all 3 element, Moderate Type 2: 2 element, Type III Mild – 1 element plus URI in past 5 days, fever of unknown cause, increased wheezing/cough, increased respiratory rate (+20%) or heart rate

1. Intervention(s) being investigated?

Antibiotic prescribing at first consultation and in the first 4 weeks, Score on the Clinical COPD Questionaire (10 item scale with score going from 0-6 with 6 being very poor) at 2 weeks

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

Usual care

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

1 week and 2 weeks over the phone, 4 weeks in person, 6 months via a questionnaire

“Secondary outcomes included the prevalence of potentially pathogenic and resistant pathogens in sputum and commensal organisms in the throat; other assessments of COPD-related health status, as measured by the Clinical COPD Questionnaire; antibiotic use for any cause during the first 4 weeks of follow-up; antibiotic prescribing during the first 4 weeks of follow-up; use of other treatments for COPD; adverse effects of antibiotics; health care utilization; health utility, as measured by the EQ-5D-5L; general health status, as measured by the EQ-5D visual analogue scale (scores range from 0 to 100, with higher scores indicating better health status), and disease-specific health related quality of life, as measured by the CRQ-SAS across four domains (dyspnea, fatigue, emotional functioning, and mastery), with scores ranging from 1 to 7 and higher scores indicating better patient outcomes on the respective domain.”

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

Between group difference in antibiotic prescribing at 4 weeks of follow up from an acute COPD exacerbation.

Total score on the Clinical COPD questionnaire

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

Predictive probability of antibiotic use for acute exacerbation of COPD during the first 4 weeks according to the number of Anthonisen criteria present.
Fewer patients in the CRP-guided group reported antibiotic use than in the usual care group (150 of 263 patients [57.0%] vs. 212 of 274 patients [77.4%]; adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.20 to 0.47).

The adjusted mean difference in the total score on the Clinical COPD Questionnaire at 2 weeks was −0.19 points (two-sided 90% CI, −0.33 to −0.05) in favor of the CRP-guided group. The two-sided 90% confidence interval for the complier average causal effect analysis ranged from −0.34 to −0.07

**Secondary outcome**

A lower percentage of patients in the CRP-guided group than in the usual-care group received antibiotic prescriptions at the initial consultation (47.7% vs. 69.7%, for a difference of 22.0 percentage points; adjusted odds ratio, 0.31; 95% CI, 0.21 to 0.45)

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

None that I found

1. The study addresses an appropriate and clearly focused question.

(select one) Well covered

Comments:

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

Comments:

1. Concealed allocation to comparison groups:
(select one) Adequately addressed

Comments: Did not do. Could have done sham testing of CRP and patients could be blind if their doctor had that result. But that's about it.

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

Comments: No but the data people were

1. Comparison groups are similar at the start of the trial:
(select one) Adequately addressed

Comments:

1. 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 significant differences
2. Were all relevant outcomes measured in a standardized, valid, and reliable way?

(select one) Well covered
Comments:

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

Yes, in addition to antibiotics, they looked at hospitalizations (~9% in both groups), diagnosis of pneumonia 3% (intervention) vs 4% (usual care group).

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

At 4 weeks 17.3% dropped out the antibiotic use outcome and 13.3% with the Clinical COPD questionnaire. The authors powered their student to 20% drop out. BIAS OF RESULTS: Potentially, but the drop out was pretty even between the groups.

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

Yes, they also did modified intention to treat where they looked at just complete data after randomization.

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

Unclear, but probably

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

Unlikely

Funded by the National Institute for Health Research Health Technology Assessment Program; PACE Current Controlled Trials number, ISRCTN24346473

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

Patient with COPD. Most patients were not GOLD stage IV, majority stage 2.

1. In what care settings might the finding apply, or not apply?

outpatient

1. To which clinicians or policy makers might the finding be relevant?

Family med and IM who practice outpatient medicine

**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}

1. DynaMed excerpts

Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations[1](https://www-dynamed-com.proxy.hsl.ucdenver.edu/condition/acute-exacerbation-of-copd#GUID-29957612-D20E-49CE-8133-D870F27BB4FA__GENREF5941)

* antibiotics, when indicated, may shorten recovery time, and reduce risk of relapse, time to recovery, and duration of hospitalization ([GOLD Evidence B](https://www-dynamed-com.proxy.hsl.ucdenver.edu/condition/acute-exacerbation-of-copd#GUID-A05F84DA-3D18-4AE7-B766-9B1272F5B916__SNIPPET-POINTER_632077404))
* consider prescribing antibiotics to patients with exacerbations who
	+ have all 3 cardinal symptoms (increased dyspnea, increased sputum volume, and increased sputum purulence)
	+ have 2 cardinal symptoms if increased purulence of sputum is one of the symptoms
	+ require mechanical ventilation

Evidence B - based on randomized controlled trials with important limitations or limited body of evidence

Use antibiotics in selected patients.

* Give [antibiotics](https://www-dynamed-com.proxy.hsl.ucdenver.edu/condition/acute-exacerbation-of-copd#ANTIBIOTICS) to patients who are in intensive care or hospitalized with severe COPD exacerbations where they reduce treatment failure and mortality.
* Give antibiotics for 5-7 days in COPD patients with purulent sputum and 1 or more of the following symptoms: increased dyspnea, sputum production.
* Consider giving antibiotics to COPD outpatients with mild-to-modertate exacerbations to reduce treatment failures.
* Select antibiotics based on local bacterial resistance pattern; initial treatment typically an aminopenicillin with or without clavulanic acid, a macrolide, or a tetracycline.
1. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at:
access date [www.DynamicMedical.com](http://www.DynamicMedical.com) Last Updated: . Accessed

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T116563, Acute Exacerbation of COPD; [updated 2018 Dec 04, cited **2020 March 19**]. Available from https://www-dynamed-com.proxy.hsl.ucdenver.edu/topics/dmp~AN~T116563. Registration and login required

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

The addition of C-reactive protein (CRP) testing to usual care to guide prescription of antibiotics reduces antibiotic use without impairing health status in patients with acute exacerbation of COPD. DynaMed Level**1 (Likely Reliable) References this study in this recommendation.**

1. UpToDate excerpts

The GOLD guidelines recommend antibiotics for moderately or severely ill patients with COPD exacerbations who have increased cough and sputum purulence. We vary slightly from the GOLD guidelines in our clinical practices

●We recommend antibiotics in outpatients with a moderate or severe exacerbation of COPD, which is defined as having at least two of these three symptoms – increased dyspnea, increased sputum volume, or increased sputum purulence.

●We do **not** initiate antibiotic therapy in patients whose exacerbation is mild, which we define as having only one of these three symptoms and not requiring hospitalization.

(article doesn't mention anything about CRP)

1. 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

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. http://www.goldcopd.org (Accessed on January 29, 2020).

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

If moderate or severe exacerbation based on dyspnea, sputum volume or sputum prurulence, give antibiotics.

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

National Institute for Health and Clinical Excellence (NICE) guideline on management of COPD in adults in primary and secondary care can be found at [NICE 2018 Dec:NG115](https://www.nice.org.uk/guidance/ng115)

American College of Chest Physicians/Canadian Thoracic Society (ACCP/CTS) guideline on prevention of acute exacerbations of chronic obstructive pulmonary disease can be found in [Chest 2015 Apr 1;147(4):894](http://www-ncbi-nlm-nih-gov.proxy.hsl.ucdenver.edu/pubmed/25321320?dopt=Abstract)

(nothing about CRP mentioned)

Global Initiative for Chronic Obstructive Lung Disease (GOLD) global strategy on diagnosis, management, and prevention of COPD can be found at [GOLD 2020](https://goldcopd.org/gold-reports/)

European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations

* consider antibiotics in ambulatory patients with COPD exacerbations ([ERS/ATS Conditional recommendation, Moderate-quality evidence](https://www-dynamed-com.proxy.hsl.ucdenver.edu/condition/acute-exacerbation-of-copd#GUID-A05F84DA-3D18-4AE7-B766-9B1272F5B916__ERSATSGRADE))

(dynamed)

1. Citations for other excerpts
2. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Moderate to severe, give antibiotics, not for mild.

**SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer as needed]**

1. **Validity**: Are the findings scientifically valid? Yes
2. 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?
3. **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

1. If **C** was coded “Other, explain or No”, please provide an explanation.
2. **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

However, not a lot of clinics can do CRP poc at this time. In the study only a couple of clinics had this capability

1. 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 clinics with the ability to do poc CRP testing, CRP should be used to help determine the appropriateness of antibiotic use in patients with a COPD exacerbation.

1. **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
2. Please explain your answer to **G**.

We don't do this now and though POC CRP might be cost prohibitive, a lot of primary care providers can get accurate CRP results in just a few hours.

1. **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? Yes

CRP machines and the test are not cheap. At least in 2015 and article concluded the cost per patient of a CRP test outweighed the cost saving or the reduction in infections in the long term. That didn't even include the cost of having machine.

Hunter, Rachael. "Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England." *Advances in therapy* 32.1 (2015): 69-85.

1. If **I** was coded “Other, explain or No”, please explain why.
2. **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

Major harm is cost

1. If **K** was coded “Other, explain or No”, please explain why.
2. In your opinion, is this a pending PURL? Yes
3. Valid: Strong internal scientific validity; the findings appear to be true.
4. Relevant: Relevant to the practice of family medicine.
5. 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.
6. Applicability in medical setting.
7. Immediacy of implementation
8. Comments on your response for question M.

Biggest barrier is the cost and availability of poct of CRPs. However, a lot of people have COPD so a new cost effectiveness analysis may be warranted given the last one was published 3 years ago.