

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 11, 2019

VOL. 381 NO. 2

## C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., KerENZA Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

### 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.)

From the Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford (C.C.B., E.R.), the Centre for Trials Research (D.G., J.B., R.L., E.T.-J., K.H., N.K.), the Division of Population Medicine (R.P., G.N., N.A.F.), and Wales Centre for Primary and Emergency Research, School of Medicine (M.G.), Cardiff University, the Specialist Antimicrobial Chemotherapy Unit, Public Health Wales, University Hospital of Wales (M.W.), Cardiff, and the School of Population Health and Environment Science, King's College, London (P.W.) — all in the United Kingdom; the General Practice Research Unit, Department of Community Medicine, University of Tromsø—the Arctic University of Norway, Tromsø, Norway (H.M.); the University Institute in Primary Care Research Jordi Gol, Via Roma Health Center, Barcelona (C.L.); and the Department of Family Medicine, Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands (J.W.L.C.). Address reprint requests to Dr. Butler at the Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care Bldg., Radcliffe Observatory Quarter, Woodstock Rd., Oxford OX2 6GG, United Kingdom, or at christopher.butler@phc.ox.ac.uk.

N Engl J Med 2019;381:111-20.

DOI: 10.1056/NEJMoa1803185

Copyright © 2019 Massachusetts Medical Society.

PRIMARY CARE PROVIDERS ARE RESPONSIBLE for the majority of antibiotic prescriptions, and the highest overall number of such prescriptions are issued by family physicians.<sup>1</sup> There is reason to believe that many of these prescriptions could be avoided.<sup>2,3</sup> Unwarranted use of antibiotics drives antimicrobial resistance, wastes resources, may cause adverse effects, negatively affects the microbiome of patients, and distracts from potentially more effective interventions.<sup>4-10</sup> Point-of-care tests for acute infections are being promoted by government organizations, the industry, and clinical guidelines to better target antibiotic prescribing, help contain antimicrobial resistance, and improve patient outcomes.<sup>11</sup> However, most evaluations of point-of-care tests for acute infections have solely examined analytic performance; only a few trials have evaluated the effectiveness of such tests in improving outcomes in the patients for whom the tests are intended to be used.<sup>12-14</sup>

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death in the United States in 2014,<sup>15</sup> and 6.4% of Americans reported receiving a diagnosis of the condition.<sup>16</sup> About 2% of the adult population in the United Kingdom have a diagnosis of COPD in their primary care medical record.<sup>17,18</sup> Each year, approximately half the patients living with COPD have one or more acute exacerbations of the disease that leads to treatment with oral glucocorticoids, antibiotics, or both or hospitalization, and a quarter have two or more acute exacerbations per year.<sup>19,20</sup> More than 80% of these patients receive antibiotic prescriptions in the United States<sup>21,22</sup> and in Europe.<sup>23</sup> Although many patients who have acute exacerbations of COPD are helped by these treatments, others are not.<sup>24-26</sup>

Noninfectious factors were thought to cause approximately 20% of acute exacerbations of COPD in a hospital study.<sup>27</sup> The guidelines of the Global Initiative for Chronic Obstructive Lung Disease recommend the use of antibiotics in moderately or severely ill patients with acute exacerbations of COPD who have increased cough and sputum purulence.<sup>28</sup> Recommendations for antibiotic prescribing in primary care practice are generally based on clinical features alone (e.g., the Anthonisen criteria,<sup>29</sup> which include increased dyspnea, increased sputum volume, and increased sputum purulence), but these features are subjective and insufficiently accurate in predicting

which patients can be treated safely without antibiotics.<sup>24</sup>

C-reactive protein (CRP), an acute-phase protein that can be measured accurately within minutes at the point of care, is a biomarker for assessing acute exacerbations of COPD.<sup>30,31</sup> A randomized, controlled trial involving patients with acute exacerbations of COPD recruited from primary care practices showed little difference in the rate of clinical cure with either antibiotics or placebo among those who had a CRP level of less than 40 mg per liter.<sup>32</sup> The results of point-of-care CRP tests may inform prescribing decisions for acute exacerbations of COPD, but data from pragmatic, randomized, controlled trials regarding the clinical effectiveness of such tests are lacking. We aimed to determine whether a CRP point-of-care test used in the assessment of acute exacerbations of COPD in primary care can safely reduce the use of antibiotics among such patients.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

This multicenter, open-label, randomized, controlled trial was conducted from January 2015 through September 2017 in accordance with a previously published protocol,<sup>33</sup> which is available with the full text of this article at NEJM.org. The trial involved patients recruited from 86 general medical practices in the United Kingdom. The Research Ethics Committee for Wales, recognized by the United Kingdom Ethics Committee Authority, approved the trial protocol on September 15, 2014, as well as the inclusion of all the recruitment sites in the trial. Health boards and clinical commissioning groups of the National Health Service gave research and development approval to participating sites. Written informed consent was obtained from all the patients by the responsible primary care physician or an appropriately trained staff member. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. An independent trial steering committee and a data monitoring and ethics committee provided trial oversight.

Afinion desktop devices for CRP point-of-care testing (Alere, now Abbott) were loaned by the company. The staff members at the general medical practices were trained in the use, care, and calibration of the devices by representatives of Alere (at no cost to the trial or to the practices)

or by members of the trial team. The company had no role in the design of the trial; in the accrual, analysis, or interpretation of the data; or in the preparation of the manuscript. Two participating practices used their own CRP test device.

#### PATIENTS

Patients who were 40 years of age or older were eligible for inclusion if they had a diagnosis of COPD in their primary care clinical record and were presenting with an acute exacerbation of COPD with at least one of the Anthonisen criteria. A full list of inclusion and exclusion criteria is provided in Section 1 in the Supplementary Appendix, available at NEJM.org. The patients were randomly assigned in a 1:1 ratio to receive usual care guided by CRP point-of-care testing (CRP-guided group) or usual care alone (usual-care group); the number of Anthonisen criteria present (one to three) was used as a minimization variable, with a random element set at 80%.

#### TRIAL PROCEDURES

Before randomization, we collected information on the number of days that symptoms of acute exacerbation of COPD were present, a patient's medical history, examination findings from clinicians, a sputum sample (if obtainable), a throat swab, patient responses to the self-administered Clinical COPD Questionnaire,<sup>34</sup> and patients' responses to the European Quality of Life-5 Dimensions 5-Level questionnaire (EQ-5D-5L; scores range from -0.28 to 1.00, with higher scores indicating a better state of health).<sup>35</sup> Clinicians recorded their antibiotic prescribing and other management decisions after randomization on a case report form.

The patients were followed up by means of telephone calls at weeks 1 and 2 and by face-to-face consultation at week 4. At 6 months, a self-administered, standardized version of the Chronic Respiratory Disease Questionnaire (CRQ-SAS)<sup>36</sup> and an EQ-5D-5L were mailed to the patients, and relevant data were collected from the primary care electronic medical records. Additional details regarding trial procedures are provided in Section 2 in the Supplementary Appendix.

#### TRIAL INTERVENTIONS

Clinicians were asked to perform a CRP point-of-care test as part of their assessment of patients in the CRP-guided group at the initial consultation and at any further consultations for acute exacer-

bations of COPD over the next 4 weeks; those in the usual-care group did not undergo CRP testing. All the participating sites were provided with a summary of guidance from the National Institute for Health and Care Excellence and the Global Initiative for Chronic Obstructive Lung Disease. Clinicians were provided with guidance on the interpretation of CRP test results emphasizing that decisions about antibiotic prescribing should be based on a comprehensive assessment of likely risks and benefits, given a patient's underlying health status and clinical features. The guidance noted that for patients with a CRP level lower than 20 mg per liter, antibiotics are unlikely to be beneficial and usually should not be prescribed; for those with a CRP level from 20 to 40 mg per liter, antibiotics may be beneficial, mainly if purulent sputum is present; and for those with a CRP level higher than 40 mg per liter, antibiotics are likely to be beneficial.<sup>24</sup>

#### OUTCOME MEASURES

We used two primary outcomes because any reduction in the use of antibiotics should be considered alongside any negative effect on the well-being of a patient.<sup>37</sup> The first primary outcome was patient-reported antibiotic use for an acute exacerbation of COPD within 4 weeks after randomization. The second primary outcome was COPD-related health status, as measured by the Clinical COPD Questionnaire at 2 weeks after randomization. The Clinical COPD Questionnaire is a 10-item scale with a score ranging from 0 (very good) to 6 (extremely poor). The minimal clinically important difference is 0.4.<sup>38</sup> Since we would need to show both a reduction in antibiotic use and no worsening of COPD-related health status in order for us to consider the CRP point-of-care test to be effective, we designed this study to answer both questions.

Key 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.

#### STATISTICAL ANALYSIS

Allowing for a loss to follow-up of 20%, we estimated that a sample size of 650 patients would provide 81 to 90% overall power to detect a between-group difference of 15 percentage points in the percentage of patients who used antibiotics for acute exacerbations of COPD during 4 weeks of follow-up, on the basis of an estimated 70% of patients with antibiotic use for acute exacerbations of COPD during the first 4 weeks of follow-up and to show that usual care with CRP-guided management did not lead to worse COPD-related health status (i.e., was noninferior) than usual care alone. Given the noninferiority research question, we were interested in the upper limit of the confidence interval of the adjusted mean difference. Therefore, our sample-size calculation was based on a one-sided 95% confidence interval, which is equivalent to a two-sided 90% confidence interval. Additional details on the sample size justification are provided in Section 3 in the Supplementary Appendix.

The main analysis of clinical effectiveness was performed in a modified intention-to-treat population, which included all the patients who had undergone randomization and had available outcome data, regardless of protocol deviations or the intervention they received. Analyses of the primary outcomes were also performed in the full intention-to-treat population, which included all the patients who had undergone randomization, with the use of multiple imputation to account for missing observations. Additional details regarding the full intention-to-treat analyses and other prespecified analyses are provided in Sections 6 and 7 in the Supplementary Appendix. The primary analysis of antibiotic use involved a two-level logistic-regression model, with the potential correlated nature of the data from the patients within practices taken into account. The model was adjusted for the number of Anthonisen criteria present before randomization. The primary analysis of the total score on the Clinical COPD Questionnaire involved a two-level analysis of covariance, with patients nested within practices and adjustment

for both the number of Anthonisen criteria present and total score on the Clinical COPD Questionnaire at baseline. A complier average causal effect (an estimate of the effect of receiving the assigned intervention that conforms with the randomization scheme)<sup>39</sup> was estimated for the primary outcome of total score on the Clinical COPD Questionnaire. Model estimates for the analysis of the total score on the Clinical COPD Questionnaire are presented as adjusted mean differences with two-sided 90% confidence intervals. In both the modified intention-to-treat and complier average causal effect analyses, noninferiority was concluded on the basis of the upper limit of the confidence interval excluding 0.3, which is slightly smaller (more conservative) than the previously published minimal clinically important difference of 0.4.<sup>40</sup> Secondary outcomes were analyzed similarly; however, because the estimated confidence intervals for our secondary outcomes have not been adjusted for multiple testing, inferences drawn from these may not be reproducible. Full details of the subgroup analyses are provided in Section 9 in the Supplementary Appendix.

## RESULTS

#### PATIENTS

Between January 2015 and February 2017, a total of 653 patients from 86 general medical practices underwent randomization (Fig. 1). Three patients withdrew consent to use their data, and 1 underwent randomization in error, which left 325 patients in the CRP-guided group and 324 in the usual-care group. The trial groups were well matched at baseline (Table 1). The microbiologic features of the sputum samples obtained at baseline are provided in Figure S1 and Table S1 in the Supplementary Appendix.

#### INTERVENTION

A total of 317 of the 325 patients (97.5%) assigned to the CRP-guided group received a CRP test during the recruitment consultation, and the median CRP value was 6 mg per liter (interquartile range, 5.0 to 18.5). Among these 317 patients, 241 (76.0%) had CRP values lower than 20 mg per liter; 38 (12.0%) had CRP values between 20 and 40 mg per liter, and 38 (12.0%) had CRP values higher than 40 mg per liter. A total of 3 of the 324 patients (0.9%) assigned to the usual-care group received a CRP test during the first 4 weeks of follow-up.

**PRIMARY OUTCOMES**

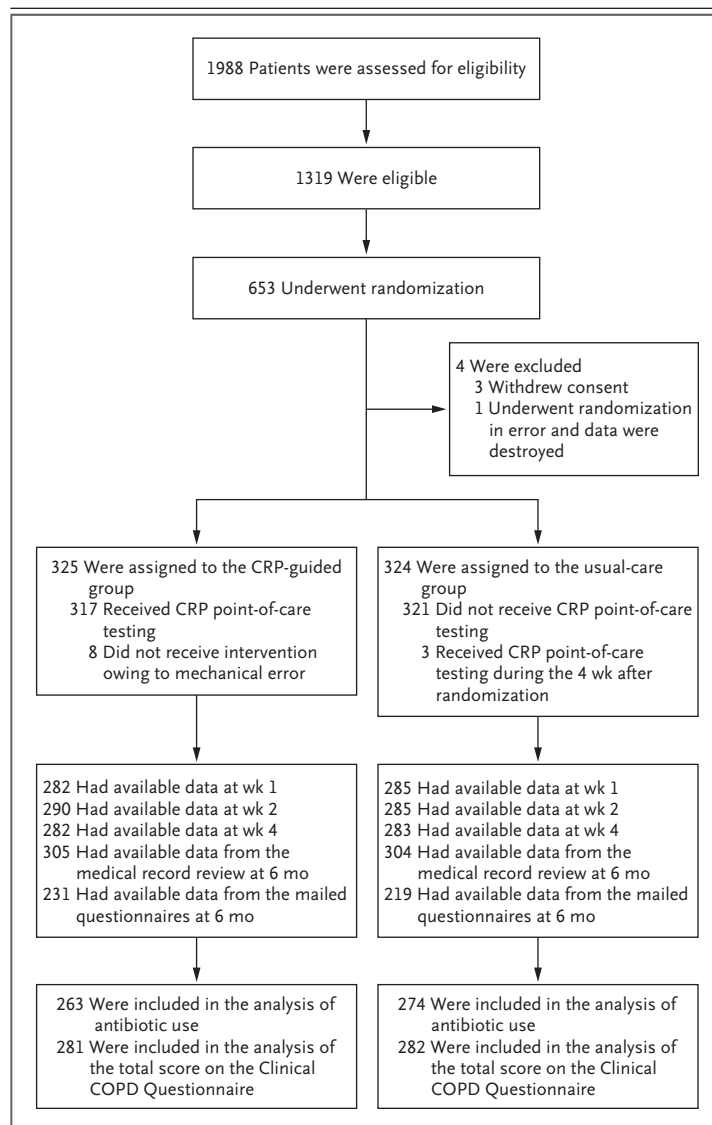
Of the 649 patients who were randomly assigned to a trial group, 537 (82.7%) contributed to the primary-outcome analysis of antibiotic use and 563 (86.7%) contributed to the primary-outcome analysis of the total score on the Clinical COPD Questionnaire. Fewer patients in the CRP-guided group reported 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  $-0.07$ . The upper limit of the confidence interval for both analyses did not contain the prespecified noninferiority margin of 0.3. Our findings were consistent in prespecified sensitivity analyses (Tables S2 through S9 and Fig. S2 in the Supplementary Appendix).

Differences in reported antibiotic use were only observed for the patients who had at last two of the Anthonisen criteria (Fig. 2). Other differential effects of the assigned interventions are described in Section 9 in the Supplementary Appendix.

**SECONDARY OUTCOMES**

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 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). A total of 158 antibiotic prescriptions were issued to the patients in the CRP-guided group, and 234 were issued to those in the usual-care group; 12 patients (3 in the CRP-guided group and 9 in the usual-care group) were issued 2 prescriptions. The majority of prescriptions were for 7 days (138 patients [87.3%] in the CRP-guided group and 185 [79.1%] in the usual-care group). The prescribed antibiotics are listed in Table S10 in the Supplementary Appendix.

At the initial consultation, antibiotics were prescribed in the CRP-guided group for 79 of 241



**Figure 1. Screening, Randomization, and Follow-up.**

The number of patients who were assessed for eligibility was estimated from screening log data obtained from 9 of 86 general medical practices that returned reliable screening log data (i.e., data that were regularly returned and consistently included details of the number of patients who were approached in addition to the number of those who were recruited). From these 9 practices, 208 patients were approached (a mean number of 23 patients approached per practice), which resulted in 1988 patients potentially assessed for eligibility ( $208/9 \times 86$ ); 138 were eligible (66.3%), which resulted in 1319 patients potentially eligible ( $138/9 \times 86$ ); and 109 (79.0%) were recruited. The main reasons for ineligibility were recent or current use of antibiotics (28 of 70 patients) or previous participation in the PACE study<sup>33</sup> (13 of 70 patients). The main reasons for eligible patients not being recruited were patient's decision to decline (18 of 29 patients) or lack of clinical time to recruit (9 of 29 patients). The recruited patients were randomly assigned to receive usual care guided by C-reactive protein (CRP) point-of-care testing (CRP-guided group) or usual care alone (usual-care group).

<b>Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*</b>			
<b>Characteristic</b>	<b>CRP-Guided Group (N=325)</b>	<b>Usual-Care Group (N=324)</b>	<b>All Patients (N=649)</b>
<b>Age — yr</b>			
Mean	67.8±9.53	68.3±9.31	68.1±9.42
Range	41–90	40–92	40–92
<b>Sex — no. (%)</b>			
Male	162 (49.8)	173 (53.4)	335 (51.6)
Female	163 (50.2)	151 (46.6)	314 (48.4)
<b>No. of days with symptoms before consultation</b>			
Mean	6.8±5.2	7.1±5.06	6.9±5.13
Range	1–28	1–21	1–28
<b>Total score on the Clinical COPD Questionnaire†</b>			
Mean	3.2±1.16	3.3±1.11	3.3±1.14
Range	0.3–6.0	0.7–5.8	0.3–6.0
<b>FEV<sub>1</sub>:FVC ratio‡</b>			
Mean	0.6±0.12	0.6±0.13	0.6±0.13
Range	0.30–0.85	0.23–0.85	0.23–0.85
<b>Percentage of predicted FEV<sub>1</sub>§</b>			
Mean	59.2±19.33	60.4±20.73	59.8±20.04
Range	9.9–125.4	11.4–150.4	9.9–150.4
<b>Coexisting illness — no./total no. (%)</b>			
Heart failure	16/325 (4.9)	15/324 (4.6)	31/649 (4.8)
Coronary heart disease	55/325 (16.9)	59/324 (18.2)	114/649 (17.6)
Diabetes	50/325 (15.4)	54/324 (16.7)	104/649 (16.0)
Chronic kidney disease	27/325 (8.3)	32/324 (9.9)	59/649 (9.1)
Hypertension	124/325 (38.2)	143/324 (44.1)	267/649 (41.1)
Other chronic disease	85/298 (28.5)	70/291 (24.1)	155/589 (26.3)
<b>Smoking status — no./total no. (%)</b>			
Nonsmoker	20/281 (7.1)	22/279 (7.9)	42/560 (7.5)
Former smoker	165/281 (58.7)	163/279 (58.4)	328/560 (58.6)
Current smoker	96/281 (34.2)	94/279 (33.7)	190/560 (33.9)
<b>Severity of COPD — no./total no. (%)¶</b>			
Mild, GOLD stage I	18/172 (10.5)	20/180 (11.1)	38/352 (10.8)
Moderate, GOLD stage II	93/172 (54.1)	100/180 (55.6)	193/352 (54.8)
Severe, GOLD stage III	52/172 (30.2)	47/180 (26.1)	99/352 (28.1)
Very severe, GOLD stage IV	9/172 (5.2)	13/180 (7.2)	22/352 (6.2)
<b>No. of Anthonisen criteria present — no. (%)  </b>			
1	76 (23.4)	81 (25.0)	157 (24.2)
2	100 (30.8)	98 (30.2)	198 (30.5)
3	149 (45.8)	145 (44.8)	294 (45.3)
<b>Auscultation findings — no./total no. (%)</b>			
Crackles	158/325 (48.6)	162/324 (50.0)	320/649 (49.3)
Wheeze	171/325 (52.6)	167/324 (51.5)	338/649 (52.1)
Diminished vesicular sounds	71/325 (21.8)	82/322 (25.5)	153/647 (23.6)
Evidence of consolidation	11/324 (3.4)	8/323 (2.5)	19/647 (2.9)

Table 1. (Continued.)

Characteristic	CRP-Guided Group (N=325)	Usual-Care Group (N=324)	All Patients (N=649)
Previous treatment — no./total no. (%)			
Received a prescription for oral antibiotics in the past 12 mo	205/304 (67.4)	198/302 (65.6)	403/606 (66.5)
Use of regular inhalers before recruitment	289/304 (95.1)	290/302 (96.0)	579/606 (95.5)

\* Plus-minus values are means  $\pm$ SD. The recruited patients were randomly assigned to receive usual care guided by C-reactive protein (CRP) point-of-care testing (CRP-guided group) or usual care alone (usual-care group). There were no significant between-group differences in the demographic and clinical characteristics of the patients at baseline. Percentage may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease.

† Data on total score on the Clinical COPD Questionnaire were missing for 11 patients in the CRP-guided group and for 8 patients in the usual-care group. The Clinical COPD Questionnaire is a 10-item scale with scores ranging from 0 (very good COPD-related health status) to 6 (extremely poor COPD-related health status).

‡ Data on the ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC) were missing for 120 patients in the CRP-guided group and for 100 patients in the usual-care group.

§ Data on the percentage of predicted FEV<sub>1</sub> were missing for 47 patients in the CRP-guided group and for 42 patients in the usual-care group.

¶ Severity of COPD was determined according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>28</sup>

|| The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence.<sup>29</sup>

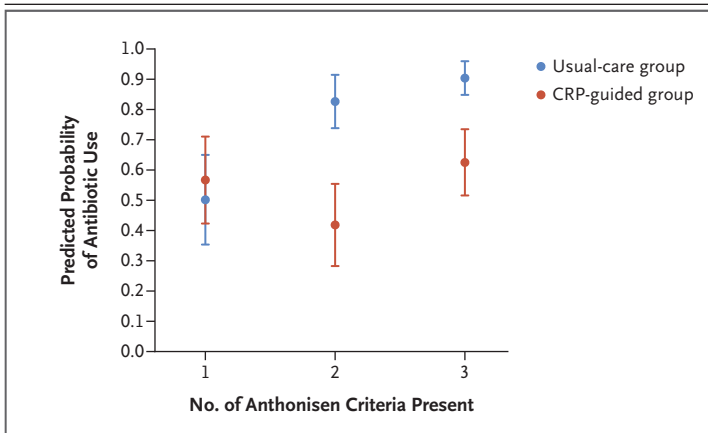
patients (32.8%) with a CRP value lower than 20 mg per liter, for 32 of 38 (84.2%) with a CRP value between 20 and 40 mg per liter, and for 36 of 38 (94.7%) with a CRP value higher than 40 mg per liter. During the first 4 weeks of follow-up, antibiotics were prescribed for 185 of 313 patients (59.1%) in the CRP-guided group and for 252 of 316 patients (79.7%) in the usual-care group (adjusted odds ratio, 0.30; 95% CI, 0.20 to 0.46). We found no evidence of any between-group difference in the use of other treatments for COPD (including oral glucocorticoids) during the first 4 weeks of follow-up (adjusted odds ratio, 0.79; 95% CI, 0.43 to 1.46). Additional details are provided in Tables S13 and S14 in the Supplementary Appendix.

There was no evidence of clinically important between-group differences in the proportion of patients who had primary care consultations (i.e., consultation with a primary care clinician outside a hospital) or secondary care consultations (i.e., planned consultation with a specialist in a hospital) during 6 months of follow-up (adjusted odds ratio, 1.39; 95% CI, 0.46 to 4.15); in the proportion of patients who received a diagnosis of pneumonia during the first 4 weeks of follow-up (adjusted odds ratio, 1.57; 95% CI, 0.28 to 8.84) and during 6 months of follow-up (adjusted odds ratio, 0.73; 95% CI, 0.29 to 1.82); and in health utility, with the scores averaged across the follow-up time points (adjusted mean difference in

score, 0.04; 95% CI, -0.02 to 0.10). With respect to general health status, patients in the CRP-guided group reported a health status score that was more than 3 points higher than that reported by the patients in the usual-care group (adjusted mean difference, 3.12; 95% CI, 0.50 to 5.74). The adjusted mean differences in the scores on the CRQ-SAS were all small, ranging from -0.09 to 0.15, with no confidence intervals containing values considered clinically important.<sup>41</sup> There was no clinically important between-group difference in the proportion of patients who had sputum samples that contained potential pathogens at 1 month (adjusted odds ratio, 0.97; 95% CI, 0.63 to 1.50); in the proportion of patients who had sputum samples that contained antibiotic-resistant bacteria (adjusted risk difference, 0.04; 95% CI, -0.03 to 0.11); or in the proportion of patients who had throat swabs that contained antibiotic-resistant commensal and potentially pathogenic organisms. (Details are provided in Section 10 in the Supplementary Appendix.)

#### ADVERSE EVENTS

Two patients in the usual-care group died within the 4-week follow-up window, one from pneumonia and one from respiratory failure; these deaths were not considered to be related to the trial interventions or procedures, as determined by the trial investigators. During 6 months of follow-up, 26 of 304 patients (8.6%) with available data in



**Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.**

Shown is the predicted probability of antibiotic use for acute exacerbations of COPD during the first 4 weeks according to the number of Anthonisen criteria present. The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. I bars denote 95% confidence intervals.<sup>29</sup>

the CRP-guided group had 35 hospitalizations, and 28 of 301 (9.3%) patients with available data in the usual-care group had 34 hospitalizations. During 6 months of follow-up, 9 of 305 patients (3.0%) in the CRP-guided group and 12 of 302 patients (4.0%) in usual-care group received a diagnosis of pneumonia (adjusted odds ratio, 0.73; 95% CI, 0.29 to 1.82). There was no evidence of a clinically important between-group difference in adverse effects from antibiotics (adjusted odds ratio, 0.79; 95% CI, 0.44 to 1.39) (Table S15 in the Supplementary Appendix).

## DISCUSSION

This randomized, controlled trial involving primary care patients presenting with an acute exacerbation of COPD showed that a management strategy with CRP point-of-care testing resulted in a lower percentage of patients reporting antibiotic use during the first 4 weeks of follow-up than those who received usual care alone, with a between-group difference of 20.4 percentage points. We found that CRP point-of-care testing also resulted in a lower percentage of patients who received an antibiotic prescription for acute exacerbation of COPD at the initial consultation and during the subsequent 4 weeks. Between-group differences in the scores on the Clinical COPD Questionnaire during follow-up were small-

er than the published minimal clinically important difference of 0.4, which indicates that less antibiotic use and fewer prescriptions from clinicians did not compromise patient-reported disease-specific quality of life. Health care-seeking behavior or measures of patient well-being at 6 months did not differ meaningfully between the trial groups, nor did secondary clinical, microbiologic, disease-specific quality-of-life, or health care utilization outcomes with respect to primary and secondary care.

We chose to include patient-reported antibiotic use for acute exacerbation of COPD during the first 4 weeks of follow-up as a primary outcome, because the main effects of interest involved actual antibiotic use. Antibiotics can be obtained from hospitals, services during out-of-office hours, leftover supplies, or rescue packs. Delayed or back-up antibiotic prescribing is fairly common for acute exacerbations of COPD in the United Kingdom, and not all of these prescriptions are collected from pharmacies or actually used.<sup>42</sup> We captured data regarding antibiotic prescribing, antibiotic use, and health care utilization to determine whether fewer initial prescriptions might have increased subsequent consulting and antibiotic prescribing and found that it did not.

We did not attempt to control for testing (e.g., sham tests for the usual-care group).<sup>43</sup> Awareness of receiving the point-of-care test may have contributed to enhanced COPD-related health status; however, this real-world effect needed to be captured because it may affect health care-seeking behavior, which is critical to assessments of overall benefit. Among the patients in the CRP-guided group, we did not observe patient-driven reconsultation during follow-up, a finding that is in line with a previous trial involving patients with lower respiratory tract infections.<sup>44</sup>

Although strategies for CRP point-of-care testing in primary care have been shown to reduce antibiotic prescribing for respiratory tract infections in general,<sup>45,46</sup> a small minority of patients in the studies that were included in systematic reviews had acute exacerbations of COPD,<sup>47</sup> and none reported effects on antibiotic use. A non-randomized Spanish study showed that the rate of antibiotic overprescribing for acute exacerbations of COPD was lower among primary care clinicians who received training in CRP testing than among those who did not.<sup>48</sup> A meta-analysis that included eight hospital-based trials showed



evidence of a lower rate of antibiotic prescriptions for acute exacerbations of COPD with procalcitonin testing, without an effect on treatment failure, duration of hospitalization, exacerbation recurrence, or mortality; however, the trials that were included in the meta-analysis were typically small, and the quality of the evidence was considered to be low to moderate.<sup>49</sup>

The evidence from our trial suggests that CRP-guided antibiotic prescribing for COPD exacerbations in primary care clinics may reduce patient-reported use of antibiotics and the prescribing of antibiotics by clinicians.

The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the National Institute for Health Research (NIHR), or the Department of Health and Social Care.

Supported by the NIHR Health Technology Assessment Program (project number 12/33/12). Dr. Butler was supported by funding from an NIHR Protection Research Unit on Health Care Associated Infections and Antimicrobial Resistance, by the NIHR MedTech and In Vitro Diagnostics Co-Operative at Oxford NHS Foundation Trust, and by an NIHR Senior Investigator Award; Dr. Cals, by a Veni grant (91614078) from the Netherlands Organization for Health Research and Development; and Drs. Phillips and Gal, by a research center grant from Health and Care Research Wales.

Dr. Butler reports receiving advisory board fees from Roche Molecular Systems and grant support from Roche Molecular Diagnostics; Dr. Wootton, receiving lecture fees from Merck Sharp & Dohme; and Dr. Llor, receiving grant support from Abbott Diagnostics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the personnel of the Centre for Trials Research, Cardiff University, and the University of Oxford Primary Care and Vaccines Clinical Trials Collaborative for providing support in the conduct of the trial and the personnel of the Health and Care Research Wales Workforce, the Thames Valley and South Midlands, Eastern, and West of England Primary Care Research Networks, the Comprehensive Local Clinical Research Networks, and the Cwm Taf University Health Board and the Cardiff and Vale University Health Board for their support in identifying the recruitment sites and in performing the medical-record reviews at these sites. We also thank the clinicians at the participating primary care practices, as well as all the patients who participated in the trial. We acknowledge the contributions of the members of the trial steering committee (Hilary Pinnock, Mike Thomas, William Hollingworth, and Derek Cummings [patient and public representative]) and the independent data monitoring and ethics committee (Martyn Lewis, Chris Griffiths, and Charis Marwick) and also of Margaret Barnard (who died in April 2016) and Jonathan Bidmead, who provided patient and public representation in the trial management group.

## REFERENCES

- Hicks LA, Bartoces MG, Roberts RM, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* 2015;60:1308-16.
- Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA* 2016;315:1864-73.
- Schroek JL, Ruh CA, Sellick JA Jr, Ott MC, Mattappallil A, Mergenhagen KA. Factors associated with antibiotic misuse in outpatient treatment for upper respiratory tract infections. *Antimicrob Agents Chemother* 2015;59:3848-52.
- Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory infections in primary care. *Lancet Infect Dis* 2007;7:749-56.
- Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
- Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48-55.
- Miravitlles M. Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? *Eur Respir J Suppl* 2002;36:9s-19s.
- Desai H, Richter S, Doern G, et al. Antibiotic resistance in sputum isolates of *Streptococcus pneumoniae* in chronic obstructive pulmonary disease is related to antibiotic exposure. *COPD* 2010;7:337-44.
- Pérez-Trallero E, Marimón JM, González A, Ercibengoa M, Larruskain J. In vivo development of high-level fluoroquinolone resistance in *Streptococcus pneumoniae* in chronic obstructive pulmonary disease. *Clin Infect Dis* 2005;41:560-4.
- Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013;13:123-9.
- O'Neill J. Rapid diagnostics: stopping unnecessary use of antibiotics. London: Review on Antimicrobial Resistance, October 2015 (<https://amr-review.org/sites/default/files/Paper-Rapid-Diagnostics-Stopping-Unnecessary-Prescription-Low-Res.pdf>).
- Horvath AR, Lord SJ, St John A, et al. From biomarkers to medical tests: the changing landscape of test evaluation. *Clin Chim Acta* 2014;427:49-57.
- Ferrante di Ruffano L, Hyde CJ, McCaffery KJ, Bossuyt PM, Deeks JJ. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. *BMJ* 2012;344:e686.
- Verbakel JY, Turner PJ, Thompson MJ, et al. Common evidence gaps in point-of-care diagnostic test evaluation: a review of horizon scan reports. *BMJ Open* 2017;7(9):e015760.
- Ni H, Xu J. COPD-related mortality by sex and race among adults aged 25 and over: United States, 2000-2014. *NCHS Data Brief* 2016;256:1-8.
- Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease — United States, 2013. *MMWR Morb Mortal Wkly Rep* 2015;64:289-95.
- Nacul L, Soljak M, Samarasinghe E, et al. COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. *J Public Health (Oxf)* 2011;33:108-16.
- Harries TH, Seed PT, Jones S, Schofield P, White P. Chronic obstructive pulmonary disease hospital admissions and drugs — unexpected positive associations: a retrospective general practice cohort study. *NPJ Prim Care Respir Med* 2014;24:14006.
- Al-ani S, Spigt M, Hofset P, Melbye H. Predictors of exacerbations of asthma and

- COPD during one year in primary care. *Fam Pract* 2013;30:621-8.
20. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128-38.
  21. Lindenauer PK, Pekow P, Gao S, Crawford AS, Gutierrez B, Benjamin EM. Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2006;144:894-903.
  22. Gonzales R, Camargo CA Jr, MacKenzie T, et al. Antibiotic treatment of acute respiratory infections in acute care settings. *Acad Emerg Med* 2006;13:288-94.
  23. Llor C, Bjerrum L, Munck A, et al. Predictors for antibiotic prescribing in patients with exacerbations of COPD in general practice. *Thorax* 2013;71:131-7.
  24. Miravittles M, Moragas A, Hernández S, Bayona C, Llor C. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest* 2013;144:1571-7.
  25. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;12:CD010257.
  26. van Velzen P, Ter Riet G, Bresser P, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. *Lancet Respir Med* 2017;5:492-9.
  27. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114-21.
  28. Global Initiative for Chronic Obstructive Lung Disease (GOLD) home page (<http://www.goldcopd.org>).
  29. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.
  30. Hurst JR, Donaldson GC, Perera WR, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;174:867-74.
  31. Minnaard MC, van de Pol AC, de Groot JAH, et al. The added diagnostic value of five different C-reactive protein point-of-care test devices in detecting pneumonia in primary care: a nested case-control study. *Scand J Clin Lab Invest* 2015;75:291-5.
  32. Llor C, Moragas A, Hernández S, Bayona C, Miravittles M. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:716-23.
  33. Bates J, Francis NA, White P, et al. General practitioner use of a C-reactive protein point-of-care test to help target antibiotic prescribing in patients with acute exacerbations of chronic obstructive pulmonary disease (the PACE study): study protocol for a randomised controlled trial. *Trials* 2017;18:442.
  34. van der Molen T, Willemsse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the clinical COPD questionnaire. *Health Qual Life Outcomes* 2003;1:13.
  35. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36.
  36. Schünemann HJ, Griffith L, Jaeschke R, et al. A comparison of the original chronic respiratory questionnaire with a standardized version. *Chest* 2003;124:1421-9.
  37. Gillespie D, Francis NA, Carrol ED, Thomas-Jones E, Butler CC, Hood K. Use of co-primary outcomes for trials of antimicrobial stewardship interventions. *Lancet Infect Dis* 2018;18:595-7.
  38. Goossens H. MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) results from Europe: comparison of antibiotic susceptibilities between countries and centre types. MYSTIC Study Group (European centres only). *J Antimicrob Chemother* 2000;46:Suppl T2:39-52.
  39. Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. *J Am Stat Assoc* 1996;91:444-55.
  40. Kocks JW, Tuinenga MG, Uil SM, van den Berg JW, Ståhl E, van der Molen T. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006;7:62.
  41. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the chronic respiratory disease questionnaire (CRQ). *COPD* 2005;2:81-9.
  42. McNulty CA, Lecky DM, Hawking MK, Quigley A, Butler CC. Delayed/back up antibiotic prescriptions: what do the public think? *BMJ Open* 2015;5(11):e009748.
  43. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009;62:464-75.
  44. Cals JW, de Bock L, Beckers PJ, et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med* 2013;11:157-64.
  45. Tonkin-Crine SK, Tan PS, van Hecke O, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. *Cochrane Database Syst Rev* 2017;9:CD012252.
  46. Aabenhus R, Jensen JU, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014;11:CD010130.
  47. Cals JW, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009;338:b1374.
  48. Strykowski DF, Nielsen AB, Llor C, Siersma V, Bjerrum L. An intervention with access to C-reactive protein rapid test reduces antibiotic overprescribing in acute exacerbations of chronic bronchitis and COPD. *Fam Pract* 2015;32:395-400.
  49. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2017;26(143):160073.

Copyright © 2019 Massachusetts Medical Society.