C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT

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Scientific summary

The PACE RCT

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Scientific summary

Background

Unnecessary antibiotic use drives antimicrobial resistance, wastes resources, may cause adverse effects and may distract from potentially more effective interventions for individuals. Point-of-care tests (POCTs) for acute infections are being promoted by government, by industry and in clinical guidelines to reduce inappropriate antibiotic prescribing, help contain antimicrobial resistance and improve patient outcomes. However, most evaluations of POCTs have examined analytic performance only, and there have been few trials evaluating clinical effectiveness and cost-effectiveness in the context in which POCTs are intended to be used. About 4.5% of the population over the age of 45 years live with diagnosed chronic obstructive pulmonary disease (COPD), and about half of these people experience one or more acute exacerbations of chronic obstructive pulmonary disease (AECOPD) that require medical treatment each year. Over 2 million antibiotic courses are prescribed for AECOPD each year in the UK, and most of these are issued in primary care. Although some patients with AECOPD are helped by these prescriptions, many are not, and so some antibiotics may simply damage the microbiome. Among patients admitted to hospital, a bacterial aetiology was identified in 30%, a viral agent was identified in 23%, both bacterial and viral agents were identified in a further 25%, and 20% of the AECOPDs were caused by other factors. The antibiotic prescribing recommendations for primary care management of AECOPD are generally based on clinical features alone (Anthonisen criteria, namely increased breathlessness, increased sputum volume and increased sputum purulence) (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). These features are subjective and have insufficient diagnostic accuracy to predict which patients can safely be managed without antibiotics.

C-reactive protein (CRP) is an acute phase protein that rises rapidly in infections and can be measured easily at the point of care, and it is considered the most selective biomarker to confirm AECOPD. A randomised controlled trial in primary care found no difference in clinical cure between patients with AECOPD treated with antibiotics and those treated with placebo who had a CRP level of < 40 mg/l. The availability of CRP POCT results may, therefore, help guide prescribing decisions for AECOPD to reduce antibiotic consumption, reduce antimicrobial resistance and improve patient outcomes. However, the clinical effectiveness and cost-effectiveness of CRP POCT have not yet been evaluated in a pragmatic controlled trial in primary care.

Objective

We aimed to establish whether or not the addition of a CRP POCT to usual care for AECOPD in primary care safely and cost-effectively reduces antibiotic consumption for AECOPD.

Methods

Trial design

The PACE (Primary care use of A C-reactive protein point-of-care test to help target antibiotic prescribing to patients with acute Exacerbations of chronic obstructive pulmonary disease who are most likely to benefit) trial was a multicentre, parallel-arm, individually randomised controlled open trial with embedded health economics and qualitative process evaluations, conducted between September 2015 and February 2017 in UK general medical practices.

Intervention guidance

All participating sites were provided with information on the current best practice for managing AECOPD, which included a brief summary of National Institute for Health and Care Excellence and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance, and were provided with a desktop CRP POCT Afinion device [Alere Afinion™ AS100 Analyzer, Alere Inc. (now Abbott Diagnostics), IL, USA]. Clinicians were given training in the use of the POCT and guidance on interpreting the test results, which emphasised that the decision about antibiotic prescribing should be based on a comprehensive assessment of the likely risks and benefits, given the patient's underlying health status and clinical features. In addition, the guidance indicated that for patients with a CRP level of < 20 mg/l, antibiotics are unlikely to be beneficial and usually should not be prescribed; for patients with a CRP level of 20–40 mg/l, antibiotics may be beneficial, mainly if purulent sputum is present; and for patients with a CRP level of > 40 mg/l, antibiotics are likely to be beneficial.

Eligibility, recruitment and randomisation

Men or women were eligible if they were aged ≥ 40 years, had a primary care diagnosis of COPD, presented with an AECOPD (with at least one of increased dyspnoea, increased sputum volume and increased sputum purulence) of between 24 hours' and 21 days' duration, and provided informed, written consent.

Participants were allocated to the trial arms using remote online computerised randomisation.

Data collection

Baseline data collected included the number of days the patient had AECOPD symptoms, the patient's medical history and clinicians' examination findings.

A sputum sample, when obtainable, and throat swab samples were taken, and participants self-completed the Clinical COPD Questionnaire (CCQ) and the EuroQol 5-Dimensions (EQ-5D) questionnaire prior to randomisation. Clinicians recorded their antibiotic prescribing and other management decisions for all participants after randomisation and assessment.

Participants were followed up with telephone calls at week 1 and week 2, and a face-to-face consultation at 4 weeks post randomisation, during which a further throat swab and sputum sample (when available) were taken. At 6 months, the Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS) and EQ-5D questionnaires were posted to participants, who completed these and returned them using provided stamped addressed envelopes, and we collected relevant data from electronic medical records.

Clinicians were asked to carry out a CRP POCT as part of their assessment of participants allocated to the intervention (CRP POCT arm). For patients allocated to usual care (control arm), clinicians were asked not to use CRP POCT in their management of those patients' AECOPD at any time during participation.

Outcome measures

We used two co-primary outcomes because any reduction in antibiotic consumption would have to be considered alongside any negative impact on patient recovery. The first co-primary outcome was patient-reported antibiotic consumption for AECOPD within 4 weeks post randomisation. The second co-primary outcome was COPD health status (total score) measured with the CCQ at 2 weeks post randomisation.

Sample size

The study aimed to have sufficient power to detect a 15% reduction from an estimated 70% of patients consuming antibiotics for AECOPD during the 4 weeks following randomisation, and sufficient power to demonstrate that participants managed with the CRP POCT do no worse (non-inferior) than those managed without the CRP POCT, in terms of their COPD health status measured with the CCQ 2 weeks post randomisation. Assuming an expected difference between the arms of zero, a non-inferiority margin of 0.3 [smaller than the lowest minimal clinically important difference and a common standard deviation (SD) of 1.1], based on a one-sided significance level of 0.05 and 90% power, the study needed 462 participants, inflated to 580 to account for the loss to follow-up of approximately 20% of participants. It was also anticipated that the outcomes would not be entirely independent. Therefore, we aimed to recruit at least 650 participants to maintain an overall power between 81% and 90%.

Clinical effectiveness and cost-effectiveness analyses

The main clinical effectiveness analysis was based on a modified intention-to-treat population, which included all randomised participants who provided outcome data, regardless of protocol deviations or intervention received. All planned analyses were described in detail in a statistical analysis plan.

A within-trial health economic analysis was undertaken from a UK NHS perspective that assessed CRP POCT implementation costs in primary care and subsequent health-care costs within the trial follow-up period of 6 months. A cost-effectiveness analysis based on the co-primary outcome of antibiotic consumption at 4 weeks and a cost–utility analysis at 6 months were performed. Furthermore, a cost–consequences analysis and a budget impact analysis were conducted and the robustness of the results was tested in sensitivity analyses.

Process evaluation

A qualitative process evaluation was undertaken to facilitate the interpretation of results and assist with implementation planning. Semistructured telephone interviews were carried out with 20 purposively sampled patients and 20 primary care staff. A topic guide focused on experiences of the management of AECOPD, the acceptability, implementation and potential mechanisms of the CRP POCT intervention and contextual factors that could influence future implementation. Audio-recordings were transcribed verbatim and analysed using framework analysis.

Results

Baseline characteristics

In total, 653 participants were randomised from 86 general practices between January 2015 and February 2017. Three withdrew consent and one was randomised in error (the patient had been randomised, but the clinician then noted that this patient was ineligible and so their baseline data were destroyed), leaving 324 usual-care and 325 CRP POCT participants. The mean age was 68.1 (SD 9.42) years; 51.6% of participants were men; 10.8% of participants had mild COPD (GOLD I), 54.8% of participants had moderate COPD (GOLD II), 28.1% of participants had severe COPD (GOLD III) and 6.3% of participants had very severe COPD (GOLD IV); the mean ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) was 0.6 (SD 0.13); the mean percentage predicted FEV_1 was 59.8% (SD 20.04%); the mean number of days with symptoms prior to consultation was 6.9 (SD 5.13) days; the mean baseline CCQ total score was 3.3 (SD 1.14) points; and the baseline health utility (EQ-5D) was 0.7 (SD 0.25). Overall, no pathogens were detected in 95 out of 386 baseline sputum samples (24.6%), bacterial pathogens were only detected in 79 out of 386 (20.5%), viral/atypical pathogens were only detected in 123 out of 386 cases (31.9%) and both bacterial and viral/atypical pathogens were detected in 89 out of 386 cases (23.1%). Participants in both trial arms were well matched for these and other characteristics at baseline.

Primary outcome

In total, 537 out of the 649 randomised participants contributed to the primary analysis of self-reported antibiotic consumption at 4 weeks post randomisation (82.7%), and 563 contributed to the primary analysis of CCQ total score at 2 weeks post randomisation (86.7%). Antibiotics were *consumed* for AECOPD by 212 (77.4%) usual-care participants and 150 (57.0%) CRP POCT participants [adjusted odds ratio (AOR) 0.31, 95% confidence interval (CI) 0.20 to 0.47]. The adjusted mean CCQ score difference at 2 weeks was –0.19 (two-sided 90% CI –0.33 to –0.05) points. The upper limit of the CI did not contain the prespecified non-inferiority margin of 0.3.

Antibiotic prescribing at index consultation and 4-week follow-up

Antibiotic prescribing at the index consultation was ascertained for all but one participant, and 22% fewer participants in the CRP POCT arm were *prescribed* antibiotics (47.7% in the usual-care arm vs. 69.7% in the CRP POCT arm, AOR 0.31, 95% CI 0.21 to 0.45), and 21% fewer participants were prescribed antibiotics over the 4-week follow-up (59.1% vs. 79.7%, AOR 0.30, 95% CI 0.20 to 0.46).

Antibiotic prescribing and C-reactive protein values at index consultation

A total of 97.5% (317/325) of participants allocated to the CRP POCT arm reported receiving a CRP POCT during the recruitment consultation, and the median CRP value was 6 mg/l (interquartile range 5–18.5 mg/l); 76.0% of participants (241/317) had CRP levels of < 20 mg/l. Antibiotics were prescribed for 33% of those patients with a CRP level of < 20 mg/l in the CRP POCT arm at the index consultation.

Secondary outcomes

There was no evidence of a difference between the arms regarding symptoms sometimes attributed as adverse effects from antibiotics and other COPD treatments (AOR 0.79, 95% CI 0.44 to 1.39; $p = 0.410$), primary or secondary care consultations during the 6 months following randomisation (AOR 1.39, 95% CI 0.46 to 4.15; $p = 0.559$), or pneumonia diagnoses at 4 weeks (AOR 1.57, 95% CI 0.28 to 8.84; $p = 0.608$) and 6 months (AOR 0.73, 95% CI 0.29 to 1.82; $p = 0.495$). There was no evidence to conclude that there were any differences between the arms for CRQ-SAS outcomes at 6 months.

No meaningful or statistically significant differences were found between the arms at 1 month in the potential pathogens and antibiotic resistant isolates from sputum, or in resistance in commensal and potentially pathogenic organisms isolated from throat swabs.

Adverse events

Two participants, both in the usual-care arm, died during the first 4 weeks following randomisation: these serious adverse events were not related to the intervention or to trial participation.

Economic evaluation

Reduced antibiotic costs at the initial consultation were offset by higher total medication costs over the following 6 months, mainly caused by a 5.4% increase in prescribing of inhaled medication in the CRP POCT arm. COPD-related primary care contacts were lower in the intervention arm, with 2.7% fewer general practitioner visits. Although outpatient attendances were reduced in the CRP POCT arm (4.1% fewer appointments at 4 weeks and 6.7% fewer at 6 months), the secondary care cost for any condition was higher for all follow-up periods as a result of increased inpatient length of stay for a small number of intervention patients. The total incremental cost was £17.59 at 4 weeks and £126.26 at 6 months, driven mainly by the higher inpatient cost and the cost of CRP testing. If only COPD-related health-care costs are considered, the cost in both arms was similar, with the CRP test cost of £11.31 per test slightly offset by savings in health-care resource use. The mean incremental cost-effectiveness ratios were £222 (95% CI –£42.00 to £518.14) per 1% reduction in antibiotic consumption compared with usual care at 4 weeks and £15,251 (95% CI £2959 to £22,813) per quality-adjusted life-year gained at 6 months. Patients in the CRP POCT arm had fewer days off work, with reduced costs of productivity loss of £510.42 (95% CI –£989.56 to –£31.28; $p = 0.022$) per patient reporting periods of worktime missed.

Process evaluation

Patients participating in the qualitative evaluation felt that the CRP POCT was useful in detecting infection and targeting treatment more appropriately, and that it seemed quick and easy to use. Clinicians reported enhanced confidence in making management decisions and reduced decisional ambiguity when withholding antibiotics, and felt that the CRP POCT was a useful tool for communicating with and reassuring patients. They were keen to emphasise that the test should be used alongside, and not as a replacement for, clinical assessment. Cartridge preparation time and the cost of the equipment presented a significant barrier when implementing the test.

Conclusions

A CRP POCT diagnostic strategy resulted in a 20% absolute reduction in patient-reported antibiotic *consumption* over 4 weeks and in clinician antibiotic *prescribing* at the index consultation, and no clinically important change in patient-reported condition-specific quality of life, without evidence of an increase in total COPD-related costs. The use of the CRP POCT strategy was broadly acceptable to patients and clinicians. There were no associated harms identified in the trial, although clinicians indicated that the time and costs associated with the CRP POCT needed careful consideration.

Awareness of receiving the POCT may have contributed to enhanced COPD health status; however, this real-world effect needed to be captured. As awareness of intervention allocation may have an impact on participant help-seeking, and, as capturing this is critical to assessments of cost-effectiveness, this was an open trial.

C-reactive protein POCT strategies in primary care have been shown to safely and cost-effectively reduce antibiotic prescribing for acute cough; however, only a small minority of participants in those studies had AECOPD, and none reported effects on antibiotic consumption rather than antibiotic prescribing.

We confirmed that bacterial infection is a likely trigger for AECOPD in a minority of patients, and that there may be potential for further safe reductions in antibiotic use for AECOPD, given that one-third of participants with a CRP level of < 20 mg/l were nevertheless prescribed antibiotics.

This trial provides good evidence that CRP POCT testing (with the associated guidance for clinicians that was used in this trial) to guide antibiotic prescribing decisions for AECOPD in primary care is safe and effective. Further research, building on our qualitative findings, could help guide effective implementation.

Trial registration

This trial is registered as ISRCTN24346473.

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This report

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