Accepted Manuscript

British Journal of General Practice

Associations with antibiotic prescribing for acute exacerbation of COPD in primary care

Gillespie, David; Butler, Christopher; Bates, Janine; Hood, Kerry; Melbye, Hasse; Phillips, Rhiannon; Stanton, Helen; Alam, Mohammed; Cals, Jochen; Cochrane, Ann; Kirby, Nigel; Llor, Carl; Lowe, Rachel; Naik, Gurudutt; Riga, Evgenia; Sewell, Bernadette; Thomas-Jones, Emma; White, Patrick; Francis, Nick

DOI: https://doi.org/10.3399/BJGP.2020.0823

To access the most recent version of this article, please click the DOI URL in the line above.

Received 07 September 2020
Revised 18 November 2020
Accepted 23 November 2020

Associations with antibiotic prescribing for acute exacerbation of COPD in primary care

Authors

David Gillespie PhD[1, 2]

Christopher C Butler FMedSci[1]

Janine Bates MPhil[2]

Kerenza Hood PhD[2]

Hasse Melbye PhD[3]

Rhiannon Phillips PhD[4]

Helen Stanton BSc[2]

Mohammed Fasihul Alam PhD[5]

Jochen WL Cals PhD[6]

Ann Cochrane MSc[7]

Nigel Kirby MA[2]

Carl Llor MD[8, 9]

Rachel Lowe PhD[2]

Gurudutt Naik MPH[10]

Evgenia Riga MSc[11]

Bernadette Sewell PhD[12]

Emma Thomas-Jones PhD[2]

Patrick White MD[13]

Nick A Francis PhD[14]

Affiliation

1. Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG

2. Centre for Trials Research, School of Medicine, College of Biomedical & Life Sciences, Cardiff University, Cardiff, CF14 4YS

3. General Practice Research Unit, Department of Community Medicine, UIT the Arctic University of Norway, Tromsø, Norway

4. Cardiff School of Sport & Health Science, Cardiff Metropolitan University, Llandaff Campus, Cardiff, UK

5. Department of Public Health, College of Health Sciences, QU-Health, Qatar University, PO Box. 2713, Doha, Qatar

6. Department of Family Medicine, School for Public Health and Primary Care, , Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands

7. York Trials Unit, Department of Health Sciences, University of York, York, YO10 5DD, UK

8. Research Unit for General Practice, Department of Public Health, University of Copenhagen

9. University Institute in Primary Care Research Jordi Gol, Via Roma Health Centre, Barcelona.

10. Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK

11. Department of Psychiatry, Medical Sciences Division, University of Oxford, Oxford, UK

12. Swansea Centre for Health Economics, Swansea University, Singleton Park, Swansea, SA2 8PP

13. School of Population Health and Environmental Sciences, Kings College London, London, UK

14. Primary Care, Population Sciences and Medical Education, University of Southampton, Aldermoor Health Centre, Southampton, SO16 5ST

Corresponding author

Dr David Gillespie. **Address:** Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG. **E-mail:** david.gillespie@phc.ox.ac.uk

How this fits in

Several demographic and clinical features are used when deciding to prescribe antibiotics to patients presenting with AECOPD in UK primary care. Studying the diagnostic and prognostic value of these features is warranted to understand how to safely reduce antibiotic use in this population.

1.

Abstract

Background

C-reactive protein point-of-care testing (CRP-POCT) has been shown to reduce antibiotic use in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in primary care by 26%, without compromising patient care. Fewer than half of AECOPD patients present with bacterial aetiology and further safe reductions may be possible.

Aim

To investigate the associations between presenting features and antibiotic prescribing in patients with AECOPD in UK primary care.

Design and Setting

This was a secondary analysis of a randomised controlled trial of participants presenting with AECOPD in primary care.

Method

Clinicians collected participant's demographic features, comorbid illnesses, clinical signs, and symptoms. Antibiotic prescribing decisions were made following participants being randomised to receive a point-of-care CRP measurement. Multivariable regression models were fitted to explore the association between patient and clinical features and antibiotic prescribing and extended to further explore any interactions with CRP measurement category (CRP not measured, CRP <20mg/L, CRP ≥20mg/L).

Results

We included 649 participants from 86 general practices across England and Wales. The odds of antibiotic prescribing were higher in the presence of clinician-recorded crackles (adjusted odds ratio (AOR)=5.22,95%CI:3.24-8.41), wheeze (AOR=1.64,95% CI:1.07-2.52), diminished vesicular breathing (AOR=2.95,95%CI:1.70-5.10), or evidence of consolidation (AOR=34.40,95% CI:2.84-417.27). Increased age was associated with lower odds of antibiotic prescribing (AOR per-year increase =0.98,95% CI:0.95-1.00), as was the presence of heart failure (AOR=0.32,95% CI:0.12-0.85).

Conclusion

Several demographic features and clinical signs and symptoms are associated with antibiotic prescribing in AECOPD. The diagnostic and prognostic value of these features may help identify further safe reductions.

Key words

COPD; exacerbation; antibiotics; C-reactive protein, secondary analysis, randomised controlled trial (RCT), primary care.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) affects around 2% of the UK population, and globally is the third leading cause of death. (1-3) Over 70% of patients presenting with acute exacerbations of COPD (AECOPD) in primary care are prescribed an antibiotic, (4) despite bacterial pathogens only being detectable in 20-50% of exacerbations. (5-7) Antibiotic use for AECOPD accounts for 5% of all primary care antibiotic prescriptions. (4)

Overuse of antibiotics contributes to the development of antimicrobial resistance, exposes patients to the risk of unnecessary side-effects, wastes money, and undermines self-care. (8) There is therefore a need for antimicrobial stewardship initiatives to target the prescribing of antibiotics for patients with AECOPD in primary care.

The PACE trial demonstrated that a management strategy involving the use of C-reactive protein point-of-care testing (CRP-POCT) for patients with AECOPD in primary care can lead to a reduction in antibiotic use without any evidence of patient harm. (9) Antibiotics were used by 77% of patients in the usual care group and 57% in the CRP-POCT group (a relative difference of 26%), while potential bacterial pathogens were isolated in the sputum of only 44% of participants. This suggests that there may be potential for further reductions in antibiotic prescribing, and it is therefore important to understand the determinants of antibiotic prescribing for this condition.

Our aim was to improve our understanding of the presenting features associated with antibiotic prescribing decisions for AECOPD in primary care. We also aimed to explore if these were different when clinicians had access to a CRP measurement (available for patients randomised to the intervention arm of the trial), and whether the CRP value was elevated (≥20mg/L) or not.

Methods

Study design

This was a secondary analysis of an open, multi-site, parallel-group, individually randomised controlled trial (RCT) evaluating the effectiveness of a CRP-POCT management strategy for patients with an AECOPD in UK primary care. Target recruitment was 650 participants. The protocol and findings for the original study are reported elsewhere. (9, 10, 11)

Ethical approval for the PACE study was obtained in September 2014 (REC reference: 14/WA/1106). The aims of this paper fall within the remit of the original ethics application.

Participants and setting

Participants aged 40 years or older with a clinically recorded diagnosis of COPD (with or without spirometry confirmation) who presented with an acute exacerbation for 1 to 21 days were recruited into the trial from general practices across England and Wales. Full inclusion and exclusion criteria have been described previously. (10)

Procedures

Following informed consent, baseline data were collected. Participants were then randomly allocated using remote online computer randomisation (ratio 1:1) to either management via usual care (no CRP-POCT) or CRP-POCT in addition to usual care.

All general practices (N=86) were provided with a POCT device and all associated materials, information on current best practice for managing AECOPD, with no other specific guidance given to clinicians with regards to the management of their patients. Participants allocated to the usual care arm were managed without the use of a CRP-POCT measurement. Those allocated to the CRP-POCT arm had a CRP measurement taken using a POCT desktop machine, to help guide initial antibiotic prescribing decisions. Clinicians received guidance and training on how to use the device and interpret the result. The guidance indicated that antibiotics were unlikely to be beneficial and should usually not be prescribed for patients with a CRP <20mg/L; that antibiotics may be beneficial, especially if purulent sputum is present, for patients with a CRP 20-40mg/L; and that antibiotics are likely to be beneficial and should usually be prescribed (unless a patient is assessed as being at low risk of complications) for patients with a CRP >40mg/L. The cut-offs were based on data from a placebo-controlled trial of antibiotics for patients with acute exacerbations of mild to moderate COPD. (12)

Following consent and prior to randomisation, clinicians recorded participant demographic details (age and sex), their medical history (presence of co-morbidities, COPD stage according to GOLD criteria), and clinical features pertaining to their exacerbation (number of days experiencing symptoms, temperature, pulse rate, oxygen saturation, ability to complete a full sentence, tachypnoea, presence and number of Anthonisen symptoms (increased shortness of breath, increased sputum volume, increased sputum purulence), (13) presence of crackles, wheeze, diminished vesicular sounds, or evidence of consolidation on auscultation of the lungs. Clinicians recorded the colour of the sputum sample using a Bronkotest chart. (14) Where a sputum sample could not be obtained, participants estimated their current sputum colour using the chart. Participants were also asked about their smoking status (non-smoker, current smoker, ex-smoker) during one week follow-up assessments.

Antibiotic prescribing and other management decisions were made and recorded after receipt of the test result for those allocated to the CRP-POCT arm.

Statistical methods

Descriptive statistics were reported as frequencies and percentages or means and standard deviations, as appropriate.

To investigate the association between patient and clinical features and antibiotic prescribing, multilevel multivariable logistic regression models were fitted, accounting for any clustering of participants within practices. Each explanatory variable (those described in the section *Procedures* above) was included in separate regression models. Sputum colour was ranked 1 (lightest colour) to 5 (darkest colour). Continuous variables were grand-mean-centred and included as linear effects following the inspection of model parsimony, when comparing linear terms to restricted cubic splines with both five and three knots, using Akaike's Information Criterion (AIC), see Supplementary Table 1. Each model was adjusted for CRP measurement (defined as no measurement taken, CRP<

20mg/L, and CRP≥20mg/L) in addition to increased sputum purulence. The latter variable was adjusted for as a potential confounder as it was an exacerbation feature specifically mentioned in the guidance on interpreting the CRP measurement. The differential association between explanatory variables and antibiotic prescribing by CRP measurement was explored by extending models to include CRP measurement interacted with explanatory variables.

The proportion of the total variance, for explanatory variable, that was attributable to differences across practices was expressed by estimating the intra-cluster correlation coefficient (ICC), with the $\pi^2/3$ estimator used where considering a binary response. These were calculated to indicate practice (as a proxy for prescriber) variation in the reporting of these features.

Statistical analyses were conducted using Stata V16.0.

Results

Participant flow

The PACE trial consented and randomised 653 participants from 86 general practices across England and Wales. Three participants withdrew their permission for their data to be used and one was randomised in error, leaving 649 participants (324 allocated to usual care and 325 allocated to CRP-POCT). CRP-POCT data were not available for 8 participants, leaving 241 allocated to CRP-POCT with a CRP value < 20mg/L, and 76 allocated to CRP-POCT with a CRP value ≥ 20mg/L (Figure 1). Descriptive statistics overall, by CRP measurement, and by antibiotic prescription receipt at the index consultation are given in Supplementary Table 2.

Numbers analysed

One participant (CRP not measured) did not have data available regarding antibiotic prescribing decisions at the index consultation. Data availability varied for each of the candidate variables and are indicated in Table 1. Antibiotics were prescribed at the index consultation to 225 (69.7%) participants in whom CRP was not measured, 79 (32.8%) with CRP < 20mg/L, and 68 (89.5%) with CRP ≥ 20mg/L.

Demographic features and comorbid illness

Higher participant age was associated with lower odds of antibiotic prescribing (AOR per additional year increase = 0.98, 95% CI: 0.95 to 1.00, p = 0.035, Table 1). The presence of heart failure was associated with lower odds of antibiotic prescribing (AOR = 0.32, 95% CI: 0.12 to 0.85, p = 0.022). There was no evidence that the association between any of the patient characteristics and antibiotics were different by CRP measurement (Supplementary Table 3).

Practice-level ICCs for demographic features and comorbid illness ranged from 0.02 (95% CI: 0.00 to 0.17) for age to 0.13 (95% CI: 0.05 to 0.28) for participants with the presence of at least one co-morbid illness (Supplementary Figure 1).

Symptoms and signs

Clinician-reported chest auscultation findings of crackles (AOR = 5.22, 95% CI: 3.24 to 8.41, p < 0.001), wheeze (AOR = 1.64, 95% CI: 1.07 to 2.52, p = 0.022),

and diminished vesicular breathing (AOR = 2.95, 95% CI: 1.70 to 5.10, p < 0.001), as well as clinician-reported evidence of consolidation (AOR = 34.40, 95% CI: 2.84 to 417.27, p = 0.005), were all associated with higher odds of antibiotic prescribing (Table 1).

ICCs for clinical features ranged from 0.02 (95% CI: 0.00 to 0.15) for pulse rate to 0.60 (95% CI: 0.32 to 0.81) for evidence of consolidation on auscultation of the lungs (Supplementary Figure 2).

There was evidence to suggest a differential association between increased sputum volume and antibiotic prescribing by CRP measurement. Specifically, while an increase in sputum volume was associated with higher odds of antibiotic prescribing for participants in whom CRP was not measured (increased sputum volume main effect OR = 2.18, 95% CI: 1.17 to 4.07; CRP < 20mg/L main effect = 0.30, 95% CI: 0.13 to 0.65; CRP ≥ 20mg/L main effect: 5.88, 95% CI: 1.36 to 25.50), there was minimal influence on antibiotic prescribing for those with CRP < 20mg/L (interaction between increased sputum volume and CRP < 20mg/L OR = 0.31, 95% CI: 0.12 to 0.80, Supplementary Table 3, Figure 2). Evidence of consolidation was reported for 18 participants in total (seven in those for whom CRP was not measured, eight with CRP < 20mg/L, and three with CRP ≥ 20mg/L). All but one of these participants (CRP < 20mg/L) were prescribed antibiotics at the index consultation. The reporting of crackles was associated with the highest odds of antibiotic prescribing, and there was no evidence of a differential association by CRP measurement (Figure 3).

Discussion

Summary of key findings

In this study, we investigated antibiotic prescribing associations for patients with AECOPD in UK primary care. We found that lower age, presence of heart failure, and clinician-reported abnormal findings on examination of the lungs (crackles, wheeze, diminished vesicular breathing, and 'evidence of consolidation') were all associated with antibiotic prescribing at the index consultation after adjusting for CRP measurement category and the presence of increased purulent sputum.

Increased patient-reported sputum volume was associated with antibiotic prescribing when CRP was not measured, but considerably less so when measured. Reporting crackles on auscultation was the feature most strongly associated with antibiotic prescribing, and the magnitude of this association was large across all three CRP measurement groups.

Strengths and limitations

These data were obtained from the largest trial of patients with AECOPD in UK primary care, covering 86 general practices across England and Wales. The trial benefitted from a representative sample of this patient population, (15, 16) and with high data completion, most participants were retained for these analyses. Clinicians in practices were trained in study procedures and data collection processes in accordance with a standardised protocol, and this minimised any biases arising from variable research practices.

This was a secondary analysis of a RCT, and no formal power calculation was conducted for these particular analyses. Furthermore, our ICC estimates should

be interpreted with some caution, as these were obtained from data arising from a RCT, and the sources of variation may reflect on the type of person a clinician was willing to include in such a trial. In addition, the calculation of ICC values on the log-odds scale for binary variables, while not depending on cluster prevalence, may not directly translate to other studies. The ICC for 'evidence of consolidation' (0.6) likely reflects the variability in clinical assessment of this feature, as well as how rare it is in primary care. Finally, we are unable to draw causal conclusions regarding our presenting features and their relationship to antibiotic prescribing.

The considerable practice variation in recording of clinical features suggests a high degree of subjectivity, as has been shown in previous studies. (21,22) We also cannot rule out the possibility of the relationship between clinical features and antibiotic prescribing being confounded by clinician's perceptions of the need for antibiotics, which have previously been shown to influence the recording of 'objective' features such as clinical findings and diagnosis. (23)

Comparison with existing literature

Several of our findings are consistent with previous studies on the determinants of antibiotic prescribing for acute cough / lower respiratory tract infection in primary care, including crackles, wheeze, diminished breath sounds (and other abnormal auscultation findings). (17-20)

Our finding that increasing age was associated with lower odds of antibiotic prescribing was unexpected and inconsistent with the study by Llor and colleagues. Our study differs in two key ways. First, ours was a randomised trial with several eligibility criteria, whereas the study by Llor and colleagues was an observational study where clinicians included all patients over a defined time period. Thus, our study may have inadvertently excluded older participants who would more likely be prescribed antibiotics, despite there being no upper age limit. Second, our association between age and antibiotic prescribing was adjusted for CRP measurement and increased sputum purulence (none, < 20mg/L, ≥ 20mg/L), whereas the study by Llor and colleagues was adjusted for several variables in a multivariable analysis (gender, days with symptoms, several different types of symptoms, utilisation of CRP, clinician-request for a chest X-ray, and patient demanding antibiotics).

The weak association between sputum volume and antibiotic prescribing may indicate that clinicians are less certain about an increase in sputum volume as an indicator of bacterial infection compared to other clinical features. This is in line with the GOLD statement that sputum purulence is the strongest predictor of bacterial infection among the Anthonisen criteria, and that sputum volume and increased dyspnoea should not be emphasized in the absence of purulence (24). This point of view is supported by Miravitlles and colleagues, who found that purulence was the only Anthonisen criterion independently predicting an unfavourable outcome in AECOPD patients treated with placebo (25).

Implications

The importance attributed to chest findings, and crackles in particular, in deciding on prescribing of antibiotics for AECOPD is not supported by a strong evidence base nor included in current guidelines. The emphasis on crackles by

clinicians is probably related to the increased frequency found in pneumonia. (26) However, crackles are commonly heard in COPD (27) and especially during exacerbations, related to worsened bronchial obstruction. (28) In the present study, while the link between crackles and antibiotic prescribing was independent of CRP result, a greater number of participants experienced crackles in the high CRP group (59%) than the low CRP group (44%), indicative of a relationship between crackles and more seriously unwell participants. The diagnostic and prognostic value of crackles and other chest sounds for the management of patients with AECOPD requires further investigation.

Conclusions

Clinicians use a range of demographic and clinical features, including age and lung sounds in their decision to prescribe antibiotics to patients presenting with AECOPD in UK primary care. Further investigation is required to determine diagnostic and prognostic value of these features and whether further safe reductions in antibiotic prescribing for AECOPD are possible.

Funder

The study was supported by funds from the NIHR Health Technology Assessment Programme (project number 12/33/12).

Contribution

DG, CCB, and NAF originally conceived the idea for this paper. DG drafted the manuscript and conducted statistical analysis. All authors were involved in the design, acquisition, and interpretation of data for the paper. All authors revised the manuscript critically and approved the final version for publication.

Ethics approval

Ethics approval for the PACE trial was given on 15 September 2014 by the Research Ethics Committee (REC) for Wales (Wales REC 6), recognised by the United Kingdom Ethics Committee Authority (REC reference 14/WA/1106).

Conflicts of interest

DG, AC, BS, ET-J, GN, HS, JB, ER, KH, NK, PW, RL, and NF report grants from National Institute for Health Research, during the conduct of the study.

CCB reports grants from National Institute for Health Research Health as NIHR Senior Investigator, grants from National Institute for Health Research Health Technology Assessment Programme to support the study, grants from the National Institute for Health Research Health Protection Research Unit on Health Care Associated Infections and Antimicrobial Resistance, grants from National Institute for Health Research Health for the MedTech and In Vitro Diagnostics Cooperative for innovative diagnostics and monitoring technology to enhance Community Healthcare during the conduct of the study; personal fees from Roche Molecular Systems, grants from Roche Molecular Diagnostics, outside the submitted work; and Afinion CRP devices and associated training to participating general practices were provided at no cost to the study by Alere; and; is part of publicly funded research consortia that include industrial partners.

RP reports grants from National Institute for Health Research, during the conduct of the study; grants from Health and Care Research Wales outside the submitted work.

CL reports grants from Abbott Diagnostics, outside the submitted work.

All other authors (HM, JC, MFA) declare no conflicts of interest.

Data sharing

Data are available upon request.

Acknowledgements

We would like to thank all patients who participated in the trial and their families, without whom this study would not have been possible. We would also like to acknowledge the contribution of other members of the PACE trial team (Angela Watkins, Miguel Cossio, Stephanie Robinson, Christy Barlow, Megan Philips-Laird, Deborah Fitzsimmons, and Micaela Gal. Margaret Barnard (who passed away in April 2016) and Jonathan Bidmead provided patient and public representation on

the Trial Management Group. Jacqueline Nuttall provided study design input). Two UK Clinical Research Collaboration registered clinical trials units were involved in the study: Centre for Trials Research, Cardiff University; and University of Oxford Primary Care and Vaccines Clinical Trials Collaborative. We would also like to acknowledge and thank the Health and Care Research Wales Workforce, the following CRNs for their support in helping to identify sites and carry out notes reviews at these sites: Thames Valley & South Midlands CRN, East Midlands CRN, West Midlands CRN, West of England CRN, North Thames CRN, North West London CRN and South London CRN. We would like to express our thanks to Abbott Rapid Diagnostics, formally Alere Ltd, which provided the Afinion analysers and CRP cartridges and controls to the recruitment sites at no cost. Alere provided training on the use of the CRP POCT to a number of the participating sites.

References

1. The top 10 causes of death [Internet]. Who.int. 2020 [accessed: 27 May 2020]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

2. Nacul L, Soljak M, Samarasundera 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.

3. Harries TH, Seed PT, Jones S, et al. 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.

4. Llor C, Bjerrum L, Munck A, et al. Predictors for antibiotic prescribing in patients with exacerbations of COPD in general practice. Ther Adv Respir Dis 2013; 7: 131-7.

5. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 2007; 29: 1224–38.

6. Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. Thorax 2003; 58: 37–42.

7. Daniels JM, Snijders D, de Graaff CS, et al. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 181: 150–7.

8. Goossens H, Ferech M, Vander et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365: 579–87.

9. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. N Engl J Med 2019; 381: 111–20.

10. 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 Sep 29; 18(1): 442.

11. Francis NA, Gillespie D, White P, et al. C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. Health Technology Assessment (Winchester, England). 2020 Mar; 24(15): 1.

12. Llor C, Moragas A, Hernández S, et al. 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.

13. Anthonisen N, Manfreda J, Warren C, Hershfield E. Antibiotic therapy in exacerbations of chronic obstructive pulmonary. Ann Intern Med. 1987; 106: 196–204.

14. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000; 117: 1638–45.

15. Khan A, Dickens AP, Adab P, Jordan RE. Self-management behaviour and support among primary care COPD patients: cross-sectional analysis of data from the Birmingham Chronic Obstructive Pulmonary Disease Cohort. NPJ Prim Care Respir Med 2017; 27: 46.

16. Rockenschaub P, Jhass A, Freemantle N, et al. Opportunities to reduce antibiotic prescribing for patients with COPD in primary care: a cohort study using electronic health records from the Clinical Practice Research Datalink (CPRD). J Antimicrob Chemother. 2020 Jan 1; 75(1): 243-51.

17. Jakobsen KA, Melbye H, Kelly MJ, et al. Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. Scand J Prim Health Care. 2010 Dec 1; 28(4): 229-36.

18. Butler CC, Kelly MJ, Hood K, et al. Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection. Eur Respir J. 2011 Jul 1; 38(1): 119-25.

19. Hopstaken RM, Butler CC, Muris JW, et al. Do clinical findings in lower respiratory tract infection help general practitioners prescribe antibiotics appropriately? An observational cohort study in general practice. Family Practice. 2006 Apr 1; 23(2): 180-7.

20. Cals JW, Butler CC, Hopstaken RM, et al. 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 May 5; 338: b1374.

21. Melbye H, Straume B, Aasebøs U, Dale K. Diagnosis of Pneumonia in Adults in General Practice Relative Importance of Typical Symptoms and Abnormal Chest Signs Evaluated Against a Radiographic Reference Standard. Scand J Prim Health Care. 1992 Jan 1; 10(3): 226-33.

22. Francis NA, Melbye H, Kelly MJ, et al. Variation in family physicians' recording of auscultation abnormalities in patients with acute cough is not explained by case mix. A study from 12 European networks. Eur J Gen Pract. 2013 Jun 1; 19(2): 77-84.

23. Little P, Dorward M, Warner G, et al. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. Bmj. 2004 Feb 19; 328(7437): 444.

24. Global Initiative for Chronic Obstructive Lung Disease - Global Initiative for Chronic Obstructive Lung Disease - GOLD [Internet]. Global Initiative for Chronic Obstructive Lung Disease - GOLD. 2020 [cited 17 June 2020]. Available from: https://goldcopd.org/

25. Miravitlles M, Moragas A, Hernández S, et al. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment?. Chest. 2013 Nov 1; 144(5): 1571-7.

26. van Vugt SF, Verheij TJ, de Jong PA, et al. Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. Eur Respir J. 2013 Oct 1; 42(4): 1076-82.

27. Aviles-Solis JC, Jacome C, Davidsen A, et al. Prevalence and clinical associations of wheezes and crackles in the general population: the Tromsø study. BMC Pulm Med. 2019 Dec 1; 19(1): 173.

28. Melbye H, Al-Ani S, Spigt M. Drop in lung function during asthma and COPD exacerbations–can it be assessed without spirometry?. Int J Chron Obstruct Pulmon Dis. 2016; 11: 3145.

Tables and Figures

Figure 1: Participant flow diagram

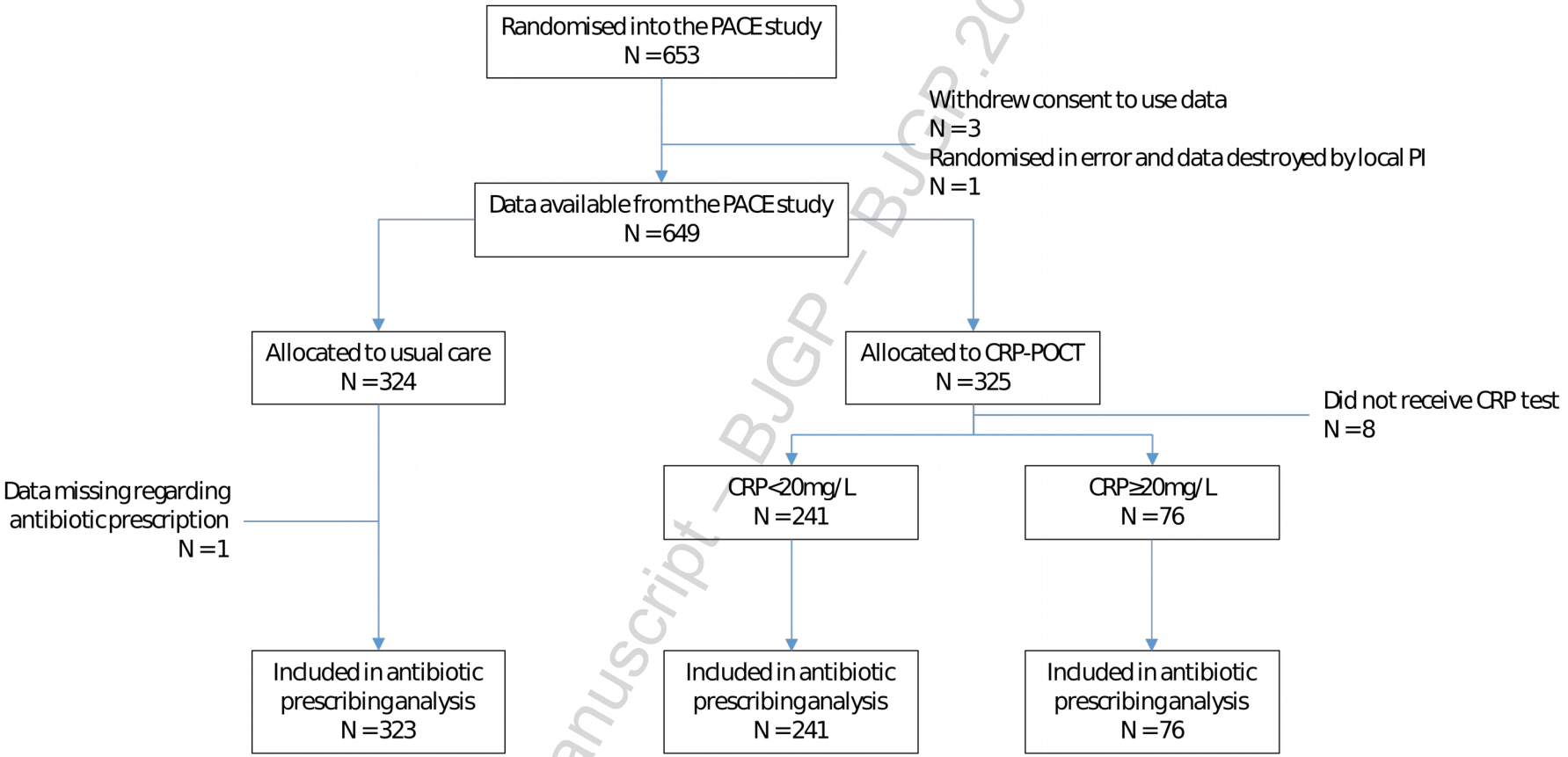

Table 1: Associations between demographic features, comorbid illness, symptoms, and signs and antibiotic prescribing at the index consultation

Variable		Adjusted odds ratio*	95% CI	p-value
Demographic features and comorbid illness				
Age (years) (n=640)		0.98	0.95 to 1.00	0.035
Gender (n=640)	Male	Ref		
	Female	1.17	0.77 to 1.78	0.472
Heart failure (n=640)		0.32	0.12 to 0.85	0.022
Chronic heart disease (n=640)		0.89	0.52 to 1.51	0.657
Diabetes (n=640)		1.43	0.81 to 2.50	0.215
Chronic kidney disease (n=640)		1.76	0.81 to 3.81	0.151
Hypertension (n=640)		1.02	0.66 to 1.56	0.934
Other chronic disease (n=581)		0.80	0.48 to 1.32	0.379
At least one co-morbid illness (n=625)		0.85	0.53 to 1.34	0.479
Smoking status (n=551)	Non-smoker	Ref		
	Current smoker	1.14	0.45 to 2.88	0.777
	Ex-smoker	1.08	0.45 to 2.59	0.867
COPD severity (n=551)	GOLD stage 1 (mild)	Ref		
	GOLD stage 2 (moderate)	1.52	0.83 to 2.81	0.179
	Gold stage 3 (severe)	1.62	0.81 to 3.27	0.176
	GOLD stage 4 (very severe)	1.15	0.43 to 3.10	0.782
Symptoms and signs				
Days with symptoms (per day) (n=640)		0.98	0.94 to 1.02	0.235
Increased breathlessness (n=640)		1.72	0.86 to 3.41	0.124
Increased sputum volume (n=640)		1.40	0.85 to 2.31	0.181
Sputum colour (n=568)	Sputum colour 1	Ref		
	Sputum colour 2	0.79	0.40 to 1.54	0.485
	Sputum colour 3	1.38	0.69 to 2.76	0.358
	Sputum colour 4	0.82	0.40 to 1.68	0.587
	Sputum colour 5	2.37	0.80 to 6.98	0.119
Crackles (n=640)		5.22	3.24 to 8.41	<0.001
Wheeze (n=640)		1.64	1.07 to 2.52	0.022

Diminished vesicular breathing (n=638)	2.95	1.70 to 5.10	<0.001
Evidence of consolidation (n=638)	34.40	2.84 to 417.27	0.005
Patient cannot complete a full sentence without stopping (n=581)	1.30	0.46 to 3.66	0.623
Patient is tachypnoeic (n=581)	1.30	0.70 to 2.43	0.405
Temperature (n=639)	1.33	0.87 to 2.04	0.186
Pulse rate (n=639)	1.01	0.99 to 1.03	0.250
Oxygen saturation (n=637)	0.96	0.89 to 1.05	0.397
Patient has been prescribed antibiotics in the past 12 months (n=597)	0.95	0.60 to 1.49	0.809

*Model adjusts for CRP measurement (CRP measurement not available, CRP < 20mg/L, CRP ≥ 20mg/L), the presence of sputum purulence, and the clustered nature of participants within practices.

Figure 2: Differential association between increased sputum volume and antibiotic prescribing by CRP measurement

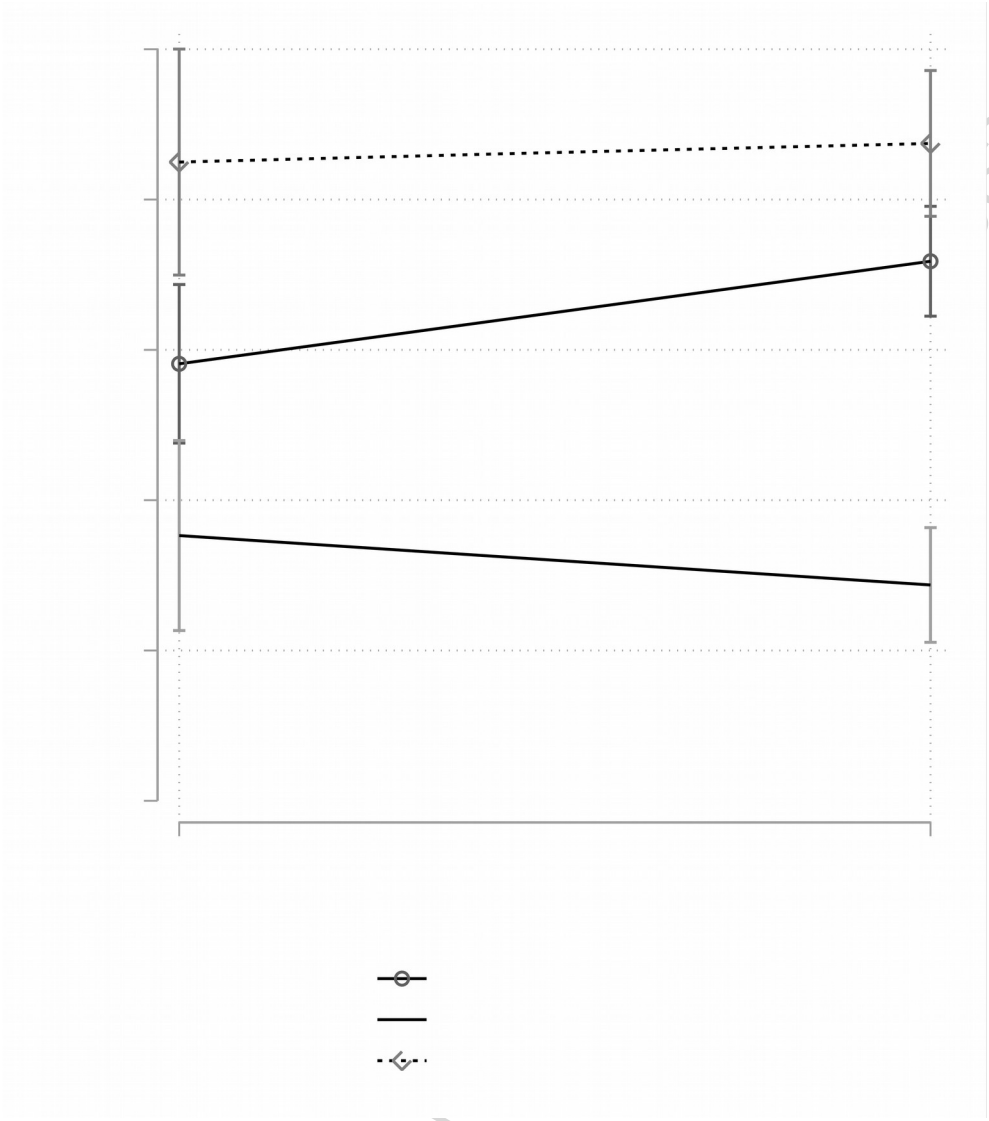

Figure 3: Differential association between reporting crackles on auscultation and antibiotic prescribing by CRP measurement