



Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection

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ABSTRACT: We investigated whether discoloured sputum and feeling unwell were associated with antibiotic prescription and benefit from antibiotic treatment for acute cough/lower respiratory tract infection (LTRI) in a prospective study of 3,402 adults in 13 countries.

A two-level model investigated the association between producing discoloured sputum or feeling generally unwell and an antibiotic prescription. A three-level model investigated the association between an antibiotic prescription and symptom resolution.

Patients producing discoloured sputum were prescribed antibiotics more frequently than those not producing sputum (OR 3.2, 95% CI 2.1–5.0), unlike those producing clear/white sputum (OR 0.95, 95% CI 0.61–1.48). Antibiotic prescription was not associated with a greater rate or magnitude of symptom score resolution (as measured by a 13-item questionnaire completed by patients each day) among those who: produced yellow (coefficient 0.00; $p=0.68$) or green (coefficient -0.01; $p=0.11$) sputum; reported any of three categories of feeling unwell; or produced discoloured sputum and felt generally unwell (coefficient -0.01; $p=0.19$).

Adults with acute cough/LRTI presenting in primary care settings with discoloured sputum were prescribed antibiotics more often compared to those not producing sputum. Sputum colour, alone or together with feeling generally unwell, was not associated with recovery or benefit from antibiotic treatment.

KEYWORDS: Acute cough, antibiotic resistance, antibiotic treatment, lower respiratory tract infection, primary care sputum

Acute cough is one of the most common reasons for consulting and for prescribing antibiotics in primary care [1–3]. Feasible clinical strategies are needed for more effective targeting of antibiotic treatment to those who will receive meaningful benefit in order to contain antimicrobial resistance, reduce cost, promote self-care and reduce unnecessary risk from side-effects [4, 5]. Physicians commonly ask their patients about the colour of their sputum and how unwell they are feeling to inform their decision of whether or not to prescribe an antibiotic for acute cough, based on the assumption that purulence is more likely to reflect a bacterial cause and predict improved outcomes from antibiotics [6–8]. Clinicians regard patients who feel both systemically unwell and who also

produce discoloured sputum an even higher priority for an antibiotic prescription [9–11]. Guidelines identify purulent sputum as one of a cluster of clinical features that should alert clinicians to possible serious lung infection [12]. Patients are also more likely to associate purulence with the need for antibiotic treatment [13, 14].

However, it is not clear which symptoms and clinical signs predict improved outcomes from antibiotic treatment, and the usefulness of sputum colour in predicting benefit from antibiotic treatment among patients with acute cough is controversial [15, 16]. Increasing diagnostic uncertainty is associated with increased unnecessary antibiotic prescription [17]. Therefore, using data from our large, prospective, observational

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study of the presentation, management and outcome of acute cough [3], we explored whether adult patients presenting to a general practice with acute cough who produced discoloured sputum and/or were feeling generally unwell were more likely to be prescribed antibiotics. We also examined whether symptom score resolution differed between these patients and those who did not produce discoloured sputum and/or were feeling generally unwell, and whether this was associated with antibiotic treatment.

MATERIALS AND METHODS

Study subjects

Eligible patients were aged ≥ 18 yrs and were presenting with an illness where an acute or worsened cough was the main or dominant symptom, or had a clinical presentation that suggested a lower respiratory tract infection (LRTI), with a duration of ≤ 28 days. We asked clinicians to attempt to enrol consecutive eligible patients from October to November 2006 and late January to March 2007. However, the networks were not able to ask clinicians to complete a log of all eligible patients. Ethical approval was obtained in each network.

Study design

This was a further analysis from a prospective observational study in 14 primary care networks in 13 European countries with clinicians recording symptoms on presentation and management. More details on this observational GRACE (Genomics to Combat Resistance Against Antibiotics in Community-Acquired LRTI in Europe; www.grace-lrti.org) study of acute cough have been reported elsewhere [3]. The objectives of the study were to investigate whether discoloured sputum and feeling unwell were associated with antibiotic prescription and predicted benefit from antibiotic treatment for acute cough. The study sample size was based on an estimate of a probability of 50% for certain events, such as treatment decisions (50% is the most conservative estimate of probabilities in statistical terms; more common or more rare events would give more power). This required a total sample size of 270 patients per network to give a 95% confidence interval of 44–56% for detecting that 50% probability within each network. This study uses all available data. The study was not, therefore, specifically powered for this analysis: we used all available data and provide confidence intervals for interpretation of the precision of our estimates.

Methods

Clinicians recorded aspects of patients' history, symptoms, comorbidities (diabetes, chronic lung disease including chronic obstructive pulmonary disease (COPD), cardiovascular disease and presence of asthma), clinical findings and management, including antibiotic prescription on a case report form (CRF). One of the symptoms that clinicians recorded was whether patients felt generally unwell. Clinicians rated whether this symptom constituted "no problem", a "mild problem", a "moderate problem" or a "severe problem" for the patient. Clinicians indicated the presence or absence of 13 other symptoms in the same way (cough, sputum production, shortness of breath, wheeze, coryza, fever during this illness, chest pain, muscle aching, headache, disturbed sleep, interference with normal activities, confusion/disorientation and diarrhoea). They were also asked to record the colour of the

patient's sputum (if present) as clear, white, yellow or green. Clear or white sputum was denoted normal, and yellow and green sputum was denoted discoloured. Clinicians were not routinely asked to check the patients' sputum colour themselves, as we wanted data to best represent everyday practice. Clinicians recorded their management, including antibiotic prescribing decisions for each patient.

Patients were given a symptom diary. They were asked to rate 13 symptoms each day until recovery (or for 28 days if symptoms were on going) on a seven-point scale comprising the following responses: "normal/not affected", "very little problem", "slight problem", "moderately bad", "bad", "very bad" and "as bad as it can be". This approach to outcome measurement has been used in other studies of acute cough/LRTI and has been found to be responsive to change and discrimination [18]. Patients rated the same symptoms as the clinicians except for confusion/disorientation and diarrhoea. They were, in addition, asked about interference with social activities. A patient-rated total symptom severity score was calculated by summing the scores for each symptom and scaling it so that it could be interpreted as a percentage symptom severity score.

The CRF and patient diary were translated into local languages and then back-translated into English for accuracy checks by the central study team. Final face-to-face validity checks were made with practicing bilingual clinicians.

Analysis

We used a two-level (patients nested within clinicians) logistic regression with antibiotic prescription as the outcome to investigate whether patients with discoloured sputum (yellow, green or yellow/green) or normal sputum were more likely to be prescribed antibiotics than those producing no sputum, and whether patients feeling generally unwell (comprising those who reported feeling mildly, moderately or severely unwell) were more likely to be prescribed antibiotics than those not feeling generally unwell.

A three-level (daily symptom scores nested within patients nested within clinicians) hierarchical ARMA (autoregressive part and a moving average) (1,1) model [19] was fitted to the log scale (to improve model fit) daily symptom scores to investigate whether patient subgroups had significantly different symptom severity at baseline and symptom score resolution over time. An ARMA (1,1) model expresses each observation as a combination of the two:

$$X_t = \epsilon_t + X_{t-1} + \epsilon_{t-1}$$

where X_t is the symptom severity score at time t , ϵ_t is the error term. This allows for each individual's symptom severity scores and the related error term to be correlated with the previous day. The subgroups were those: reporting yellow sputum; reporting green sputum; who felt mildly unwell; who felt moderately unwell; who felt severely unwell; and who had discoloured sputum (yellow or green) and felt generally unwell. The reference category for these analyses was those not producing sputum and who did not report feeling generally unwell. Interaction terms were fitted for each of these subgroups to investigate whether being prescribed an antibiotic was associated with a difference in symptom

resolution. This was investigated using a three-way interaction term between belonging to one of these subgroups, being prescribed an antibiotic and time measured in days.

These analyses controlled for clinical presentation by including patient information on 12 out of the 14 clinician-recorded symptoms (cough was excluded as it was present in 99.8% of cases and feeling generally unwell is one of the symptoms of interest), temperature, age, comorbidities (cardiovascular, respiratory including COPD, COPD alone, diabetes and asthma), the number of days waited before presentation, smoking status and network. We did not sum clinician ratings of symptoms into a scale. Comorbidities, including COPD and asthma, were ascertained by the treating clinician from their knowledge of the patient and the clinical record. Additional diagnostic tests were not performed for the purposes of this study. No imputation was performed on the patient-reported symptom scores.

In order to illustrate the differences in symptom resolution between subgroups and between those prescribed antibiotics or not within the subgroups, estimated patient-reported symptom scores on day 7 are presented for each of the subgroups, split by whether they were prescribed antibiotics or not. We performed sensitivity analyses to investigate differences in patient-reported symptom score resolution between those prescribed and those not prescribed antibiotics in three subgroups of patients with discoloured sputum who were also feeling generally unwell (*i.e.* those who also had COPD, those who also had asthma and those who were aged >65 yrs).

RESULTS

A total of 3,402 patients were recruited by 387 practitioners. Six networks included ≥ 270 patients, and all included >100. Four patients were later found to be ineligible and were therefore excluded from further analysis. CRFs were completed for 3,368 (99%) and diary data was obtained from 2,714 (80%) patients (fig. 1). Online supplementary table 1 shows the characteristics of included patients by network.

Patients who returned the diary data were generally older (median age 47 *versus* 36 yrs) and more frequently prescribed antibiotics (54 *versus* 46%), but were otherwise similar (table 1).

We analysed data from 2,419 patients with both useable CRF and patient diary data. The following variables had some missing values: phlegm production (n=75), shortness of breath (n=4), wheeze (n=6), coryza (n=11), fever (n=18), chest pain (n=7), muscle aching (n=11), headache (n=8), disturbed sleep (n=18), feeling generally unwell (n=13), interference in normal activities (n=13), confusion (n=4), diarrhoea (n=5), temperature (n=20), smoking status (n=3) and sputum colour (n=57). Of these, 638 (26.4%) were producing yellow sputum and 451 (18.6%) were producing green sputum, 1,940 (80.2%) were feeling generally unwell, and 897 (37.1%) were producing yellow or green sputum and also feeling generally unwell. 137 (5.7%) had COPD. Those who the clinician rated as feeling generally unwell (mild n=734, 30.3%; moderate n=947, 39.1%; severe n=259, 10.7%) also had higher self-rated symptom severity scores for day 1 of the self-completed diary compared with those for whom the clinician recorded that feeling generally unwell was "not a problem". This suggests that

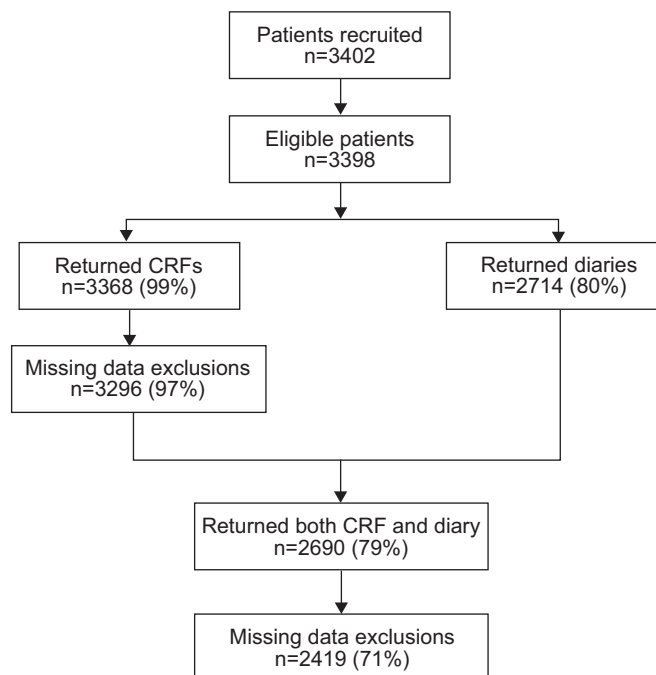


FIGURE 1. Patient flowchart. CRF: case report form.

clinicians' ratings of illness severity was congruent with patients' own assessments of the severity of their symptoms.

Those producing normal sputum were not prescribed antibiotics more frequently than those not producing sputum (OR 0.95, 95%

TABLE 1 Comparison of responders and nonresponders to the diary on key patient characteristics

	Responders	Nonresponders
Males	973 (36)	255 (38)
Age yrs	47 (35–60)	36 (27–48)
Temperature °C	36.8 (36.4–37.2)	36.7 (36.2–37.1)
Total clinician-recorded symptom severity score	26 (22–31)	27 (23–32)
Antibiotic prescription	1464 (54)	312 (46)
Comorbidity		
Respiratory	395 (15)	120 (18)
Diabetes	126 (5)	12 (2)
Cardiovascular	240 (9)	26 (4)
Discoloured sputum	1223 (45)	321 (47)
Yellow	689 (26)	150 (22)
Green	498 (19)	159 (23)
Blood-stained	36 (1)	12 (2)
Feeling generally unwell		
No problem	557 (21)	151 (22)
Mild problem	803 (30)	146 (22)
Moderate problem	1036 (39)	273 (40)
Severe problem	281 (10)	90 (13)
Patients	2690	678

Data are presented as n, n (%) or median (interquartile range).

CI 0.61–1.48). Those with discoloured sputum were more likely to be prescribed antibiotics compared with those not producing sputum (OR 3.2, 95% CI 2.1–5.0). Those feeling generally unwell (any category) were not prescribed antibiotics any differently than those not feeling generally unwell (overall $p=0.24$).

Online supplementary table 2 shows the symptom severity at baseline and symptom resolution over time for the various subgroups and whether this was associated with antibiotic treatment for both adjusted (adjusted for clinician-recorded symptoms, temperature, age, comorbidities, number of days waited before presentation and smoking status) and unadjusted models. The three subgroups of feeling generally unwell (mild, moderate or severe) were observed to have higher symptom severity at baseline and to recover slightly faster than those who were recorded as not feeling generally unwell. However, within these subgroups those treated with antibiotics were no different in terms of symptom severity or resolution compared to those not treated with antibiotics (supplementary table 2).

Sputum colour (yellow or green) was not associated with symptom severity at baseline or with resolution over time in the adjusted models. Moreover, producing discoloured sputum while also feeling generally unwell was not associated with symptom severity at baseline or resolution over time. All of this information is presented in the supplementary material.

Table 2 provides estimates of the differences in % symptom severity scores based on the coefficients presented in the supplementary material. These differences in symptom resolution were small (table 2), with the estimated symptom severity scores on day 7 ranging between 3.9% (green sputum group) and 5.1% (yellow/green and feeling severely unwell group) for those who were not prescribed antibiotics, and between 3.9% (yellow/green sputum and feeling mildly generally unwell) and 5% (yellow/green and feeling severely unwell group) for those who were. The differences between those who were and were not prescribed antibiotics were not statistically significant. The estimated symptom resolution for each subgroup is illustrated in figure 2.

Antibiotics were prescribed for 67.4% ($n=124$) of patients with COPD, 57.9% ($n=195$) of patients with asthma, and 54.5%

($n=265$) of patients aged >65 yrs. In these subgroups of patients, symptom resolution for patients with discoloured sputum who were also feeling generally unwell was not associated with antibiotic treatment (final three entries in supplementary table 2).

DISCUSSION

Summary of main results

This is the only large prospective study in a primary care setting to examine the relationship between sputum colour and/or feeling generally unwell and symptom resolution, and whether or not this was associated with antibiotic treatment. We found that adults presenting in primary care with an acute cough and who produced discoloured sputum were more likely to be prescribed antibiotics. However, we also found no clinically meaningful associations between sputum colour and/or feeling generally unwell with symptom resolution. Furthermore, symptom resolution was not associated with antibiotic treatment in patients with discoloured sputum who were also feeling generally unwell and those who belonged to both of these subgroups. The biggest difference between those who were and were not treated with antibiotics was less than one half of a percentage point on a symptom severity scale (table 2).

We have previously considered the relationship between antibiotic prescription in general and prescribing by antibiotic class with outcomes for all patients, and found no clinically meaningful association with patients' outcomes in this group [3, 20].

Strengths and weaknesses

An advantage of this observational study design is that treatment decisions were left up to the treating clinician, unlike in a randomised study, making our results more applicable to actual practice. Not requiring additional non-routine investigations also makes this study more applicable to everyday practice. Randomising patients with discoloured sputum to either receive or not receive antibiotic treatment could increase internal validity, but some patients might not wish to participate if they risk being randomised to a particular treatment or to placebo when they feel particularly unwell. Furthermore, there is some evidence that older patients may derive benefit from antibiotic treatment [21].

TABLE 2 Estimated patient recorded symptom scores (from patient diary data) for days 0 and 7 for subgroups of adult patients with acute cough stratified by whether they were prescribed antibiotics or not (from the three-level hierarchical autoregressive part and a moving average model)

	Day 0		Day 7	
	Not prescribed antibiotics	Prescribed antibiotics	Not prescribed antibiotics	Prescribed antibiotics
Yellow sputum	25.6	24.5	4.3	4
Green sputum	24.1	23.9	3.9	4
Yellow/green sputum and feeling generally unwell				
Mild	23.3	21.3	4.3	3.9
Moderate	24.9	24.9	4.5	4.5
Severe	28	29.1	5.1	5

Data are presented as symptom scores.

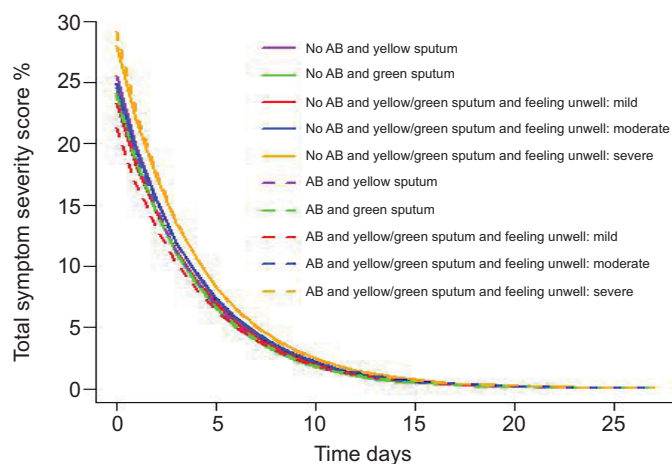


FIGURE 2. Estimated patient-recorded scaled symptom severity scores over 28 days after presentation for the subgroups of adult patients with acute cough from the three-level hierarchical autoregressive part and a moving average model. AB: antibiotic.

We did not attempt to infer causality from these data. Our analyses were designed to identify associations.

We included a large number of patients from a variety of primary care settings across Europe with close to complete ascertainment of baseline characteristics by clinicians and with an 80% return rate of patients' self-completed follow-up symptom diary data. We were able to control for several known possible confounders (illness severity at the time of the index consultation, standardised measurement of body temperature, patient age, number of days ill before the index consultation, diabetes, cardiovascular or respiratory (including COPD and asthma) comorbidities and smoking status). A wide range of physician-assessed symptoms and signs were individually included in our models. However, this observational design could not account for unknown confounders. The patients in this study represent the larger, but milder, end of the clinical spectrum of patients with acute cough, and the findings cannot be uncritically applied to patients with more severe lung disease, who, for example, may have well-defined acute exacerbations of COPD. However, our sensitivity analysis for the patients with COPD, those with asthma and those aged >60 yrs showed sputum colour while feeling generally unwell was not associated with benefit from antibiotic treatment. Therefore, in these subgroups of patients antibiotic treatment was not associated with greater rate or magnitude of symptoms resolution, even in those with discoloured sputum and who were feeling generally unwell (final three entries in supplementary table 2). We did not record data on sputum consistency. Sputum colour was determined, as is common in routine practice, by asking the patient rather than confirming colour using charts, which adds to applicability of findings to everyday primary care. We did not monitor change in sputum colour over time, as our goal was to explore the prognostic usefulness of sputum colour at the time of presentation. The clinicians who recruited patients also recorded data on them. Ideally, severity assessment would have been separated from management decisions, but it was not possible to have researchers at each participating practice,

which is usually the case with most primary care research of this nature. However, patient outcome was not assessed by recruiting clinicians and, as this was not a randomised study, ascertainment bias is unlikely. Clinicians did not keep a log of all eligible patients, those approached and the outcome as this was considered too burdensome in a pragmatic study. We only considered antibiotic treatment at the initial consultation in our analyses. As our main study questions related to associations between symptoms, antibiotic prescription and outcomes, patient adherence to antibiotic prescriptions were not considered in the analysis.

Comparison with existing literature

We found that patients presenting with acute cough in primary care who have discoloured sputum are more likely to be prescribed antibiotics than those not producing sputum or producing white sputum. This confirms previous findings that physicians are more likely to prescribe antibiotics to patients with presumed respiratory tract infections (RTIs) who produce purulent sputum. COENEN *et al.* [22] analysed data from 72 Flemish general practitioners (GPs) on the management of 1,448 patients with acute cough. The presence of sputum was associated with an increased risk of antibiotic prescription independent of patient and clinician characteristics (OR 2.5, 95% CI 1.62–3.92). FISCHER *et al.* [10] directly observed 30 GPs in Germany managing 237 patients with RTIs. Purulent sputum was associated with an increased chance of antibiotic prescription (OR 2.1, 95% CI 1.1–4.1). In another study from Germany, HUMMERS-PRADIER *et al.* [7] found increased antibiotic prescription for RTIs when patients had yellow or green sputum (OR 4.4, 95% CI 1.84–10.69). In the Netherlands, discoloured sputum was related to antibiotic treatment and was one of the reasons for overprescribing in LRTI [23]. In the USA, GONZALES *et al.* [24] found antibiotic prescription for upper RTI was increased when patients produced green sputum (OR 4.8, 95% CI 2.4–11.1) and DOSH *et al.* [25] found antibiotic prescription increased in association with smokers coughing up green or yellow sputum (OR 2.5, 95% CI 1.7–3.8). ALTINER *et al.* [26] obtained sputum samples from 241 patients with acute cough in primary care and found 136 of these were coloured yellow or greenish. Only 28 samples yielded pathogens on culture. The sensitivity of yellowish or greenish sputum as a test for bacterial infection was 0.79 (95% CI 0.63–0.94) and the specificity 0.46 (95% CI 0.038–0.53).

We know from a trial in volunteers that antibiotic-resistant oral streptococci persist for ≥ 180 days as a consequence of antibiotic exposure [27]. In that study, follow-up was for ≤ 28 days, so was unable to capture either possible harm from resistance or benefits from reducing bacterial colonisation and possible subsequent inflammation.

None of these studies explored the relationships between sputum colour and outcomes. We were not able to identify any previous large prospective studies examining the associations between sputum colour or feeling generally unwell and outcome, and whether or not this was associated with antibiotic treatment.

Previous trials have, however, showed no meaningful benefit from antibiotic treatment, on average, for patients consulting in primary care with acute cough and purulent sputum [18, 21, 28, 29].

The European Respiratory Society guidelines for the management of adult LTRIs recommend that for patients managed outside hospital, antibiotics should be considered only for those with suspected or definite pneumonia, selected exacerbations of COPD and in patients with acute bronchitis, and with age >75 yrs and fever, and/or cardiac failure, insulin dependent diabetes and serious neurological disorders [30]. The US Centers for Disease Control and Prevention Physician Information Sheet on Acute Cough Illness (Acute Bronchitis) recommends against empiric antibiotic treatment [31]. They cite evidence that >95% of patients with purulent sputum do not have symptoms of pneumonia [32].

Implications for policy and practice

This study focused on a broad category of adult patients, namely those with acute cough consulting in a broad range of general medical practice settings in Europe. The findings suggest that physicians should not rely on sputum colour, either on its own or in conjunction with patients feeling generally unwell, when deciding whether or not to prescribe an antibiotic for such patients. These data will have relevance to a large number of health care encounters. Acute cough is the largest single acute cause of consultation in primary care in the UK [1]. In the USA, there were about 10 million office visits for acute bronchitis in 1997 [33]. Implementing this evidence is likely to reduce antibiotic prescription for those with acute cough who are unlikely to benefit from antibiotic treatment and, thus, contribute to containing antibiotic resistance [26].

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CLINICAL TRIAL

This study is registered at ClinicalTrials.gov with identifier number NCT00353951.

STATEMENT OF INTEREST

Statements of interest for T. Schaberg, T. Verheij and A. Torres can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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