



Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis

Marc Miravittles*, Frank Kruesmann#, Daniel Haverstock¹, Renee Perroncel¹,
Shurjeel H. Choudhri⁺ and Pierre Arvis[§]

ABSTRACT: We examined the correlation between sputum colour and the presence of potentially pathogenic bacteria in acute exacerbations of chronic bronchitis (AECBs).

Data were pooled from six multicentre studies comparing moxifloxacin with other antimicrobials in patients with an AECB. Sputum was collected before antimicrobial therapy, and bacteria were identified by culture and Gram staining. Association between sputum colour and bacteria was determined using logistic regression.

Of 4,089 sputum samples, a colour was reported in 4,003; 1,898 (46.4%) were culture-positive. Green or yellow sputum samples were most likely to yield bacteria (58.9% and 45.5% of samples, respectively), compared with 18% of clear and 39% of rust-coloured samples positive for potentially pathogenic microorganisms. Factors predicting a positive culture were sputum colour (the strongest predictor), sputum purulence, increased dyspnoea, male sex and absence of fever. Green or yellow *versus* white sputum colour was associated with a sensitivity of 94.7% and a specificity of 15% for the presence of bacteria.

Sputum colour, particularly green and yellow, was a stronger predictor of potentially pathogenic bacteria than sputum purulence and increased dyspnoea in AECB patients. However, it does not necessarily predict the need for antibiotic treatment in all patients with AECB.

KEYWORDS: Acute exacerbations of chronic bronchitis, bacteria, chronic obstructive pulmonary disease, sputum colour

One of the most difficult decisions faced daily in primary care clinical practice is whether or not to prescribe an antimicrobial agent in patients with an exacerbation of chronic bronchial disease (*i.e.* chronic bronchitis, bronchiectasis or chronic obstructive pulmonary disease (COPD)). Such decisions are made empirically, based on clinical evidence. Overuse of antimicrobials in the community is clearly associated with an increased risk of the development of bacterial resistance [1]. A diagnostic tool that can be implemented at the point of care to identify patients who may be safely managed without an antimicrobial may reduce the occurrence of inappropriate prescribing.

ANTHONISEN *et al.* [2] reported that patients presenting with at least two of increased dyspnoea, sputum production and sputum purulence were more likely to recover if prescribed an antimicrobial *versus* those with only one of the symptoms. However, their study included individuals with severe and very severe COPD, and these criteria have never been validated in patients with nonobstructive chronic bronchitis. More recently, STOCKLEY *et al.* [3] observed that

purulent sputum alone, compared with mucoid sputum, was significantly associated with the presence of bacteria during an exacerbation. The change to a darker colour of sputum during an exacerbation is clinically detectable and would be consistent with increased neutrophil recruitment, indicative of a new or significant bacterial stimulus. This darkening of sputum colour represents the presence of myeloperoxidase, which is the green-coloured enzyme from neutrophil azurophil granules [3].

To provide further evidence that darker sputum colour is indicative of the presence of bacteria during acute exacerbations of chronic bronchitis (AECBs), data were collected from randomised clinical trial of moxifloxacin for the treatment of this condition. They were used in a pooled analysis to determine the correlation between sputum colour and the presence of a potentially pathogenic microorganism (PPM) in the sputum of patients with an AECB. All the studies had similar inclusion and exclusion criteria, and used the same questionnaire to record sputum colour and aspect. As previous investigations of sputum colour as a diagnostic marker were single-centre

AFFILIATIONS

*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Ciber de Enfermedades Respiratorias (CIBERES), Hospital Clínic, Barcelona, Spain.

#Bayer Schering Pharma, Leverkusen, Germany.

¹Bayer HealthCare Pharmaceuticals, Montville, NJ, USA.

⁺Bayer HealthCare Pharmaceuticals, Toronto, ON, Canada.

[§]Bayer Schering Pharma, Loos, France.

CORRESPONDENCE

M. Miravittles

Servei de Pneumologia

Hospital Clínic

Villarroel 170

08036 Barcelona

Spain

E-mail: marcm@separ.es

Received:

March 08 2011

Accepted after revision:

Oct 03 2011

First published online:

Oct 27 2011

European Respiratory Journal

Print ISSN 0903-1936

Online ISSN 1399-3003

studies [3–5], these data from many different centres in Europe and North America may provide new insights into the usefulness of sputum colour as an aid to treatment decisions in clinical practice in patients with an AECB of varying severity.

METHODS

Study design

Baseline data were pooled from six clinical trials with similar methodologies comparing moxifloxacin with other antimicrobials in patients with an AECB (table 1) to determine the relationship between infection and sputum colour [6–10]. All clinical trials were prospective, randomised, controlled, multi-centre studies conducted in Europe and North America.

Patients

Male and female patients aged >18 yrs with chronic bronchitis presenting with clinical symptoms of an exacerbation were eligible to join the studies. Inclusion criteria included type I Anthonisen exacerbations (all studies) or type II Anthonisen exacerbations (one study). A type I exacerbation was defined as the presence of increased dyspnoea, sputum production and sputum purulence [2]. Diagnosis of a type II Anthonisen exacerbation required two of these symptoms to be present. Chronic bronchitis was defined as daily production of sputum on most days for at least three consecutive months for more than two consecutive years [11]. Fever was assessed at inclusion in all studies. Exclusion criteria were significant renal or hepatic impairment; severe respiratory tract infection requiring parenteral antimicrobial therapy or mechanical ventilatory support; a diagnosis of pneumonia; unresolved chest malignancy; tuberculosis; cystic fibrosis; bronchiectasis; history of severe cardiac failure; pregnancy or lactation;

radiological evidence of bronchopulmonary infiltrates or the requirement for concomitant systemic antimicrobial therapy with agents not specified in the study protocols; allergy to fluoroquinolones, carboxyquinolone derivatives or comparator antimicrobials; a prolonged QTc interval or receipt of medication to increase the QTc interval; tendinopathy related to fluoroquinolones; any illness likely to lead to death within 6 months; receipt of systemic antimicrobial therapy for >24 h within 7 days of enrolment; or the receipt of any investigational drug within 30 days of enrolment.

All studies were conducted in accordance with the Declaration of Helsinki, and received appropriate approval from local ethical committees and regulatory authorities. Each patient provided written, informed consent before the start of the study. Individual patient data were obtained in all studies.

Microbiological assessment

In each study, sputum was collected before initiation of antimicrobial therapy (baseline). All sites and investigators used the same questionnaire to record sputum aspect, including sputum colour. All samples of sufficient quality were analysed by culture and Gram stain at each investigator's local laboratory. Only samples with <10 squamous cells per low-power field and >25 polymorphonuclear leukocytes per low-power field identified by Gram stain were included. The presence of PPMs (*Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis* and other *Haemophilus* spp.) was determined by culture.

Statistical analysis

All parameters related to the impact and treatment of an AECB were analysed using descriptive statistics. To define the utility

TABLE 1 Designs of the six studies included in the sputum analysis

Study number [ref.]	Design	Treatment (moxifloxacin and comparator) [#]	Patients n	Patients with a causative organism n
84 [6]	Prospective, multicentre, multinational, nonblind, randomised study in Europe	Moxifloxacin, 400 mg <i>q.d.</i> for 5 days; amoxicillin/clavulanate, 625 mg <i>t.i.d.</i> for 7 days	575	251
100033 [7]	Prospective, randomised, double-blind, multicentre study in the USA	Moxifloxacin, 400 mg <i>q.d.</i> for 5 days; moxifloxacin, 400 mg <i>q.d.</i> for 10 days; clarithromycin, 500 mg <i>b.i.d.</i> for 10 days	926	491
100034 [†]	Prospective, randomised, double-blind, multicentre study in the USA and Canada	Moxifloxacin, 400 mg <i>q.d.</i> for 10 days; moxifloxacin, 200 mg <i>q.d.</i> for 10 days; cefuroxime axetil, 500 mg <i>b.i.d.</i> for 10 days	682	274
100160 [8]	Prospective, randomised, double-blind, multicentre study in the USA and Canada	Moxifloxacin, 400 mg <i>q.d.</i> for 5 days; azithromycin, 250 mg <i>q.d.</i> (500 mg on day 1) for 5 days	567	280
100243 [9]	Prospective, randomised, double-blind, multicentre study in the USA	Moxifloxacin, 400 mg <i>q.d.</i> for 5 days; levofloxacin, 500 mg <i>q.d.</i> for 7 days	594	315
240017 [10]	Prospective, randomised, double-blind, multicentre study in Europe	Moxifloxacin, 400 mg <i>q.d.</i> for 5 days; clarithromycin, 500 mg <i>b.i.d.</i> for 7 days	745	287

[#]: all treatments were administered orally; [†]: data held on file by Bayer Schering Pharma.

of using green or yellow sputum colour as a diagnostic test for the presence of a PPM, the following diagnostic test statistics, including 95% confidence intervals were calculated for each of the six clinical trials: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio. Pooled estimates were calculated for sensitivity and specificity using the bivariate method [12]. As recommended by the Cochrane Collaboration [13], pooled estimates were not calculated for positive and negative predictive values because these depend on the underlying prevalence which varied somewhat across the six trials. Additionally, no pooled estimates for positive and negative likelihood ratios were calculated as recommended by ZWINDERMAN and BOSSUYT [14].

A logistic regression model was used to examine whether or not sputum colour was a statistically significant predictor of the presence of a microorganism. First, a stepwise logistic regression was performed using the following potential explanatory variables: sex, age group (<65 *versus* ≥65 yrs), long-term use of inhaled bronchodilators and/or corticosteroids, geographical region, study, sputum aspect (purulent, mucopurulent or mucoid), number of previous exacerbations, increase in dyspnoea, pre-treatment C-reactive protein (CRP) level and white blood cell count, presence of fever and duration of exacerbation before the study. In this stepwise procedure, each variable was added to the existing model, one at a time. If the p-value for the new variable was <0.05 (meaning that it was probably a significant predictor of microorganism presence even accounting for the other variables already in the model), it was added to the model. If a new variable was added, the overall model was run again; if any variable in the new model had a p-value >0.05, it was then dropped from the model. This step was followed for each of the potential variables. Once the stepwise procedure was complete, a final model was run with only the variables identified by the stepwise procedure. p-values, point estimates and 95% confidence intervals for the odds ratios were provided for each variable in the final model. The main purpose of the logistic regression model was to show that sputum colour is a significant predictor of PPM presence, even when adjusting for other important predictor variables in the model. A model with random study effects was fitted as a sensitivity analysis to confirm the findings from the model with fixed study effects.

RESULTS

Patient characteristics

A total of 4,089 patients provided a sputum sample. Patients were mainly male (55.0%), white (78.6%) and aged >45 yrs (74.8%) (table 2). Overall, 44.5% of patients had experienced three or more exacerbations in the previous year. While the characteristics of the overall population and patients with positive or negative cultures were generally similar, one notable difference was that patients with positive cultures were more likely to be past or current smokers than those with negative cultures (85.8% *versus* 75.4%, respectively; $p < 0.001$).

Sputum characteristics and microbiology

Of the 4,089 sputum samples, a colour was reported in 4,003 (97.9%) and 1,898 (46.4%) were culture-positive at baseline. Most patients had yellow (56.7%) or green (29.8%) sputum; a

further 466 patients had white (8.6%) or rust-coloured (2.8%) sputum (table 3). Following culture, 2,331 PPMs were found from the 1,898 samples.

Infecting organisms were most likely to be isolated from green or yellow sputum, with 58.9% and 45.5% of these samples, respectively, being bacteriologically positive (fig. 1). Patients with clear or white sputum were least likely to have a PPM (18.4%).

H. influenzae was the most frequently isolated organism in sputum of all colours (table 3). Green or yellow was the most commonly seen sputum colour where PPMs were present, followed by rust or white. The patterns of colours were similar for all species of PPMs isolated; therefore no specific colour can be associated with a given microorganism (fig. 2).

Having green or yellow sputum *versus* white sputum had a sensitivity for the presence of a PPM between 91.1% and 96.8% across trials, with a pooled estimate of 94.7%, and a specificity of between 4.7% and 24.4%, with a pooled estimate of 15.0%. The positive predictive value varied between 41.6% and 56.6%, and the negative predictive value between 65.2% and 87.9% across trials. All positive likelihood ratios across trials were >1 and the negative likelihood ratios were <1 (table 4).

Regression analysis: predicting bacterial infection from patient and sputum characteristics

In the logistic regression analysis, factors that predicted the presence of an infecting organism were sputum colour, sputum purulence, increased dyspnoea, male sex and absence of fever (table 5). Sputum colour was found to be a stronger predictor for the presence of a PPM than other factors (table 5), although all factors were significant. Chi-squared analysis of the null hypothesis ("no association between sputum colour and the presence of a PPM") gave a p-value of <0.001 (Chi-squared 108, three degrees of freedom) indicating a strong association between sputum colour and bacterial presence. The presence of bacteria was also strongly predicted by sputum purulence ($p < 0.001$, Chi-squared 27, four degrees of freedom). The model with random study effects confirmed that sputum colour is the strongest predictor for the presence of a PPM.

DISCUSSION

The present study has shown sputum colour to be the best marker for the presence of a PPM in sputum during an AECB compared with sputum aspect, dyspnoea or presence of fever. A PPM was isolated in 46.4% of samples from patients with a type I or II exacerbation, with almost 60% of culture-positive samples being from green sputum and only 18.4% from white sputum. Consistent with other studies [15], *H. influenzae* was the PPM most often isolated in our large series and we found no specific colour pattern for the different PPMs present in sputum samples.

The Anthonisen criteria (*i.e.* increased dyspnoea, sputum production and sputum purulence) have been considered the most reliable predictors of bacterial infection as a cause of an exacerbation, requiring antimicrobial treatment, for >20 yrs [2]. However, these criteria were described for COPD, with all patients having a forced expiratory volume in 1 s (FEV1) <80% predicted; in fact, the mean FEV1 was only 33% in the study by ANTHONISEN *et al.* [2], which represents a population with severe to very severe COPD. These criteria have never been

TABLE 2 Demographics of patients included in the sputum analysis

Characteristic	All patients	PPM positive	PPM negative	p-value [#]
Subjects n	4089	1898	2191	
Male sex %	55.0	61.0	49.8	<0.001
Age yrs	56 ± 15.3	55.3 ± 15.5	57.2 ± 15.0	<0.001
Exacerbations in previous year [†]	2.5 ± 1.9	2.4 ± 1.6	2.5 ± 2.1	0.614
Median (IQR) duration of exacerbation before study entry days	2 (5)	2 (5)	2 (6)	0.130
Past or present smoker [†]	3280 (80.2)	1629 (85.8)	1651 (75.4)	<0.001
Use of long-term bronchodilators or steroids	261 (6.4)	116 (6.1)	147 (6.7)	0.135
Median (IQR) CRP level [†] mg·L ⁻¹	0.70 (1.79)	0.69 (2.17)	0.71 (1.56)	0.551
Fever present	744 (18.2)	294 (15.5)	389 (20.5)	0.005

Data are presented as mean ± SD or n (%), unless otherwise stated. PPM: potentially pathogenic microorganism; IQR: interquartile range; CRP: C-reactive protein. [#]: PPM positive versus PPM negative; [†]: data were not collected for all patients in the study for these characteristics. Cochrane–Mantel–Haenszel test, adjusting for study, categorical variables, and using an ANOVA, also adjusting for study, for the continuous variables.

validated in simple, nonobstructive chronic bronchitis. Moreover, the most relevant advance in our ability to predict bacterial involvement in exacerbations of chronic bronchial disease was the observation that not all three criteria had the same predictive value. STOCKLEY *et al.* [3], with the aid of a colour chart, demonstrated that a change in sputum colour during the course of an exacerbation was a sensitive and specific marker for bacterial presence and was also predictive of a high bacterial load in bronchial secretions. These findings have been repeated by other groups [4, 5] and have been validated using more specific and sensitive sampling methods, such as the protected specimen brush technique in hospitalised patients. This method has demonstrated that a change in sputum purulence described by the patient had a sensitivity of 89.5% and a specificity of 76.2% for the presence of a PPM during the episode of exacerbation [16].

Our results agree with previous observations, demonstrating a relationship between darker sputum colour and higher frequency

of isolation of a PPM. We have extended the total number of observations by including a very large sample of patients from many centres in Europe and North America, including not only individuals with COPD but also those with nonobstructive chronic bronchitis. The results suggest that the yellow, and particularly green, sputum colour is a good marker for the presence of a PPM across the spectrum of chronic bronchial disease, including acute cough [17], stable COPD [18] and bronchiectasis [19].

One limitation of the present study is that, unlike in previous investigations [3–5], a standardised colour chart was not used. However, the consistency of the results in this large multinational sample suggests that sputum colour is easily recognised by physicians, and even by patients. In the study by SOLER *et al.* [16], the sputum samples were not seen by the investigators; their colour was described exclusively by the patients themselves and provided good diagnostic accuracy for the presence of PPMs.

TABLE 3 Commonly isolated potentially pathogenic microorganisms: number overall and proportion by sputum colour

Microorganism	Total isolates n	Samples containing specific pathogen [#] %			
		Yellow sputum	Green sputum	White sputum	Rust sputum
Samples of each colour [†] n		2319	1218	353	113
<i>Haemophilus influenzae</i>	605	14.1	20.0	10.6	5.9
<i>Streptococcus pneumoniae</i>	313	7.4	9.5	12.4	2.5
<i>Moraxella catarrhalis</i>	319	7.3	11.2	2.3	4.4
<i>Haemophilus parainfluenzae</i>	262	5.8	9.2	2.5	5.3
<i>Staphylococcus aureus</i>	158	3.4	5.4	1.7	5.3
<i>Klebsiella pneumoniae</i>	133	3.9	3.1	0.8	1.8
<i>Pseudomonas aeruginosa</i>	105	2.4	3.1	2.5	1.8
<i>Haemophilus spp.</i> [‡]	64	1.4	2.4	0.3	0.0
Negative culture [§]	2191	54.5	41.1	81.6	61.1

[#]: percentage of isolates of each species based on the total number of culture samples; [†]: one sample obtained per patient; [‡]: *Haemophilus spp.* other than *H. influenzae* and *H. parainfluenzae*; [§]: total number of negative cultures.

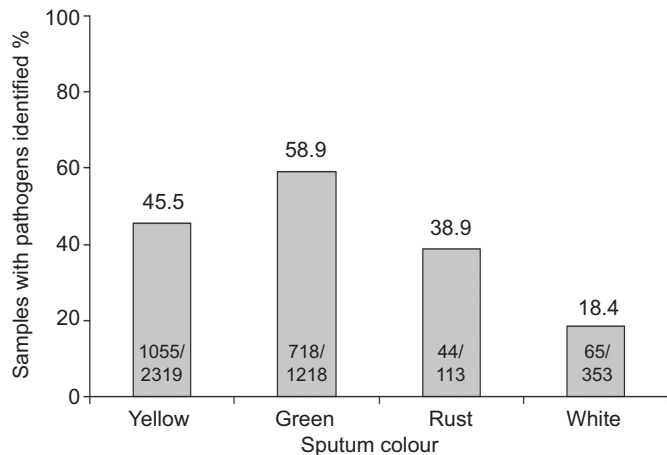


FIGURE 1. Percentage of sputum samples with an identified pathogen according to sputum colour. Data in the bars are presented as n/N.

Information about sputum purulence was also collected. Purulence is strongly related to colour, but is even more subjective. In prospective studies, mucoid sputum is usually described as colourless to white, and purulent sputum as ranging from pale yellow to dark green [20]. We found a significant and consistent relationship between purulence and the presence of a PPM in sputum, although it had less predictive value than the colour of the sample.

The second limitation of the present study is that only patients with type I and II exacerbations were included because the population comprised candidates in an antimicrobial trial in AECBs. We were able to demonstrate the relationship between sputum colour and the presence of a PPM studying only patients with a high probability of bacterial exacerbation. It is likely that extending the study to include patients with type III exacerbations, even with the same severity of the underlying disease [21], would show an even stronger relationship between sputum colour and bacterial infection. This is reflected in the

low specificity observed in our study (15%). This is probably due to the very low number of patients with white sputum in our sample, because only one of the trials enrolled patients with a type II exacerbation (*i.e.* patients who could potentially have white sputum). Our results show greater similarity to those observed by DANIELS *et al.* [22], who reported a sensitivity and specificity of 70% and 39%, respectively, for reported sputum colour, but contrary to our study, up to one-third of their patients had mucoid sputum. An important implication of our results is that white sputum is a good predictor of a negative sputum culture, and it may help prevent the use of antibiotics in those patients unlikely to benefit.

The results obtained in our selected population of patients fulfilling the inclusion criteria of clinical trials may not be extrapolated to a more heterogeneous population of patients with chronic bronchitis in primary care. However, our results are consistent with those of other studies performed in patients in usual clinical practice, with different degrees of severity [3–5, 16, 18].

No information was collected about viral infection. Viruses may be isolated in up to 45% of exacerbations of severe COPD, either alone or together with bacteria [23]. Viral exacerbations in COPD are likely to be present with fever [24]. The presence of fever was consistently significantly associated with a lower probability of bacterial isolation in our patients, suggesting again that febrile exacerbations are more likely to be related to viruses. In another study, febrile exacerbations of COPD were not significantly associated with purulent sputum compared with exacerbations without fever [25].

Plasma CRP level did not predict the presence of a PPM in sputum. A previous study indicated that point-of-care testing for CRP in lower respiratory tract infections in primary care significantly reduced antimicrobial prescribing without compromising patient recovery [26]. However, the patients had mild disease and a mean age of 50 yrs, and only 7% had a diagnosis of COPD. In individuals with more severe disease, GOMPertz *et al.* [20] and STOCKLEY *et al.* [3] reported

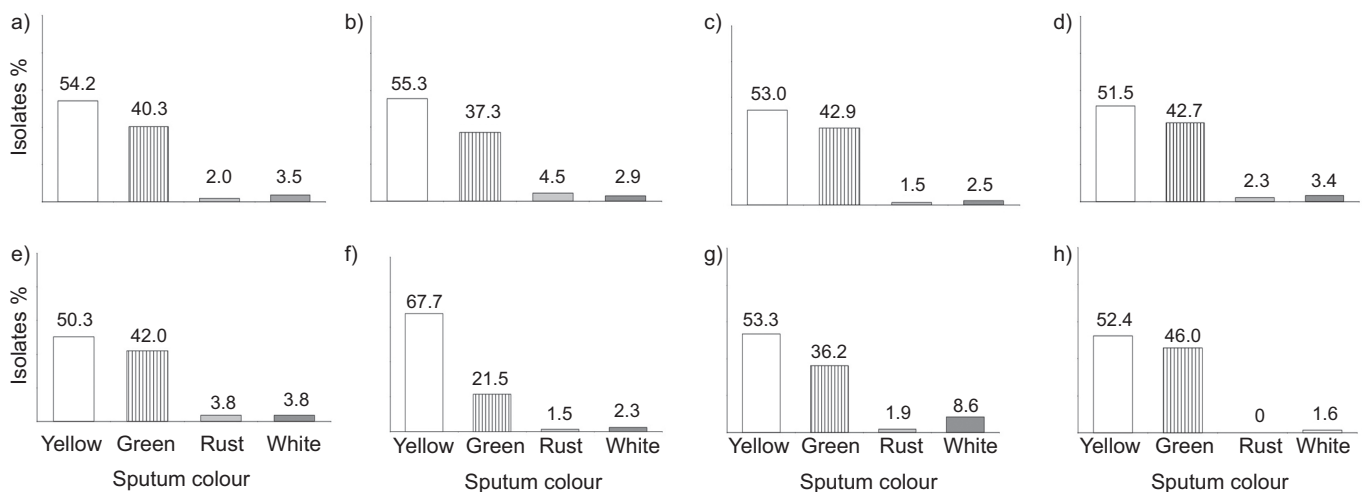


FIGURE 2. Distribution of sputum colour by infecting species. a) *Haemophilus influenzae*, b) *Streptococcus pneumoniae*, c) *Moraxella catarrhalis*, d) *Haemophilus parainfluenzae*, e) *Staphylococcus aureus*, f) *Klebsiella pneumoniae*, g) *Pseudomonas aeruginosa* and h) *Haemophilus spp.*

TABLE 4 Performance parameters of the colour of sputum in the diagnosis of the presence of a potential pathogenic microorganism by study

Study number [ref.]	Sensitivity %	Specificity %	PPV %	NPV %	PLR	NLR
84 [6]	96.8 (93.8–98.6)	4.6 (2.6–7.6)	44.1 (39.3–48.4)	65.2 (42.7–83.6)	1.02 (0.98–1.05)	0.68 (0.30–1.59)
100033 [7]	91.8 (88.9–94.0)	19.2 (15.6–23.3)	56.6 (53.1–60.1)	66.9 (57.8–75.2)	1.14 (1.08–1.20)	0.43 (0.30–0.61)
100034[#]	95.3 (92.0–97.5)	24.4 (20.2–29.0)	47.0 (42.8–51.3)	88.0 (80.3–93.4)	1.26 (1.18–1.34)	0.19, (0.11–0.34)
100160 [8]	96.8 (93.9–98.5)	16.5 (12.3–21.5)	54.1 (49.6–58.6)	83.3 (97.7–92.10)	1.16 (1.09–1.23)	0.20 (0.10–0.39)
100243 [9]	95.6 (92.7–97.6)	13.6 (9.7–18.2)	56.1 (51.7–60.3)	72.6 (58.3–84.1)	1.11 (1.05–1.17)	0.33 (0.18–0.59)
240017 [10]	91.1 (87.2–94.2)	18.9 (15.4–22.9)	41.6 (37.6–45.6)	77.1 (68.0–84.6)	1.12 (1.06–1.19)	0.47 (0.31–0.72)
Pooled	94.8 (92.1–97.4)	15.0 (6.7–23.3)	NC	NC	NC	NC

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; NC: not calculated. [#]: data held on file by Bayer Schering Pharma.

significantly higher concentrations of CRP in patients with purulent compared with mucoid exacerbations; the patients with positive sputum cultures in the present study also had higher (although not significantly higher) concentrations of CRP. Perhaps the inclusion of patients with type III exacerbations would have made this difference more evident. In multivariate analysis, CRP was not predictive of the presence of a PPM in sputum; in a systematic review, testing for CRP was consistently neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate on chest radiography and a bacterial aetiology of lower respiratory tract infection [27]. In the field of biomarkers, measurement of procalcitonin level shows promise as a means of identifying

patients with exacerbations of COPD who require antimicrobial treatment [28].

The fourth limitation of our study was the use of sputum culture as the marker for bacterial involvement in the aetiology of the exacerbation. It is well known that a negative sputum culture does not rule out bacterial infection [29]. In fact, studies using invasive techniques in more severe, hospitalised patients, such as the protected specimen brush method, have demonstrated the high prevalence of bacteria in patients with coloured sputum [16], which is more reliable than the percentage of positive cultures. More importantly, these studies have demonstrated the high accuracy of using mucoid sputum to rule out bacterial infection [3, 16]. Clearly, it is not feasible to use invasive diagnostic techniques in routine clinical practice, and sputum sampling is yet irreplaceable in the diagnostic approach to lower respiratory tract infections in the community. However, it should be noted that the presence of a PPM in the sputum does not confirm its role as a cause of an exacerbation and does not necessarily imply that antibiotic therapy will be beneficial in aiding resolution of the exacerbation.

TABLE 5 Regression analysis of significant factors predicting the presence of potentially pathogenic microorganisms in sputum

Variable	Wald Chi-squared	p-value	OR point estimate (95% CI)
Sputum colour	108.4	<0.001	
Yellow versus white			3.2 (2.3–4.2)
Green versus white			4.9 (3.6–6.8)
Rust versus white			2.3 (1.4–3.7)
Study	32.7	<0.001	
84 versus 240017 [6, 10]			1.0 (0.8–1.3)
100033 versus 240017 [7, 10]			1.6 (1.3–2.0)
100034 [#] versus 240017 [10]			1.1 (0.8–1.3)
100160 versus 240017 [8, 10]			1.3 (1.0–1.6)
100243 versus 240017 [9, 10]			1.4 (1.1–1.9)
Sputum aspect	27.0	<0.001	
Purulent versus mucoid			2.0 (1.6–2.5)
Purulent versus mucopurulent			1.1 (1.0–1.2)
Dyspnoea	6.6	0.036	
Increased versus not increased			1.27 (1.1–1.5)
Sex	40.7	<0.001	
Male versus female			1.5 (1.3–1.8)
Fever	14.8	0.001	
Absent versus present			1.3 (1.1–1.6)

[#]: data held on file by Bayer Schering Pharma.

Conclusion

This pooled analysis of clinical trial results in AECB showed sputum colour to be a stronger predictor of the presence of a PPM than other factors, including sputum purulence and increased dyspnoea. The greatest association between sputum colour and bacterial presence was found with darker (green and yellow) sputum. The change in colour of sputum in the course of an exacerbation can be used in self-management plans [30, 31], leading to early antimicrobial therapy that may reduce the duration of the exacerbation and improve outcomes [32, 33]. In addition, avoiding the use of antimicrobials to treat exacerbations when sputum is white will reduce inappropriate antibiotic prescribing in the community and help slow down the development of bacterial resistance [1].

SUPPORT STATEMENT

This study was funded by Bayer Schering Pharma. Highfield Communication Consultancy, funded by Bayer Schering Pharma, provided editorial assistance in the preparation of this manuscript.

STATEMENT OF INTEREST

Statements of interest for all authors and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

- 1 Goossens H, Ferech M, Vander Stichele R, *et al.* Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365: 579–587.
- 2 Anthonisen NR, Manfreda J, Warren CPW, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
- 3 Stockley RA, O'Brien C, Pye A, *et al.* Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117: 1638–1645.
- 4 Johnson AL, Hampson DF, Hampson NB. Sputum color: potential implications for clinical practice. *Respir Care* 2008; 53: 450–454.
- 5 Allegra L, Blasi F, Diano PL, *et al.* Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 742–747.
- 6 Schaberg T, Ballin I, Huchon G, *et al.* A multinational, multicentre, non-blinded, randomized study of moxifloxacin oral tablets compared with co-amoxiclav oral tablets in the treatment of acute exacerbation of chronic bronchitis. *J Int Med Res* 2001; 29: 314–328.
- 7 Chodosh S, DeAbate CA, Haverstock D, *et al.* Short-course moxifloxacin therapy for the treatment of acute bacterial exacerbations of chronic bronchitis. *Respir Med* 2000; 94: 18–27.
- 8 DeAbate CA, Mathew CP, Warner JH, *et al.* The safety and efficacy of short course (5-day) moxifloxacin *vs.* azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. *Respir Med* 2000; 94: 1029–1037.
- 9 Hautamaki D, Bruya T, Kureishi A, *et al.* Short-course (5-day) moxifloxacin *versus* 7-day levofloxacin therapy for treatment of acute exacerbations of chronic bronchitis. *Today's Ther Trends* 2002; 19: 117–136.
- 10 Wilson R, Kubin R, Ballin I, *et al.* Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1999; 44: 501–513.
- 11 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77–S121.
- 12 Reitsma JB, Glas AS, Rutjes AW, *et al.* Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; 58: 982–990.
- 13 Macaskill P, Gatsonis C, Deeks JJ, *et al.* Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* Version 1.0. Oxford, The Cochrane Collaboration, 2010.
- 14 Zwinderman AH, Bossuyt PM. We should not pool diagnostic likelihood ratios in systematic reviews. *Stats Med* 2008; 27: 687–697.
- 15 Miravittles M, Espinosa C, Fernández-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999; 116: 40–46.
- 16 Soler N, Agustí C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 62: 29–35.
- 17 Altiner A, Wilm S, Däubener W, *et al.* Sputum colour for diagnosis of a bacterial infection in patients with acute cough. *Scand J Prim Health Care* 2009; 27: 70–73.
- 18 Miravittles M, Marin A, Monsó E, *et al.* Colour of sputum is a marker for bacterial colonisation in chronic obstructive pulmonary disease. *Respir Res* 2010; 11: 58.
- 19 Murray MP, Pentland JL, Turnbull K, *et al.* Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34: 361–364.
- 20 Gompertz S, O'Brien C, Bayley DL, *et al.* Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001; 17: 1112–1119.
- 21 Miravittles M, Anzueto A, Ewig S, *et al.* Characterization of exacerbations of chronic bronchitis and COPD in Europe. The GIANT study. *Ther Adv Respir Dis* 2009; 3: 267–277.
- 22 Daniels JMA, de Graaf CS, Vlaspoolder F, *et al.* Sputum colour reported by patients is not a reliable marker of the presence of bacteria in acute exacerbations of chronic obstructive pulmonary disease. *Clin Microbiol Infect* 2010; 16: 583–588.
- 23 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: 1114–1121.
- 24 McManus TE, Marley AM, Baxter N, *et al.* Respiratory viral infection in exacerbations of COPD. *Respir Med* 2008; 102: 1575–1580.
- 25 Lieberman D, Shmarkov O, Gelfer Y, *et al.* Prevalence and clinical significance of fever in acute exacerbations of chronic obstructive pulmonary disease. *Eur J Clin Microbiol Infect Dis* 2003; 22: 75–78.
- 26 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; 338: b1374.
- 27 Van der Meer V, Neven AK, van den Broek PJ, *et al.* Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005; 331: 26–29.
- 28 Stolz D, Christ-Crain M, Bingisser R, *et al.* Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007; 131: 9–19.
- 29 Murphy TF, Brauer AL, Schiffmacher AT, *et al.* Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 266–272.
- 30 Bourbeau J, Julien M, Maltais F, *et al.* Reduction of hospital utilization in patients with chronic obstructive pulmonary disease. A disease-specific self-management intervention. *Arch Intern Med* 2003; 163: 585–591.
- 31 Rice KL, Dewan N, Bloomfield HE, *et al.* Disease management program for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 182: 890–896.
- 32 Wilkinson TMA, Donaldson GC, Hurst JR, *et al.* Early treatment improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 1298–1303.
- 33 Aburto M, Esteban C, Moraza FJ, *et al.* COPD exacerbation: mortality prognosis factors in a respiratory care unit. *Arch Bronconeumol* 2011; 47: 79–84.