Sputum colour reported by patients is not a reliable marker of the presence of bacteria in acute exacerbations of chronic obstructive pulmonary disease

J. M. A. Daniels[1], C. S. de Graaff[1], F. Vlaspolder[2], D. Snijders[1], H. M. Jansen[3] and W. G. Boersma[1]

1) *Department of Pulmonary Diseases,* 2) *Department of Microbiology, Medical Centre Alkmaar, Alkmaar and* 3) *Department of Pulmonary Diseases, Amsterdam Medical Centre, University of Amsterdam, Amsterdam, The Netherlands*

Abstract

Sputum colour is regarded as a good marker of bacterial involvement in acute exacerbations of chronic obstructive pulmonary disease (COPD) and guides many physicians in deciding on antibiotic treatment. Although most doctors rely on the sputum colour that is reported by patients, it can also be assessed using a validated colour chart. In this study, reported sputum colour and assessed sputum colour were compared as markers of the presence of bacteria, bacterial load, and systemic inflammation. Data on 257 exacerbations in 216 patients hospitalized with an acute exacerbation were analysed (mean age, 72 years; mean forced expiratory volume in 1 s, 44.8% ± 17.8% (± standard deviation)). Sputum colour was reported by the patients and assessed at the laboratory with a colour chart. Subsequently, quantitative sputum cultures were performed. C-reactive protein was measured as a marker of systemic inflammation. A sputum sample was obtained in 216 exacerbations (84%), of which 177 (82%) were representative. A pathogen was identified in 155 patients (60%). Assessed sputum colour was a better marker of the presence of bacteria (OR 9.8; 95% CI 4.7–20.4; p <0.001) than reported sputum colour (OR 1.7; 95% CI 1.0–3.0; p 0.041). The sensitivity and specificity were 73% and 39% for reported sputum colour, and 90% and 52% for assessed sputum colour. Assessed sputum colour was clearly related to sputum bacterial load and C-reactive protein levels, whereas reported sputum colour was not. It is concluded that sputum colour reported by patients is an unreliable marker of the presence of bacteria in acute exacerbations of COPD. Assessed sputum colour is clearly superior and is also related to bacterial load and systemic inflammation.

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Corresponding author and reprint requests: J. M. A. Daniels, Department of Pulmonary Diseases, VU University Medical Centre, PO Box 7057, 1007 MB, Amsterdam, The Netherlands
E-mail: j.daniels@vumc.nl

Introduction

Chronic obstructive pulmonary disease (COPD) constitutes a major health problem. Acute exacerbations of COPD (AECOPDs) have considerable impact on morbidity, mortality, and quality of life [1,2]. The hallmark of acute exacerbations is an increase in airway inflammation, which can by triggered by a viral or bacterial infection or changes in environmental conditions such as air pollution. This increased inflammation causes frequently reported symptoms such as increased sputum volume and changes in sputum colour.

While studying the efficacy of antibiotics in acute exacerbations, Anthonisen *et al.* [3] attempted to classify exacerbations according to severity. A type 1 AECOPD is defined by the triad of increased dyspnoea, sputum volume, and sputum purulence. In a type 2 AECOPD, two of these symptoms are present. Type 3 AECOPD is characterized by one of these three symptoms in addition to one of the following: upper respiratory infection within the past 5 days; fever without a cause; increased wheezing; increased cough; or a 20% increase in respiratory or heart rate as compared with baseline. Antibiotics were particularly effective in type 1 exacerbations [3]. Since this study, sputum colour has been used as a marker for bacterial infection, and guides many physicians in deciding whether to prescribe antibiotics. Unfortunately,

no microbiological analysis was performed in their trial [3]. Whereas Antonisen *et al.* [3] used change of sputum colour, other investigators assessed the colour of sputum with a colour chart on the day of consultation [4,5]. Although these studies show that a sputum colour chart can be a valuable tool with which to predict bacterial involvement, most physicians make therapeutic decisions according to the sputum colour that is reported by patients.

The aim of this study was two-fold: first, to compare sputum colour reported by patients with sputum colour assessed with a colour chart as markers of bacterial presence in AECOPD; and second, to investigate whether reported and assessed sputum colour are related to bacterial load and systemic inflammation (C-reactive protein (CRP)).

Materials and Methods

Population

Data from 257 exacerbations from 216 patients admitted for AECOPD at the Medical Centre Alkmaar, The Netherlands who were enrolled in a randomized trial from August 2002 to September 2007 were analysed. The goal of that placebo-controlled trial was to assess the efficacy of doxycycline in patients hospitalized with AECOPD. Patients aged 45 years or older with COPD, stage I–IV according to the GOLD classification [6], presenting with an acute (≤14 days in duration) exacerbation of Anthonisen type I (increased dyspnoea, sputum volume, and sputum purulence) [3] or type 2 (two of three symptoms), and requiring hospitalization were screened. Exclusion criteria included inability to take oral medication, fever (≥38.5°C), antibiotic treatment for ≥24 h, steroid treatment (>30 mg of prednisolone equivalent for more than 4 days), new abnormalities upon chest radiograph, history of severe AECOPD requiring mechanical ventilation, recently diagnosed or unresolved lung malignancy, other infectious diseases requiring antibiotic therapy (e.g. sinusitis), congestive heart failure (NYHA III–IV), apparent immunodeficiency (e.g. AIDS or immunosuppressive drugs), and impaired renal function (creatinine clearance, <20 mL/min). Criteria for hospital admission were adapted from the GOLD workshop summary 2001 [6]. All patients provided written informed consent, and the study was approved by the local medical ethics committee.

Data collection

Upon admission, sputum colour was recorded as reported by the patient (referred to as 'reported sputum colour' hereafter). White or grey reported colour was interpreted as mucoid sputum, whereas yellow or green reported colour was interpreted as purulent. A freshly expectorated sputum sample and a serum sample were acquired on the first day of admission. Patients were instructed to rinse their mouth with water before expectorating. The sputum sample was stored in a refrigerator (4°C) before transport to the laboratory. Further specimen collection and handling was in accordance with the guidelines of the American Society for Microbiology [7]. At the laboratory for microbiology, sputum colour was assessed with a previously validated five-point sputum colour chart (BronkoTest; Heredilab Inc., Salt Lake City, UT, USA) by one of two specifically instructed analysts. Colours 1 and 2 are regarded as non-infective and colours 3–5 as infective (referred to as 'assessed sputum colour' hereafter). Gram stain was performed, and sputum quality was assessed according to the Bartlett criteria [8]. A sputum sample with >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field was defined as a sputum sample representative of the lower airways. Subsequently, quantitative cultures were performed. Bacterial infection was defined as the presence of a potential pathogen in a representative sputum sample. Serum CRP (Beckman Coulter Inc., Fullerton, CA, USA) was measured as a marker of systemic inflammation.

Statistical analysis

Data are presented as mean ± standard deviation unless stated otherwise. Differences among groups were determined using the chi-Square test or Fisher exact test for nominal variables, Student's *t*-test for normally distributed interval variables, and the Mann–Whitney *U*-test for non-normally distributed variables. Bayesian analysis was performed, with the calculation of sensitivity, specificity, positive predictive value and negative predictive value.

Results

Patients

In the original randomized trial, 265 patients with an exacerbation were enrolled. Eight patients with exacerbation were not included in the current analysis: two were enrolled at another centre, two had asthma rather than COPD, two did not meet the lung function criteria for the diagnosis of COPD, one had a myocardial infarction, and one had community-acquired pneumonia. We evaluated 257 exacerbations in 216 patients (Table 1). The mean stable state forced expiratory volume in 1 s was 44.8% ± 17.8% of the predicted value.

Sputum purulence was reported in 175 exacerbations (68%), and mucoid sputum was reported in 82 exacerbations (32%). The mean duration of the exacerbation prior to

TABLE 1. Baseline characteristics of 257 cases of exacerbation in 218 patients

Characteristics	Data
Sex, *n* (%)	
Male	146 (57)
Female	111 (43)
Age (years)	72.0 ± 9.3
FEV_1 (% predicted)	44.8 ± 17.8
GOLD stage, *n* (%)[a]	
I (FEV_1 ≥ 80% of predicted)	9 (4)
II (FEV_1 ≥50% of predicted and <80% of predicted)	83 (32)
III (FEV_1 ≥30% of predicted and <50% of predicted)	100 (39)
IV (FEV_1 <30% of predicted)	65 (25)
Smoker, *n* (%)	232 (90)
Recent smoker[c], *n* (%)	75 (29)
Pack years	39.9 ± 24.1
Sputum colour reported by patients, *n* (%)	
Mucoid	82 (32)
Purulent	175 (68)
Duration of AECOPD (days)	5.8 ± 3.7
P_aO_2 (mmHg)	68.6 ± 13.5
P_aCO_2 (mmHg)	42.7 ± 9.4
ICS treatment prior to admission, *n* (%)	209 (81)
SCS treatment prior to admission, *n* (%)[b]	74 (29)
Serum CRP (mg/L)	55.5 ± 68.1

Values are listed as mean ± SD unless stated otherwise.
FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; SCS, systemic corticosteroid; CRP, C-reactive protein.
[a]Based on the last recorded value in a stable state.
[b]Oral steroid treatment for 2 weeks preceding admission.
[c]A person who smokes daily or occasionally in the last six months.

admission was 5.8 ± 3.7 days. Eighty-one per cent of patients were treated with maintenance inhaled corticosteroids, and 29% had been treated with systemic corticosteroids for the current exacerbation. The mean serum CRP level was 55.5 ± 68.1 mg/L.

Sputum samples

A sputum sample was obtained in 216 of 257 exacerbations (84%), and 177 (82%) of these were found to be representative of the lower airways (Table 2). According to the sputum colour charts, 168 sputum samples (78%) were purulent (Table 2). Agreement between reported and assessed sputum colour was observed in 148 (69%) of 215 exacerbations. One or more potential pathogens were identified in 155 exacerbations (60%). *Haemophilus influenzae* was the predominant primary pathogen (52%), followed by *Streptococcus pneumoniae* (19%) and *Moraxella catarrhalis* (19%).

Markers of bacterial infection

Bacteria were found in 51% of patients with reported mucoid sputum and in 65% of patients with reported purulent sputum (OR 1.7, 95% CI 1.0–3.0, p 0.041) (Table 3). There was a greater difference in bacterial isolation rates between assessed sputum colours, as bacterial cultures were positive in 32% of mucoid and 82% of purulent sputum samples (OR 9.8, 95% CI 4.7–20.4, p <0.001). The sensitivity and specificity for reported sputum colour were 73% and 39%, respectively. The sensitivity and specificity for assessed sputum colour were 90% and 52%, respectively.

TABLE 2. Sputum colour and cultures, *n* = 216

	n (%)
Sputum colour assessed with a colour chart	
Mucoid	
1	13 (6)
2	34 (16)
Total	47 (22)
Purulent	
3	65 (30)
4	63 (29)
5	40 (19)
Total	168 (78)
Missing data	1
Sputum sample quality[a]	
Representative	177 (82)
Not representative	39 (18)
Bacterial pathogen identified	
Yes	155 (60)
No	102 (40)
Primary pathogen (only pathogen or pathogen with the highest bacterial load)	
Haemophilus influenzae	80 (52)
Streptococcus pneumoniae	30 (19)
Moraxella catarrhalis	30 (19)
Pseudomonas spp.	6 (4)
Haemophilus parainfluenzae	5 (3)
Staphylococcus aureus	1 (0.6)
Escherichia coli	1 (0.6)
Chlamydophila pneumoniae	1 (0.6)
Mycoplasma pneumoniae	1 (0.6)

[a]A sample with >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field in a Gram-stained sputum was defined as a representative sputum sample.

TABLE 3. Test characteristics of sputum colour reported by patients and assessed sputum colour (colour chart [4]) as markers for bacterial infection

	Sputum colour reported by patients	Sputum colour assessed with a colour chart
Sensitivity (%)	73	90
Specificity (%)	39	52
PPV (%)	65	82
NPV (%)	49	68
OR (95% CI)	1.7 (1.0–3.0) p 0.041	9.8 (4.7–20.4) p <0.001

PPV, positive predictive value; NPV, negative predictive value.

Bacterial load

The mean bacterial load of the isolated primary pathogens was 7.6 ± 1.4 CFU/mL. A significant difference in log bacterial load was observed between purulent and mucoid sputum as assessed by a sputum colour chart (7.6 ± 1.4 CFU/mL vs. 6.7 ± 1.2 CFU/mL, p 0.009), but not between purulent and mucoid sputum as reported by patients (7.6 ± 1.4 CFU/mL vs. 7.4 ± 1.2 CFU/mL, p 0.30) (Fig. 1).

CRP

The median serum CRP level was 26 mg/L (interquartile range (IQR) 7–79). We found no significant difference in

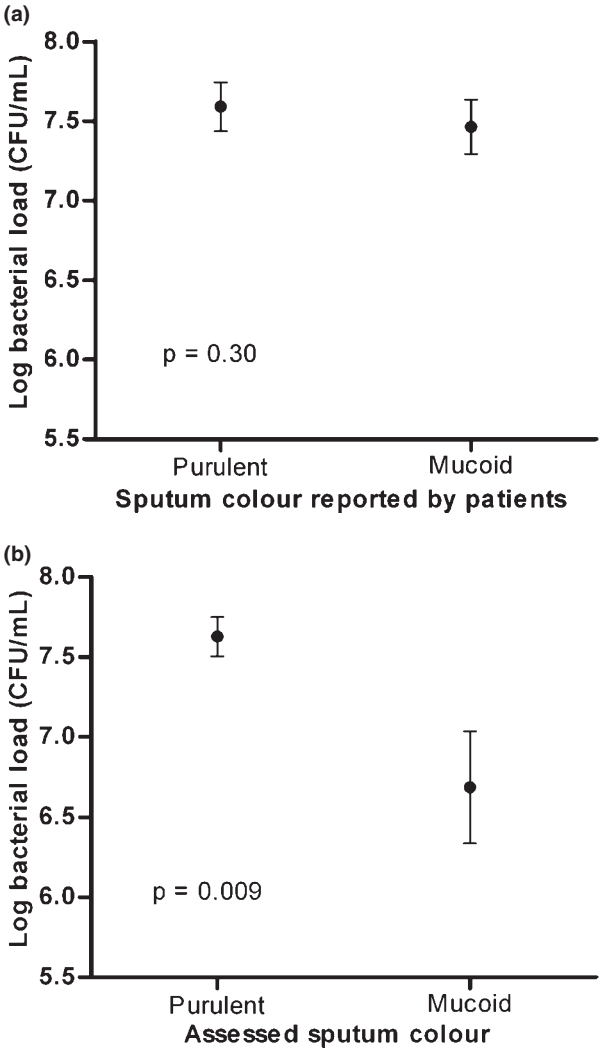

FIG. 1. Mean log bacterial load (± standard error of the mean and p-value) of the primary pathogen for mucoid and purulent sputum as reported by patients (a) and as assessed with a sputum colour chart (b) [4].

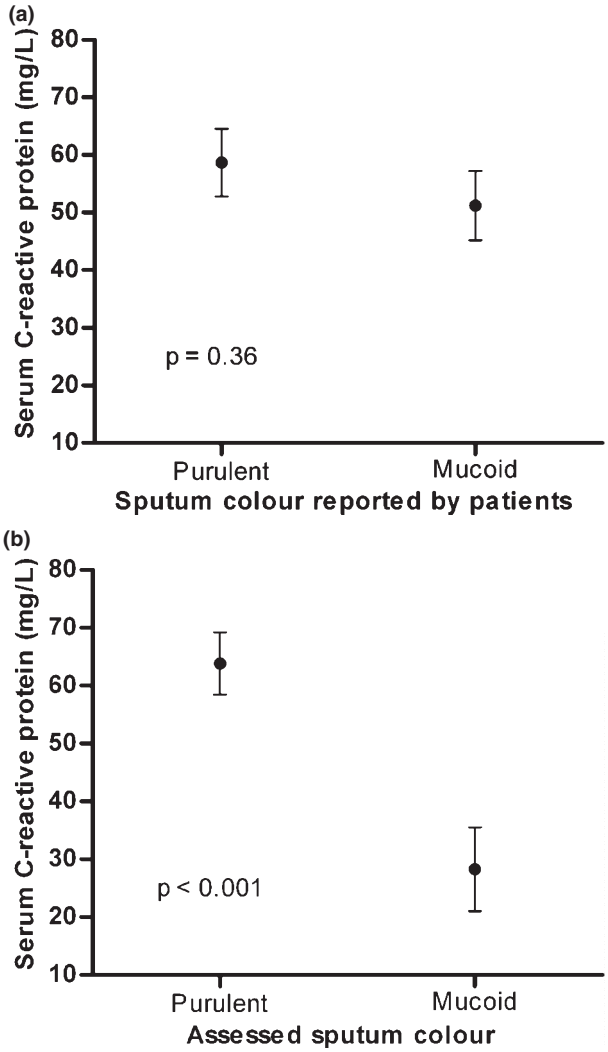

FIG. 2. Mean serum C-reactive protein (± standard error of the mean and p-value) in exacerbations with mucoid and purulent sputum as reported by patients (a) and as assessed with a sputum colour chart (b) [4].

CRP levels between patients with reported purulent sputum and mucoid sputum (28 mg/L (IQR 8–88) and 29 mg/L (IQR 7–76), respectively, p 0.36). By contrast, assessed sputum purulence was associated with significantly higher CRP levels than assessed mucoid sputum (36 mg/L (IQR 12–92) and 9 mg/L (IQR 4–39), respectively, p <0.001) (Fig. 2).

Discussion

This study demonstrates that sputum colour assessed with a sputum colour chart is a better marker for bacterial involvement than sputum colour reported by patients. Assessed sputum colour is also clearly related to sputum bacterial load and, in particular, systemic inflammation consistent with infection, whereas reported sputum colour is not.

Two other studies specifically investigated the diagnostic accuracy of routinely assessed sputum colour [4,5]. Stockley *et al.* [4] studied 121 patients with AECOPD, and assessed sputum colour with a nine-point colour chart. Patients with purulent sputum were treated with antibiotics, and those with mucoid sputum were not. All patients with mucoid sputum recovered without antibiotic therapy. The sputum colour chart had a sensitivity of 85% and a specificity of 84%. It was pointed out that 40% of the patients with mucoid sputum subjectively reported a change in sputum colour. The authors concluded that assessment of sputum colour can be

used to avoid unnecessary antibiotic therapy in patients with mucoid sputum. In our study, the specificity of assessed sputum colour was only 52%. The fact that our population consisted of hospitalized patients with more severe COPD might explain this difference. More severe non-bacterial exacerbations could result in intense neutrophilic airway inflammation and increased myeloperoxidase levels, with subsequent sputum discolouration; that is, severe airway inflammation in the absence of bacterial infection might result in false-positive sputum purulence. Also, antibiotic therapy could result in a false-negative sputum culture with sputum purulence, although our protocol ensured that sputum samples were collected before the start of antimicrobial therapy, making this unlikely. Finally, Stockley *et al.* [4] used a nine-point sputum colour chart, whereas we used a commercially available five-point sputum chart, which is based on the nine-point chart.

Allegra *et al.* [5] investigated a ten-point colorimetric scale for assessment of sputum colour. White or grey sputum samples were considered to be mucoid, and yellow, green and brown sputum samples were considered to be purulent. Although a higher rate of bacterial growth was found in purulent samples, 78% of mucoid samples showed bacterial growth. Deepening sputum colour (from yellowish to brownish) was associated with Gram-negative bacteria, particularly *Pseudomonas aeruginosa* and *Enterobacteriaceae*. Interestingly, patient and investigator definitions of sputum colour were confirmed in only 41% and 45%, respectively, of cases after assessment with the colorimetric scale.

Bearing these two studies in mind, one would expect that sputum colour reported by patients would not be a valuable marker for bacterial infection, which is confirmed by the current study. There could be several explanations. First, not all patients routinely inspect their expectorated sputum, and the answer given to the doctor could be a 'best guess'. Second, sputum colour can change rapidly, especially during acute exacerbations. A patient who reports mucoid sputum could expectorate a purulent sample for culture, and vice versa. Finally, expectorated sputum is not always homogeneous. A predominantly mucoid sample can contain purulent parts, which can be confusing. In contrast with our study, Soler *et al.* [9] concluded that self-reported sputum purulence is a good predictor of bacterial infection and that self-reported mucoid sputum precludes it (negative predictive value of 94%). We found bacteria in 51% of samples reported as mucoid and 32% of samples assessed as mucoid, and other studies have reported even higher rates of bacterial infection in samples assessed as mucoid [4,5]. This difference might be explained by the fact that 81% of our reported mucoid sputum samples were representative, as opposed to 6% in the study of Soler *et al.*, and by the fact that they used protective brush specimens (PSBs) for culturing.

An important problem for clinicians is whether the presence of bacteria in a sputum sample represents infection or colonization. In approximately 50% of exacerbations, significant amounts of potential bacterial pathogens can be isolated from PSBs obtained by bronchoscopy [9–11]. However, the same pathogens are found in the airways of patients in a stable phase of the disease [11–15]. Isolation of a new bacterial strain is more likely to represent infection, but this cannot be readily assessed in daily practice [16]. Another possible way in which to discern infection from colonization is assessment of the bacterial load. A study using PSB specimens found that patients with exacerbations had higher airway bacterial loads than patients in a stable phase [11]. Furthermore, an increase in airway bacterial load has been associated with increased airway inflammation [17,18]. These and other observations led to the 'rise and fall' or quantitative hypothesis, i.e. that exacerbations are caused by a local inflammatory response to a rise of the bacterial load above a certain threshold [19]. Finally, one could assess local and systemic inflammation in order to distinguish infection from colonization. Neutrophilic airway inflammation and systemic inflammation are more intense with well-defined bacterial exacerbations than with non-bacterial exacerbations [20]. Stockley *et al.* found that sputum colour is correlated with airway inflammation [21] and systemic inflammation [4]. The current study confirms the relationship between assessed sputum colour and systemic inflammation (serum CRP). The fact that assessed sputum colour is related to bacterial load and to systemic inflammation strengthens its value as a marker in AECOPDs.

In conclusion, sputum colour reported by patients is not useful in determining bacterial presence in AECOPDs. Although its specificity is limited, assessed sputum colour is clearly superior in predicting bacterial presence and is also related to bacterial load and systemic inflammation, and might thereby help clinicians to distinguish infection from colonization. We therefore advise inspection of expectorated sputum with a validated sputum colour chart in patients with AECOPDs.

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Transparency Declaration

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