

# Paper I

*“When should acute exacerbations of COPD be treated with systemic corticosteroids and antibiotics in primary care: a systematic review of current COPD guidelines”*

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## REVIEW ARTICLE OPEN

# When should acute exacerbations of COPD be treated with systemic corticosteroids and antibiotics in primary care: a systematic review of current COPD guidelines

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Not all patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) benefit from treatment with systemic corticosteroids and antibiotics. The aim of the study was to identify criteria recommended in current COPD guidelines for treating acute exacerbations with systemic corticosteroids and antibiotics and to assess the underlying evidence. Current COPD guidelines were identified by a systematic literature search. The most recent guidelines as per country/organisation containing recommendations about treating acute exacerbations of COPD were included. Guideline development and criteria for treating acute exacerbations with systemic corticosteroids and antibiotics were appraised. Randomised controlled trials directly referred to in context with the recommendations were evaluated in terms of study design, setting, and study population. A total of 19 COPD guidelines were included. Systemic corticosteroids were often universally recommended to all patients with acute exacerbations. Criteria for treatment with antibiotics were mainly an increase in respiratory symptoms. Objective diagnostic tests or clinical examination were only rarely recommended. Only few criteria were directly linked to underlying evidence, and the trial patients represented a highly specific group of COPD patients. Current COPD guidelines are of little help in primary care to identify patients with acute exacerbations probably benefitting from treatment with systemic corticosteroids and antibiotics in primary care, and might contribute to overuse or inappropriate use of either treatment.

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## INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) occur frequently in the course of COPD.<sup>1</sup> They can differ in severity and many require hospitalisation, but the majority of mild to moderate AECOPD can be managed in primary care.<sup>2</sup> Antibiotics and systemic corticosteroids are beneficial treatment options that are often used.<sup>3,4</sup> However, the benefit of antibiotics in mild to moderate AECOPD remains controversial,<sup>5</sup> and their overuse can contribute to the development of bacterial resistance.<sup>6</sup> Systemic corticosteroids bear the risk of adverse side effects,<sup>3</sup> especially in patients with co-morbidities.<sup>7</sup> Inappropriate use of either treatment should be avoided, and targeting patient treatment requires careful patient assessment. Clinical practice guidelines are intended to assist treatment decisions, based on the best available evidence.<sup>8</sup> A critical appraisal of 15 COPD guidelines found variations in the content and between recommendations on several management strategies for COPD, and concluded that these were rather a result of 'selective experience' than based on scientific evidence.<sup>9</sup> Consequently, we designed this study to identify recommended assessment strategies for treating AECOPD patients with systemic corticosteroids and antibiotics in COPD guidelines. Furthermore, we aimed to evaluate the quality of guideline development and the applicability of underlying evidence to primary care.

## METHODS

A systematic literature review was conducted in Web of Science, SCOPUS, SveMed+, PubMed, Embase, Cihnal (EBSCO) and Ovid MD

to identify COPD guidelines. Throughout the entire search, 'COPD' as Mesh-term was used whenever applicable. If a database did not support Mesh-terms, 'COPD' was searched in keywords, abstract and title. 'COPD' was combined with the search phrases 'guideline' and 'recommendation'. The search string used throughout the search was as follows:

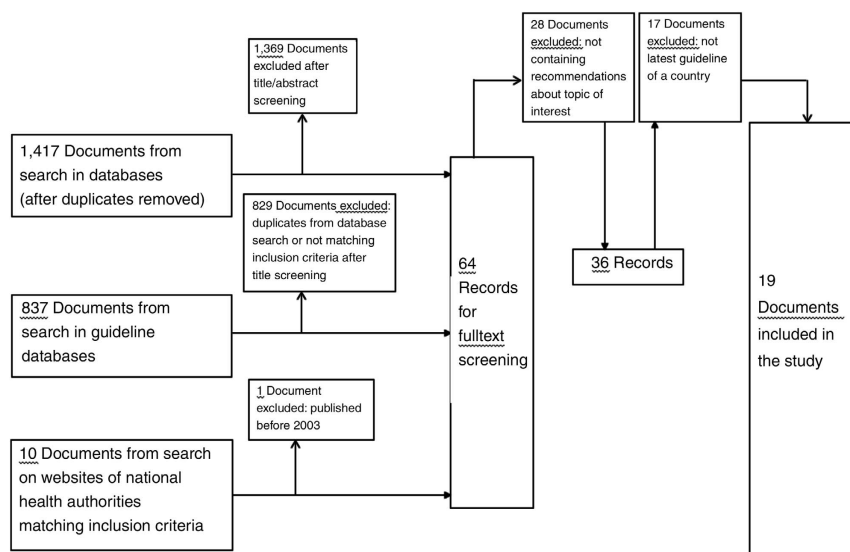
- Chronic Obstructive Pulmonary Disease AND (Guideline OR Recommendation).

Our initial search was performed with a time limit set for publications between 2003 and 2013. It was then extended to 8 May 2014 to ensure the inclusion of any new publications during our work on this project. Eligibility assessment was conducted by the first and the last author, and the approach from the preferred reporting items for systematic reviews and meta-analyses statement was followed<sup>10</sup> (Figure 1). To avoid overlooking documents that were published elsewhere than in the searched databases, a supplemental search was conducted in the guideline databases UpToDate, Best Practice, National Guideline Clearinghouse, Cochrane Library, Guidelines International Network and websites of the Canadian Medical Association, and American College of Physicians. Furthermore, websites of national health authorities (Germany, Denmark, Sweden, Norway, Austria, Switzerland, and Netherlands) were searched for eligible guidelines. This search was not repeated after 2013. Only guidelines and published documents with recommendations on adults with AECOPD and/or infectious diseases of the lungs when containing AECOPD were

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**Figure 1.** Flowchart describing the systematic search and eligibility assessment.

included in this study. They also had to be published in English, German, Dutch, or a Scandinavian language. The most recent guideline from each country was included. The included guidelines were analysed in terms of guideline development by applying criteria from the AGREE II tool (Appraisal of guidelines for research and evaluation II).<sup>11</sup> The criteria applied belonged to the domains 2 (stakeholder involvement), 3 (rigor of development), and 6 (editorial independence). We extracted recommendations about patient assessment for treatment with systemic corticosteroids and antibiotics. If recommendations were given separately for inpatients and outpatients, only those for outpatients were considered. Evidence explicitly linked to the recommendations, as described in domain 3 of the AGREE II tool,<sup>11</sup> was obtained, and randomised controlled trials published in scientific medical journals were assessed in terms of study setting, study design, and inclusion and exclusion criteria. Furthermore, we decided to add the trials included in the latest versions of the Cochrane reviews about treating AECOPD with systemic corticosteroids<sup>3</sup> and antibiotics,<sup>4</sup> although not directly referred to in the guidelines.

## RESULTS

The systematic database search resulted in 1,417 documents, and the supplemental search in the guideline databases in 837 documents. Further, 10 documents were retrieved from the websites of national health authorities. A total of 64 documents (47, 8, and 9 documents, respectively) remained for full-text screening after excluding duplicates and those not matching the inclusion criteria. After full-text screening, 36 documents remained, of which 17 outdated versions were excluded. Finally, 19 guidelines were included in the study (Figure 1).

### Characteristics of guideline development

The guidelines were published between 2004 and 2014, and 12 of these were updates from earlier versions (Table 1). The time between previous and current editions varied from continuous updating to 15 years between two versions. Four guidelines gave a date for planned revision. A total of 14 guidelines provided information about the development committee, and in 10 committees at least one general practitioner was included. The guidelines from the Netherlands and from the International

Primary Care Respiratory Group were especially targeted towards primary care physicians, and this was reflected in the high number of general practitioners in the development groups (Table 1). Furthermore, eight guidelines gave separate recommendations for inpatients and outpatients. Information about funding or conflict of interests was provided in 11 guidelines, 5 of which were sponsored by pharmaceutical companies (Table 1). A detailed description of important steps in the guideline development process, such as literature review, was only given in six guidelines (Table 1). AECOPD definitions across the guidelines were symptom based including the terms 'dyspnoea', 'cough', and 'changes in sputum' in the majority of cases.

### Criteria for initiating treatment with systemic corticosteroids

A total of 17 of the 19 guidelines addressed the treatment option 'systemic corticosteroids', with 11 criteria being identified (Table 2). The guidelines from the European Respiratory Society and Germany addressed infectious diseases and did not contain recommendations about systemic corticosteroids. We found that nine guidelines recommended systemic corticosteroids universally to all AECOPD patients, and the Spanish guideline reserved such treatment to all patients with an at least moderate exacerbation (without providing information about different severity grades). One guideline reserved such treatment to patients with severe underlying COPD, and two guidelines to patients with moderate to severe COPD (Table 2). Three guidelines recommended basing treatment decisions on patients' actual respiratory symptoms, namely a significant increase in dyspnoea and wheezing. The Dutch guideline recommended waiting for the response to increased dosage of bronchodilators, as first-line emergency treatment, and assessing the patients' general condition before starting a course with systemic corticosteroids in all patients not requiring hospitalisation. The Swedish guideline was the only guideline to suggest objective measures by clinical examination (respiratory rate and heart rate) and to recommend the use of the diagnostic tests pulse oximetry and blood gas analysis (Table 2).

### Characteristics of the primary evidence supporting recommendations for systemic corticosteroids

We found 11 randomised controlled trials directly referred to in context with a certain recommendation<sup>12–22</sup> and two trials in the Cochrane review,<sup>3</sup> which were not directly referred to in context

**Table 1.** Overview of guidelines included in the study and characteristics of the development process

Guidelines <sup>a</sup> (country or organisation and year of publication)	Time (years) between current and previous version	Date for planned revision presented	Comprehensible description of literature search	GPs/all members in development committees (n)	Separate recommendations for inpatients and outpatients	Funding by the pharmaceutical industry
Austria <sup>61</sup> 2004	15	No	No	NA	No	NA
IPCRG <sup>62</sup> 2006	NA	No	No	4/8	For primary care	Yes
Denmark <sup>63</sup> 2007	NA	No	No	1/20	Yes	NA
Netherlands <sup>64</sup> 2007	6	No	No	7/9	For primary care	No
Sweden <sup>65</sup> 2009	NA	No	No	2/8	Yes	NA
Germany <sup>66</sup> 2009	4	Yes	No	0/14	No	No
NICE <sup>67</sup> 2010	6	No	Yes	4/31	Yes	No
South Africa <sup>68</sup> 2011	2	No	Yes	NA	No	Yes
Canada <sup>69</sup> 2011	NA	No	No	NA	No	NA
ERS <sup>70</sup> 2011	6	No	Yes	1/12	Yes	No
Australia/New Zealand <sup>71</sup> 2012	9	No	No	3/45	No	Yes
Norway <sup>72</sup> 2012	NA	No	No	2/8	Yes	NA
Switzerland <sup>73</sup> 2013	10	No	No	1/13	Yes	NA
ICSI <sup>74</sup> 2013	1	Yes	Yes	0/10	No	No
GOLD <sup>75</sup> 2013	1	Yes	Yes	2/25	No	Yes
UpToDate <sup>76,77</sup> 2013	Cont.	Yes	No	NA	No	NA
India <sup>78</sup> 2013	NA	No	Yes	NA	No	NA
Saudi <sup>79</sup> 2014	NA	No	Yes	0/12	Yes	No
Spain <sup>46</sup> 2014	4	No	No	0/19	Yes	Yes

Abbreviations: cont., guidelines are continuously updated; GP, general practitioner; NA, information not available or remained unclear.

<sup>a</sup>Abbreviations for organisations: ERS, European Respiratory Society; GOLD, Global initiative for chronic obstructive lung disease; IPCRG, International Primary Care Respiratory Group; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence.

**Table 2.** Recommendations for assessing outpatients for treatment with systemic corticosteroids and antibiotics

Criteria	No. of guidelines	Countries/organisations applied (ISO codes) <sup>a</sup>
<b>Systemic corticosteroids</b>		
All patients with AECOPD	9	ZA, AU/NZ, IN, NO, SW, ES <sup>b</sup> , ICSI, GOLD, UpToDate
Baseline FEV1% predicted < 50%	1	AT
Stadium III	1	AT
Moderate to severe COPD	2	CA, DK
Significant increase in dyspnoea/wheezing	3	SE, IPCRG, NICE
Impaired general condition	1	NL
Treatment failure of first-line treatment (bronchodilators)	1	NL
Respiratory rate > 25/min, heart rate > 110/min, SpO2 < 90%, PaO2 < 8 kPa	1	SE
<b>Antibiotics</b>		
All patients with AECOPD	2	IN, KSA
Severe underlying COPD	4	DE, NO, ERS, NL
Increase in dyspnoea, cough, sputum volume and purulence	3	CA, IPCRG, NL
Increase in dyspnoea, sputum volume and purulence (2 or 3 of 3 symptoms)	6	ZA, GOLD, ERS, SUI, ICSI, UpToDate
Increase in sputum volume and colour	2	AT, AU/NZ
Change in sputum colour/purulent sputum	6	NO, SE, DK, NICE, DE, ES
Insufficient improvement after 4 days	1	NL
Clinical signs of pneumonia	2	DK, NICE
Fever	5	AU/NZ, AT, NO, DK, NL
Impaired general condition	2	DK, NL
Use of accessory muscles	1	NL
Respiratory rate > 30/min, heart rate > 120/min	1	NL
Leukocytosis	1	AU/NZ
CRP > 50 mg/l	1	NO
Procalcitonin > 0.1 ng/ml	1	DE
Chest radiography	1	NICE

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; PaO2, partial oxygen pressure; SpO2, blood oxygen saturation.

<sup>a</sup>ISO codes of countries and abbreviations of organisations: AT, Austria; AU/NZ, Australia/New Zealand; CA, Canada; DE, Germany; DK, Denmark; ES, Spain; GOLD, Global initiative for chronic obstructive lung disease; ICSI, Institute for Clinical Systems Improvement; IN, India; IPCRG, International Primary Care Respiratory Group; KSA, Saudi; NICE, National Institute for Health and Care Excellence; NL, Netherlands; NO, Norway; SE, Sweden; SUI, Switzerland; ZA, South Africa.

<sup>b</sup>To all patients with at least moderate exacerbation.

with a certain recommendation in the guidelines (Table 3). Publication dates varied between 1980 and 2011, and 9 of the 11 trials were hospital based. The number of study participants ranged from 27 to 210 patients (Table 3). The majority were male, and one trial had included only male patients (Table 3). The percentage of the patients who were finally randomised among those screened for eligibility varied between 14 and 96% (Table 3). Cardiovascular co-morbidities were explicitly described as exclusion criteria in 7 trials (uncontrolled heart failure in 5 trials, diabetes mellitus in 2 trials, and uncontrolled arterial hypertension in 1 trial). The forced expiratory volume after 1 s (FEV<sub>1</sub>% predicted) or FEV<sub>1</sub> in litre at inclusion were provided in 10 trials. Their values ranged between 24.7 and 59.6%, or between 0.5 and 1.3 litre, respectively (Table 3).

#### Criteria for initiating treatment with antibiotics

All guidelines contained recommendations about treatment with antibiotics, and 12 assessment criteria were identified (Table 2). Two guidelines recommended antibiotics to all patients with AECOPD. All others, apart from the Dutch guideline, recommended basing antibiotic treatment on an increase of the respiratory symptoms 'dyspnoea', 'cough', 'sputum volume', or 'sputum purulence'. A total of eight of these guidelines only recommended changes in sputum (mostly purulent or changes in sputum colour). These guidelines also provided additional criteria (Table 2), which were mostly the severity of underlying COPD or systemic symptoms such as 'fever' and 'impaired general condition'. Only four guidelines recommended conducting additional diagnostic tests: C-reactive protein (CRP), white blood cell count, procalcitonin, and chest radiography (Table 2). The guidelines from India<sup>23</sup> and Saudi<sup>24</sup> emphasised that the use of biomarkers has no role in the assessment of AECOPD. The Dutch guideline was exceptional, as they did not recommend any of the respiratory symptoms. Here, the focus was only on the patient's general condition and fever as signs for bacterial infection, in combination with severe underlying COPD and insufficient improvement after 4 days. However, it was stated that a course of antibiotics might be initiated in all patients with a severe exacerbation, characterised by heavy dyspnoea, use of accessory

muscles, respiratory rate >30/min and heart rate >120/min (Table 2).

#### Characteristics of the primary evidence supporting recommendations for antibiotics

We found 4 randomised controlled trials that were directly referred to in context with a certain recommendation<sup>25-28</sup> and 11 trials in the Cochrane review<sup>4</sup> that were not directly referred to in the guidelines<sup>28-39</sup> (Table 4). They were published between 1960 and 2013. In four trials, patients were excluded owing to both cardiovascular diseases (left ventricular failure in one trial, severe heart disease in two trials, and stroke in one trial) and a broad range of infectious diseases. Almost all trials included significantly more men than women (Table 4). A total of 11 trials provided information about initial exclusion rates before randomisation, which ranged between 56 and 3%. The average baseline FEV<sub>1</sub>% predicted or peak expiratory flow of the included study patients was presented in 13 trials, with the FEV<sub>1</sub>% predicted ranging from 33.9 to 65% and peak expiratory flow from 63 to 295 l/min (Table 4).

## DISCUSSION

### Main findings

There was a considerable lack of transparency regarding guideline development, as the literature review was often not documented comprehensively. It is also problematic that a considerable number of guidelines were financed by pharmaceutical companies, or their funding sources were not reported.<sup>40</sup> Owing to the small number of general practitioners in the guideline development committees, primary care expertise might not be considered sufficiently during guideline development.

Treatment recommendations were mostly universal and unspecific and often recommended for all AECOPD patients or all patients with underlying moderate to severe COPD, or, in terms of antibiotics, patients with certain symptoms. The use of diagnostic tests was only recommended in a few guidelines.

The patients in the trials that the recommendations were based on were a rather selected group of COPD patients. Most trials were conducted in hospitalised patients, the exclusion rates before

**Table 3.** Characteristics of randomised controlled trials underlying recommendations for treating acute exacerbations of chronic obstructive pulmonary disease with systemic corticosteroids.

Author, year of Publication	No. of patients (m/f)	% Of patients included of those initially screened	Cardiovascular co-morbidities in exclusion criteria	Average baseline lung function (FEV <sub>1</sub> % predicted or FEV <sub>1</sub> in litre) of study patients at the time of inclusion	Study setting (hospital or outpatient)
Albert <i>et al.</i> <sup>12</sup>	44 (44/0)	NA	No	0.6 l	H
Thompson <i>et al.</i> <sup>13</sup>	27 (26/1)	19%	Yes	1.3 l	O
Niewoehner <i>et al.</i> <sup>14</sup>	271 (268/3)	15%	NA	0.8 l	H/O
Davies <i>et al.</i> <sup>15</sup>	50 (34/16)	20%	Yes	24.7%	H
Maltais <i>et al.</i> <sup>16</sup>	199 (162/37)	29%	No	NA	H
Aaron <i>et al.</i> <sup>17</sup>	147 (84/63)	14%	Yes	38.0%	O
DeJong <i>et al.</i> <sup>18</sup>	210 (157/53)	48%	Yes	37.0%	H
Gunen <i>et al.</i> <sup>19</sup>	121 (103/18)	NA	No	37.2%	H
Ställberg <i>et al.</i> <sup>20</sup>	109 (56/53)	NA	No	45.0%	H/O
Alia <i>et al.</i> <sup>21</sup>	83 (66/17)	23%	Yes	NA	H
Leuppi <i>et al.</i> <sup>22</sup>	311 (188/123)	43%	No	31.5	H
<i>Trials from the Cochrane review</i> <sup>3</sup>					
Emerman <sup>79</sup>	96 (50/46)	96%	Yes	59.6%	H
Bullard <sup>46</sup>	113 (97/16)	82%	No	0.5 l	H

Abbreviations: f, female; FEV<sub>1</sub>, forced expiratory volume in 1 s; H, hospital-based study; m, male; NA, information not available or unclear; O, study conducted with outpatients.

**Table 4.** Characteristics of randomised controlled trials underlying recommendations for treating acute exacerbations of chronic obstructive pulmonary disease with antibiotics

Author, year of Publication	No. of patients (m/f)	% Of patients included of those initially screened	Cardiovascular co-morbidities in exclusion criteria	Average baseline lung function (FEV1 % predicted, FEV1 in litre or PEF litre/min) of study patients at the time of inclusion	Study setting (hospital or outpatient)
Anthonisen <i>et al.</i> <sup>25</sup>	173 (134/39)	—	Yes	33.9%	O
Seemungal <i>et al.</i> <sup>26</sup>	83 (59/24)	—	Yes	41.3%	O
Patel <i>et al.</i> <sup>27</sup>	29 (21/8)	—	No	38.7%	O
Nouira <i>et al.</i> <sup>28</sup>	93 (84/9)	44%	No	0.7 l	H
<i>Trials from the Cochrane review</i> <sup>4</sup>					
Berry <i>et al.</i> <sup>29</sup>	53 (31/21) <sup>a</sup>	NA	NA	NA	O
Fear <i>et al.</i> <sup>30</sup>	62 (NA)	NA	No	NA	O
Elmes <i>et al.</i> <sup>31</sup>	74 (47/27)	76%	Yes	79.2 l/min	H
Pines <i>et al.</i> <sup>32</sup>	186 (186/0)	No	76.0 l/min	H	H
Pines <i>et al.</i> <sup>33</sup>	259 (259/0)	NA	No	146.0 l/min	H
Manresa <i>et al.</i> <sup>34</sup>	19 (NA)	NA	No	172.0 l/min	H
Jørgensen <i>et al.</i> <sup>35</sup>	270 (115/278)	97%	Yes	295.0 l/min (circa)	O
Sachs <i>et al.</i> <sup>36</sup>	71 (30/41)	NA	No	63 l/min	O
Brusse-Keizer <sup>37</sup>	35 (21/14)	56%	No	48.6%	O
Daniels <i>et al.</i> <sup>38</sup>	223 (133/90)	70%	No	45.4%	H
Llor <i>et al.</i> <sup>39</sup>	310 (251/59)	88%	No	65.0%	O

Abbreviations: f, female; FEV1, forced expiratory volume in 1 s; H, hospital-based study; m, male; NA, information not available or unclear; O, study conducted with outpatients; PEF, peak expiratory flow.

<sup>a</sup>One not recorded.

randomisation were high in many trials, and the patients were often characterised by severely reduced lung function and low prevalence of cardiovascular co-morbidities or diabetes.

#### Strengths and limitations

We conducted a rigorous and systematic literature search to get hold of the COPD guidelines. However, we might have missed guidelines published in languages other than the ones included.<sup>41</sup> As we did not use the AGREE II tool to its full extent, we are limited in making reliable statements on the guideline quality. Further, we only considered primary studies that were explicitly linked to the recommendations in the appraisal of underlying evidence. Whether studies are cited directly linked to a recommendation or not could be owing to the technical presentation of recommendations, and it does not necessarily reflect the existence of the evidence used. However, according to the AGREE II tool, an explicit link between recommendations and evidence is important for judging the source of a recommendation.<sup>11</sup> As we additionally appraised the trials included in the latest Cochrane reviews on treating AECOPD with systemic corticosteroids<sup>3</sup> and antibiotics,<sup>4</sup> we are able to make a valid statement about the evidence that the current treatment recommendations are based on.

Interpretation of findings in relation to previously published work  
*Relevance of the underlying evidence for primary care patients.* The characteristics of the trial patients of the studies underlying the recommendations were not necessarily comparable to the 'common' COPD patient in primary care, who tend to have milder airflow obstruction<sup>42</sup> and frequently suffer from co-morbidities.<sup>43</sup> When evidence is based on patients without co-morbidities, it could be risky to follow the guidelines in primary care patients who also suffer from heart failure or diabetes. Herland *et al.* expressed similar concerns, questioning whether results of the trials on obstructive lung diseases really can be extrapolated to 'real-life' populations of patients.<sup>43</sup> Considering that frequent co-morbidities,<sup>43</sup> such as heart failure, can mimic the symptoms of increased cough and dyspnoea,<sup>44,45</sup> adherence to the current guidelines might lead to over-treatment or inappropriate

treatment with antibiotics and systemic corticosteroids. In addition, the authors of the latest Cochrane reviews about antibiotics<sup>4</sup> and systemic corticosteroids<sup>3</sup> for AECOPD underline that the effect of both treatments in outpatients and patients with mild airflow obstruction still remains unclear. They emphasise the need for diagnostic tests and biomarkers to identify patients who may benefit from the treatment.

*Criteria for systemic corticosteroids.* According to many guidelines, systemic corticosteroids seemed to be universally useful. Diagnostic tests or clinical examination were rarely recommended, but prescribing a corticosteroid should rather be based on the patient's respiratory symptoms. It is striking that the recommended criteria for treating AECOPD with systemic corticosteroids resemble in most cases the (clinical) definition of an AECOPD, which is an 'acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication'.<sup>46</sup> Thus, once the clinical diagnosis of AECOPD is made, most patients would fit the criteria for a course of systemic corticosteroids according to the guidelines. Yet, common adverse side effects, such as hyperglycaemic episodes in patients with diabetes,<sup>7</sup> call for a rather critical use of systemic corticosteroids. An 'increase in dyspnoea' might be caused by other (non-)respiratory conditions that are not necessarily responsive to systemic corticosteroids.<sup>44,45</sup> Therefore, a more careful assessment to identify patients with a clear benefit would be of major importance. Yet, no reliable method for further investigation beyond assessment of symptoms has been established, and this is probably the reason for rather speculative recommendations such as those recommended in the Swedish guidelines (pulse oximetry and blood gas analysis). Interestingly, spirometry was explicitly advised against in, for instance, the Global initiative for chronic obstructive lung disease (GOLD) guidelines, as it is 'difficult to perform' and 'measurements are not accurate enough'.<sup>47</sup> When looking at clinical trials, we find spirometry being a common outcome measure to quantify airflow obstruction and to show the effect of, for instance, systemic corticosteroids.<sup>3</sup> Thus, the arguments to abandon spirometry from the assessment of AECOPD do not seem to be thoroughly

deliberated. Further evaluation in primary care might help identify a role for spirometry in the assessment of AECOPD.

**Criteria for antibiotic treatment.** Most guidelines recommend antibiotic treatment based on respiratory symptoms, and increased purulence in particular. This recommendation rests on the subgroup analyses in Anthonisens landmark study.<sup>25</sup> The special weight laid on increased purulence is supported by the increased risk of positive bacterial culture in COPD patients with purulence<sup>48</sup> and, recently, by Miravittles' study of predictors of treatment failure in AECOPD in patients with mild to moderate disease not treated with antibiotics.<sup>49</sup> However, sputum colour alone might not be sufficient to identify patients possibly benefiting from antibiotics,<sup>50</sup> and therefore biomarkers could be very valuable: in the study by Miravittles,<sup>49</sup> a CRP value > 40 mg/l was found to be the strongest predictor of treatment failure. Results from another study emphasise the usefulness of the CRP test in general practice, as it was found that sputum-guided therapy alone resulted in higher prescription rates than when combined with CRP.<sup>39</sup> However, by now, CRP is only recommended in the Norwegian guideline. 'Procalcitonin', which was recommended in the German and also mentioned in the Suisse guideline, has also been found to be a promising biomarker for targeting antibiotic treatment.<sup>51</sup> It is, however, not yet available as a point-of-care test for use in primary care. The strict clinical criteria in the Dutch guideline indicating a severe AECOPD are similar to those in the systemic inflammatory response syndrome score<sup>52</sup> and in the CRB65 score.<sup>53</sup> Yet, they do not refer to supporting evidence. Although the CRB65 score can be helpful to identify severe AECOPD with high inpatient mortality,<sup>54</sup> it might be problematic to apply these criteria as indicators for antibiotic treatment in AECOPD.

#### Future perspectives and conclusion

Our results lead to the conclusion that current COPD guidelines are of little help in identifying which AECOPD patients might benefit from treatment with systemic corticosteroids and antibiotics in a primary care setting. Increased purulence has been shown to be a useful criterion for antibiotic treatment in patients with severe disease,<sup>25</sup> but we still do not know whether reliance on purulence leads to over-treatment in patients with mild to moderate disease. Despite little evidence supporting the usefulness of biomarkers, some guidelines have started to include tests in the diagnostic work-up. However, a better understanding of how COPD/AECOPD interferes with other conditions will probably be as important as establishing a test or biomarker to meet the current challenges, such as differentiation between AECOPD and other diseases. Future guidelines will surely be influenced by currently ongoing research on the use of biomarkers in AECOPD.<sup>55–59</sup> Further, the new understanding of how COPD should be subclassified into phenotypes<sup>60</sup> may also lead to a new way of understanding the exacerbations, which may vary by phenotype. Antibiotics may be more frequently needed in a phenotype associated with chronic bronchitis than in those dominated by emphysema or when the patient can be classified as COPD-asthma overlap. We recommend that future research should, to a larger extent, focus on AECOPD in patients with mild to moderate airflow obstruction (FEV1% predicted > 50%), similar to the study by Llor *et al.*,<sup>39</sup> and consider the concern of multimorbidity in COPD patients. Moreover, we find it necessary to reconsider the uncritical way in which the use of systemic corticosteroids is presented in current COPD guidelines, and to stress the importance of developing better methods for targeting treatment with systemic corticosteroids. Such moves will be necessary to make future guidelines more helpful in primary care and to improve care for COPD patients.

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## CONTRIBUTIONS

JL is the main author as she was primarily engaged in designing and conducting the study. ER performed the systematic literature search and contributed with guidance relevant for the method used in the study. HM supervised the whole work and assisted in the eligibility assessment of the search results.

## COMPETING INTERESTS

The authors declare no conflict of interest.

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