

Antibiotics in COPD Exacerbations: The Debate Continues

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Definition of COPD exacerbation

COPD exacerbation is defined as episodes of worsening of respiratory symptoms which affect the health.¹⁻³ status of COPD patients and mortality and the course^{4,5} of the disease. Cardinal features of COPD exacerbations are breathlessness, sputum purulence and sputum volume.^{6,7} Anthonisen *et al* graded these exacerbations into type 1 (all the three features), type 2 (only two features) and type 3 (single feature).⁸ There are small reductions in PEF, FEV₁, FVC at exacerbations.⁹ The arterial blood gases may worsen and progression to respiratory failure can occur.¹⁰ Right now there is no sputum or a plasma biomarker which can identify these episodes with high sensitivity and specificity. This may be due to heterogeneity in etiology, onset of presentation and symptom logy.^{7,9-11}

Antibiotics in COPD exacerbation

Traditionally the mainstay of treatment of exacerbation has been oral corticosteroids and antibiotics.^{1,3,4,6,7,9-12} Although there is a considerable evidence of benefit of a course of oral corticosteroids and antibiotics when two of the three cardinal symptoms are present, the use of corticosteroids is well accepted but the role of antibiotics in COPD exacerbation is still debated.^{1,3-6,9,11-13} This is because of multiple reasons. Firstly, involvement of bacteria in COPD exacerbation is well documented but viruses do trigger the COPD episodes as well.^{7,9,14} Moreover it is now understood that exacerbations are associated with increased LABC (lower airway bacterial colonization) or change in bacterial strain. This again makes the use of antibiotics in COPD exacerbation controversial because

even in the stable state patients also have lower airway bacterial colonization.^{12,14,15} Secondly, a high concern is there about antimicrobial resistance in the community due to frequent use of antibiotics without knowing the actual causative strain.¹⁶ Thirdly, in primary care studies antibiotics seem to have little effect on the COPD exacerbation where patients with milder disease have been recruited.^{9,7,15-17} Patients recruited have been heterogeneous with respect to lung function, frequency of exacerbation, comorbidity and stable treatment. The antibiotic effects have been studied only in short term trials with little information on long term outcomes.¹⁵⁻¹⁷ In MOSAIC trial of antibiotic, Moxifloxacin versus standard therapy at COPD exacerbation, Wilson *et al* showed that the response to Moxifloxacin was worst in short term (10 days) in patients with coexistent cardiac disease. In contrast, when exploring longer outcome up to 9 months after the study onset, response to moxifloxacin was much better in old patients above 60 years and with higher exacerbation rates.^{17,18} Thus benefits are more in patients with frequent episodes of exacerbation. Further information on long term benefits on use of antibiotics was seen by Roede and Colleagues in a cohort based study. In Dutch Parma database results, they showed that the time taken for next second exacerbation was longer when corticosteroids were combined with antibiotics than steroid alone. There was a reduction in the mortality. However it was a data based study, with no information on spirometry to classify the patients.¹⁹ These results suggest the long term benefits of using antibiotics in COPD exacerbations. We assume that the use of antibiotics at COPD reduce the bacterial load and inflammatory changes, thus a single course of antibiotics may also have significant effect on the degree of LABC in the subsequent stable state.^{19,20}

Exacerbation episodes are associated with increased sputum purulence and volume and, it is also possible that symptoms related to sputum, prompt patients to seek treatment for their exacerbation early after onset.^{3,7,21} As mentioned, the study by Roede and colleagues shows that patients treated

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with steroids and antibiotics had more stable medications dispensed including inhaled corticosteroids leading to wide intervals between the exacerbations.²²⁻²⁴ In a recent study patients prescribed an inhaled corticosteroids addition to a long acting beta 2 agonist had a greater requirement for antibiotics than pts. taking a long acting anticholinergic bronchodilator alone.²⁵⁻²⁷ This also suggests that an individual patients stable medication may have differential effects on the character of their exacerbation and this in turn affects the nature of the therapy prescribed.²⁷⁻³¹

Conclusion

It is now clear that COPD exacerbations are complex events, occurring in patients depending on disease severity, susceptibility of exacerbation with underlying LABC and airway inflammation besides age and other comorbid factors.^{5,9,31,32} The character of an exacerbation may be modulated by the nature of the patients stable medication.^{33,34} Thus future clinical studies of exacerbation therapy must be performed in carefully phenotyped patients with COPD with assessment of airway microbiology at rest or during worsening, using validated outcomes and longer time follow up. Thus debate may continue as many questions are to be answered.^{35,36}

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