HHS Public Access

Author manuscript

Lancet Respir Med. Author manuscript; available in PMC 2018 March 19.

Published in final edited form as:

Lancet Respir Med. 2017 June ; 5(6): 461–462. doi:10.1016/S2213-2600(17)30166-2.

Antibiotics for the outpatient treatment of COPD exacerbations: the debate continues

Wassim W. Labaki, MD and **MeiLan K. Han, MD**

Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

While the benefit of antibiotics in severe COPD exacerbations requiring intensive care is well established (1, 2), their role in moderate exacerbations treated in the ambulatory setting remains controversial. The most recent Cochrane meta-analysis on this topic did not show a reduction in treatment failure with currently used antibiotics compared to placebo (2). However, only two of the five pooled trials were full manuscripts, enrolled participants with a confirmed diagnosis of COPD and excluded subjects with asthma (3, 4). In 1987, Anthonisen and colleagues showed a higher rate of 21-day symptom resolution after treatment with doxycycline, trimethoprim-sulfamethoxazole or amoxicillin (3); this effect was more pronounced in patients with increased dyspnea, sputum volume and sputum purulence. More recently, a trial by Llor and coworkers also demonstrated a higher rate of clinical resolution and time to the next exacerbation with amoxicillin-clavulanate (4).

In this issue of *Lancet Respiratory Medicine*, van Velzen and colleagues examined the impact of doxycycline in 301 COPD patients recruited from pulmonary and primary care clinics in the Netherlands and diagnosed with a respiratory exacerbation in the outpatient setting (Ref). The primary outcome was time to the next exacerbation. All patients received a 10-day course of oral corticosteroids and were additionally randomized to a 7-day course of doxycycline 100 mg daily (loading dose of 200 mg on the first day) versus placebo. Median time to the next exacerbation was 148 (95% CI 95-200) days in the doxycycline-treated group and 161 (95% CI 118-211) days in the placebo group (p=0·81). A secondary outcome measure was treatment failure at day 21 defined as lack of improvement in patient-reported respiratory symptoms, prescription of open-label antibiotics or a new course of oral corticosteroids, hospitalization for an exacerbation or death. Treatment failure rate at day 21 was 21·3% in the doxycycline group and 30·5% in the placebo group (p=0·07; number needed to treat to prevent treatment failure in one patient: 10·9). There was also no difference in treatment failure rate between exacerbations with or without sputum purulence at day 21 (p=0·54) or day 84 (p=0·82).

There are some important caveats to this study. Patients with FEV_1 < 30% predicted were excluded. The study may have been underpowered to examine treatment failure at 21 days as the p-value of 0·07 approaches statistical significance. Furthermore, as the authors note, if the results of this study were to be combined with data from the aforementioned Cochrane

Corresponding author: MeiLan K. Han, 3916 Taubman Center, Box 0360, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5360, mrking@umich.edu, Phone: 734-936-5201, Fax: 734-936-5048.

meta-analysis (2), then this would result in significantly reduced short-term treatment failure rates with the use of antibiotics (RR 0·77 (95% CI 0·63-0·94)) (2). Although no difference in treatment failure was noted between patients with and without sputum purulence, the study was also likely underpowered to examine these subgroups. Therefore, while this trial suggests that antibiotics for the treatment of outpatient COPD exacerbations do not prolong time to the next exacerbation, it actually lends support for the role of antibiotics in hastening symptom resolution when analyzed in the context of other data.

The pendulum of thought has swung back and forth regarding the role of bacteria in acute exacerbations of COPD. Bacteria with pathogenic potential can be cultured from respiratory specimens in 51-70% of patients during COPD exacerbations, but those same organisms can also grow in 25-48% of respiratory specimens obtained during stability (5). While the total bacterial load present in the lung may not actually increase during an exacerbation, changes in the composition of bacterial communities have been reported (6). Using a rhinovirus infection model of exacerbations in humans, Molyneaux et al. demonstrated a 16% increase in Proteobacteria sequences in COPD subjects compared to controls 15 days after viral infection (7). Notably, they identified an increase in *Haemophilus influenzae* species from a pre-existing community, suggesting that a disturbance in the lung environment can lead to selective outgrowth of newly favored species from a previously homeostatic microbial ecosystem. In a study by Huang et al., sputum samples from COPD patients collected during exacerbations also showed a significant increase in members of the Proteobacteria phylum compared to samples collected at baseline (8). Hence exacerbations may result from a complex interaction between a disrupted community of airway microbiota and the host's immune response. If real, the benefit of antibiotics in COPD exacerbations may result from manipulation of the lung's microbial composition or even microbial metabolite production (9) that leads to a decrease in inflammation. Ultimately, a better understanding of the relationship between the lung microbiome and the host immune response may provide insight on how best to treat exacerbations. In the meantime, the current weight of available evidence suggests that antibiotic therapy for moderate COPD exacerbations may reduce the risk of treatment failure, while the data on delaying future exacerbations are conflicting.

References

1. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet. 2001; 358(9298):2020–5. DOI: 10.1016/S0140-6736(01)07097-0 [PubMed: 11755608]
2. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012; 12:CD010257.doi: 10.1002/14651858.CD010257 [PubMed: 23235687]
3. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Annals of internal medicine. 1987; 106(2):196–204. [PubMed: 3492164]
4. Llor C, Moragas A, Hernandez S, Bayona C, Miravitlles M. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2012; 186(8):716–23. DOI: 10.1164/rccm.201206-0996OC [PubMed: 22923662]

5. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. Lancet. 2014; 384(9944):691–702. DOI: 10.1016/S0140-6736(14)61136-3 [PubMed: 25152271]

6. Sethi S, Sethi R, Eschberger K, Lobbins P, Cai X, Grant BJ, Murphy TF. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2007; 176(4):356–61. DOI: 10.1164/rccm.200703-417OC [PubMed: 17478618]

7. Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, Trujillo-Torralbo MB, Elkin S, Kon OM, Cookson WO, Moffatt MF, Johnston SL. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2013; 188(10):1224–31. DOI: 10.1164/rccm.201302-0341OC [PubMed: 23992479]

8. Huang YJ, Sethi S, Murphy T, Nariya S, Boushey HA, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. Journal of clinical microbiology. 2014; 52(8):2813–23. DOI: 10.1128/JCM.00035-14 [PubMed: 24850358]

9. Segal LN, Clemente JC, Wu BG, Wikoff WR, Gao Z, Li Y, Ko JP, Rom WN, Blaser MJ, Weiden MD. Randomised, double-blind, placebo-controlled trial with azithromycin selects for anti-inflammatory microbial metabolites in the emphysematous lung. Thorax. 2017; 72(1):13–22. DOI: 10.1136/thoraxjnl-2016-208599 [PubMed: 27486204]