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Antibiotic Retreatment for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Resolution of exacerbations of chronic obstructive pulmonary disease (COPD) can be incomplete and, even after resolution, relapse after a short period of baseline symptoms is common. It has been shown that incomplete resolution of exacerbations is associated with persistent airway and systemic inflammation (1, 2). One possible explanation of this persistent inflammation is either incomplete resolution of airway bacterial infection or a bacterial superinfection in the airway following an initial viral infection (3). A course of antibiotics, often a repeat course, is commonly prescribed in this situation, with little evidence to support this practice.

In this issue of the *Journal*, the study by Ritchie and colleagues (pp. 549–557) admirably sets out to address this difficult clinical question in a randomized controlled trial (4). The investigators studied whether antibiotic retreatment of incompletely recovered COPD exacerbations with ciprofloxacin prevented subsequent exacerbations or prolonged the time to next exacerbation within a 90-day period. The study randomized 144 patients but was unable to show an effect of antibiotic retreatment on time to the next exacerbation or significant effects on lung function or quality of life.

Although the Ritchie and colleagues' study is very important because it is the first of its kind to examine the question of antibiotic retreatment in a randomized controlled trial, the study has some potential flaws (4). Importantly, before we abandon the use of additional antibiotics in nonresolving exacerbations of COPD, we need to carefully examine whether the patients enrolled in this study would have been the ones who would have been expected to benefit from additional antibiotics.

Reliable indicators of bacterial infection in COPD are sputum purulence and the presence of an Anthonisen type 1 exacerbation with dyspnea, increased sputum volume, and increased sputum purulence (5). Of the patients in this study, only a small minority (22/144; 15%) had a type 1 exacerbation, and sputum purulence was present in only 41/144 (28%) at the time of randomization. Furthermore, at the time of entry into the study, 17% of the study patients reported complete resolution of their symptoms but were randomized to retreatment with antibiotics because of an elevated serum CRP (C-reactive protein). In retrospect, it seems apparent from examination of the baseline characteristics of the patients enrolled in this study that most did not have clinical evidence of bacterial airway infection at the time of randomization, and thus they did not meet traditional clinical criteria for antibiotic treatment nor would they have been expected to benefit from additional antibiotics.

Studies that have examined the symptomatic resolution of exacerbations with validated patient-reported outcome tools have shown that the median time to symptomatic resolution ranges from 9 to 16.5 days (6). However, there is considerable variation around this time frame, and some patients who are destined to recover have not yet reached their baseline level of symptoms 14 days after the initial onset of their exacerbation. These slow resolvers appear to be a significant proportion of the patients included in this study, as evidenced by the fact that the median time to full resolution of symptoms following randomization to retreatment was only 3 days in those treated with antibiotics and 4 days in the group treated with placebo. If these patients were indeed experiencing a persistent or superimposed bacterial infection, spontaneous resolution in 3 to 4 days would be highly unusual.

Understanding the value of an antibiotic treatment is enhanced by corresponding bacteriological data. If exacerbations are suspected to be bacterial, sputum yields potential pathogens in about half the instances (7). If bacterial persistence or superinfection are

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mechanisms of exacerbation nonresolution, then antibiotic resistant bacteria such as *Pseudomonas aeruginosa* or *Moraxella catarrhalis* should be prevalent. In fact, the recognition of *M. catarrhalis* as an important cause of COPD exacerbations came from several reports of patients failing treatment with a β -lactam antibiotic who were infected with a β -lactamase-producing strain of this pathogen (8). In this study, only 32% of patients could provide a sputum sample for bacteriology and only 15% of randomized patients had sputum that yielded a positive bacterial culture. This is not surprising given that most patients had very mild symptoms and did not display clinical characteristics suggesting they had a bacterial infection.

A final caveat to consider is the study power. The study was designed with a modest number of randomized patients and was only powered to detect a large (54%) prolongation in the time to next exacerbation in those treated with antibiotics. It is thus possible that the study findings are due to type II statistical error, whereby an important clinical effect goes undetected due to lack of power. Furthermore, this limitation in study power means that a subgroup analysis of patients with type 1 exacerbations would be too small to be reliable.

Despite these limitations, this important study informs our daily practice in managing exacerbations of COPD. It tells us that indiscriminate antibiotic retreatment in many patients with exacerbations of COPD is not of benefit, even if they have persistent symptoms (albeit mild) and/or an increased CRP. Such an approach will not reduce relapse rates or hasten the time to complete resolution. However, the study results do not inform us whether antibiotic treatment is useful when a patient experiences nonresolution with persistent or increased sputum purulence and/or a type 1 exacerbation. In fact, in clinical practice, these patients do not or should not be waiting 14 days for reassessment and additional management (9). A placebo-controlled trial in which only such patients are included in adequate numbers would be highly desirable to support or refute such a discriminate approach. In the meantime, we can reduce inappropriate antibiotic use and its undesirable consequences by stopping indiscriminate use. ■

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⌚ The Dark Side of Spontaneous Breathing during Noninvasive Ventilation From Hypothesis to Theory

Breathing by our own respiratory muscles is physiologically natural. The diaphragmatic contraction with spontaneous breathing (vs.

muscle paralysis) tends to distribute ventilation into dorsal, well-perfused lung regions, the benefit of which was first observed in healthy subjects or anesthetized patients (1). Subsequent to these classical studies, the role of spontaneous breathing in critically ill patients has been vigorously examined (2); now it is well known that spontaneous breathing during mechanical ventilation brings various benefits to ICU patients (e.g., better gas exchange, maintenance of peripheral muscles, and diaphragm function) (2, 3). Of course, because liberation from the ventilator has been a

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