Who Should Receive Antibiotics for Exacerbations of Chronic Bronchitis? A Plea for More Outcome-Based Studies

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(See the article by van der Valk et al. on pages 980–6)

For many years, there has been controversy about whether bacteria play a role in acute exacerbations of chronic bronchitis (AECB) and, thus, whether antibiotics have a role in disease management [1]. Many experts have recognized that there is widespread use of antibiotics in this population and have considered such therapy to often be unnecessary, arguing that the use of antibiotics adds to the problem of antimicrobial resistance [1–3]. This is an important concern, because most studies have shown that the repeated use of antibiotics in patients with chronic obstructive pulmonary disease (COPD) can lead to the emergence of drug-resistant pneumococci. In a recent consensus conference, the American College of Physicians (ACP)/American Society of Internal Medicine (ASIM)/American College of Chest Physicians (ACCP) stated that antibiotics have a limited role for treatment of this illness and should only be used by patients with severe exacerbations [2, 3].

In the current issue of *Clinical Infectious Diseases*, van der Valk et al. [4] have tried to identify clinical predictors of bacterial exacerbation of COPD in an effort to promote more judicious use of antibiotics. This may be a valuable goal, because they conclude that 38% of patients with non-bacterial exacerbation of COPD received antibiotics, whereas 36% of those with a documented bacterial infection did not receive antibiotic therapy.

Although the role of bacterial infection in AECB is debated, most evidence on this topic has been derived from bacteriologic cultures of respiratory secretion samples (collected either by expectoration or by bronchoscopy) that were studied either qualitatively or quantitatively, as was the case in the studies by van der Valk et al. [4] and others [5, 6]. This information has not always been useful for addressing the role of infection, because patients with chronic bronchitis typically have chronic airway colonization, and the presence of bacteria in airway secretions (even in high concentrations) does not establish an etiologic role in exacerbations.

Recently, this topic was elegantly studied by Sethi et al. [7, 8], who reported both bacteriologic and serologic observations that bolster the argument that bacteria do cause exacerbations. They found that exacerbations are more common after patients acquire colonization with a new strain of either *Haemophilus influenzae*, pneumococcus, or *Moraxella catarrhalis* (defined by molecular methods) than if the airway persistently harbors the same strain [7]. In a longitudinal study of outpatients, 33% of clinic visits that were associated with the acquisition of a new bacterial strain were accompanied by an exacerbation, compared with 15.4% of visits without the acquisition of a new bacterial strain [7]. In addition, these investigators showed that the acquisition of a new strain of *H. influenzae* is also accompanied by an antibody response to this same new organism [8]. They observed that, if patients acquired a new strain at the time of an exacerbation, a specific antibody response to this strain (determined by both an ELISA and a bactericidal antibody assay) was present 58.3% of the time, whereas only 15.2% of exacerbations characterized by the presence of a persistent strain were accompanied by an antibody response [8]. These data differ from findings from prior studies, which often examined only a single serum sample (rather than serial samples) and which measured levels of generic antibodies rather than antibodies directed to surface-exposed epitopes present on the actual strain in the airway during the exacerbation [8].
Together, these studies describe a cohesive mechanism for bacteria to cause exacerbation. Patients with chronic bronchitis are colonized with organisms such as *H. influenzae* and remain healthy, presumably because of the presence of an adequate host response to these organisms. Then, for unclear reasons, the strain of the organism changes, and the patient becomes ill because protective antibodies are not present. That this change in the strain is actually causing the exacerbation is also suggested by the finding that most patients who acquire a new strain of *H. influenzae* then develop a homologous antibody response to this organism. The development of an antibody response presumably protects the patient until either another new strain emerges or another pathogen infects the patient. It still remains unclear whether this paradigm also applies to *M. catarrhalis,* *pneumococcus,* and other pathogens implicated in exacerbations of chronic bronchitis.

Although bacteria can play a role in AECB, they probably account for no more than one-half of all exacerbations, and thus the question still remains: which patients should receive antibiotics? In the past, outcome studies have demonstrated that certain clinical features can define individuals who benefit from therapy. These include patients with ≥2 of the 3 “cardinal symptoms” of exacerbation—namely, increased dyspnea, increased sputum volume, and increased sputum purulence [9]. In addition, severe exacerbations requiring mechanical ventilation should be treated with antibiotics, and in one placebo-controlled study, the failure to do this led to increased mortality, primarily through the progression of bronchitis to pneumonia [10].

The study by van der Valk [4] uses a bacteriologic approach rather than an outcome-based approach to define whether antibiotic therapy is needed. This is a major limitation, because there is no information about whether patients with positive results of bacteriologic tests, either treated or untreated, had different clinical courses than did patients with negative results of bacteriologic tests. The study used quantitative cultures of expectorated sputum samples (shown to come from the lower airway by using criteria for the presence of both epithelial cells and neutrophils), which may be less accurate than cultures of bronchoscopic specimens. A bacterial exacerbation was defined by a quantitative predominance of a potentially pathogenic microorganism, but the authors did not provide information about which bacteria were isolated, so it is difficult to know the distribution of etiologic organisms. They found that 22 of 116 exacerbations were bacterial, but by using less-stringent microbiologic criteria, the proportion of bacterial exacerbations increased to 46%. Using stringent criteria, the predictors of a positive bacteriologic test result in a multivariate logistic regression model were a positive Gram stain result, a decrease in the forced expiratory volume in 1 s of >12% (and of ≥200 mL) from baseline, and the occurrence of ≥2 exacerbations in the preceding year. If this “rule” was used, it had a positive predictive value (if all 3 variables were present) of 67% and a negative predictive value (if all 3 variables were absent) of 100%. It is this last finding that may be most significant, because it may be very difficult to say who should be treated with antibiotics. On the other hand, these data seem reliable for telling us who should not be treated—namely, patients with none of the 3 predictor variables present. The authors calculated that 40% of the 28 patients for whom all 3 predictors were absent (all of whom had negative results of bacteriologic tests) had received antibiotics; thus, the use of this rule could have eliminated some unnecessary therapy.

Although the data are interesting, many unanswered questions remain. Most importantly, if such a rule is used—even if only to decide who not to treat—it must be validated by outcome-based information. In addition, for patients who are treated, the choice of therapy remains controversial as well. Although the ACP/ASIM/ACCP consensus conference concluded that there is no evidence that newer antibiotics are any better than older agents, other groups have disagreed [2, 3, 11, 12]. A Canadian consensus conference recommended that clinical features be used to define which therapy should be used for certain well-defined populations [12]. Although some retrospective data suggest that patients with more-complex acute and chronic disease may benefit from newer therapies, there are now prospective data regarding both gemifloxacin and moxifloxacin that show an outcome-based advantage for these agents, compared with older agents, in complex populations with AECB [13–15]. In the end, what we still need in the area of AECB are more outcome-based studies, including studies that involve end points other than bacteriologic eradication and clinical cure. Future studies should also examine the impact of specific therapies on time to resolution of symptoms, time lost from productive activity, disease-free intervals, and the impact of specific choices on the long-term emergence of antibiotic resistance.

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**References**


