Treatment Strategy for Asthma
One for All and All for One?

Treatment with inhaled antiinflammatory drugs and inhaled bronchodilators is the mainstay of treatment of asthma. Traditionally, inhaled corticosteroids have been considered to be the most effective treatment for the inflammatory component of asthma, and $\beta_2$-agonists have been considered as the most effective bronchodilator. The demonstration that the combination of an inhaled corticosteroid with a long-acting $\beta_2$-agonist, on average, improved measures of airflow better than higher doses of inhaled corticosteroids alone\(^1\)–\(^3\) prompted national and international guidelines to recommend therapy with a combination of the two drugs when asthma is inadequately controlled with a moderate dose of inhaled corticosteroids.\(^4\)

Two combinations of medications are currently available for clinical use: fluticasone combined with salmeterol; and budesonide combined with formoterol. Formoterol, in addition to providing sustained bronchodilation, has a rapid onset of action that enables it to be used as a reliever medication.\(^5\) This pharmacologic property, in theory, enables the combination of budesonide and formoterol to be used as a maintenance and reliever medication. This has now been tested in three randomized clinical trials, including the report by Rabe et al\(^6\) in this issue of CHEST (see page 246).\(^7\),\(^8\) Rabe and colleagues\(^6\) report the results of a comparison of the following two treatment strategies: a combination of budesonide (160 $\mu$g) and formoterol (9 $\mu$g) in a single inhaler used once daily as maintenance therapy and up to eight additional puffs of the combination as required; and a higher dose of budesonide (320 $\mu$g) once daily and additional therapy with terbutaline as required. Over a period of 6 months in this multicenter parallel-group study, the combination strategy significantly improved morning peak expiratory flow (primary outcome) and reduced the risk of severe exacerbations by 54\% compared to maintenance therapy with a higher dose of corticosteroids alone (number-needed-to-treat to prevent one severe exacerbation, 3.5). This was achieved with a mean less cumulative inhaled budesonide dose of 80 $\mu$g. This is consistent with the results of two previous studies,\(^7\),\(^8\) which examined the efficacy of this treatment strategy over a period of 1 year in patients with more severe asthma. The study by O’Byrne and colleagues\(^8\) further demonstrated that the combination therapy received during an exacerbation, compared to therapy with a short-acting bronchodilator alone, improved the resolution of the exacerbation.

The relevance of these observations is that it enables the simplification of the treatment of asthma for both patients and prescribers, while effectively improving clinically relevant asthma outcomes such as decreasing asthma exacerbations and improving symptoms and airflow obstruction. However, before it becomes widely endorsed as the most effective

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References
clinical strategy to prevent and treat asthma exacerbations, there are a number of issues to be considered. First, one needs to recognize the heterogeneity of airway inflammation associated with a loss of asthma control and exacerbations. A patient with an exacerbation associated with eosinophilic bronchitis almost always responds to therapy with an inhaled corticosteroid alone. A long-acting $\beta_2$-agonist is not necessary. Despite ex vivo data, there is no convincing clinical evidence that a long-acting $\beta_2$-agonist potentiates the antiinflammatory effect of a steroid. A patient with an exacerbation that is associated with neutrophilic bronchitis (usually due to a viral or a bacterial infection) usually does not respond to increased doses of corticosteroids. There is currently no effective therapy for this phenotype of exacerbation because this has not been investigated. A $\beta_2$-agonist (rapid or long-acting) may simply provide symptom relief while the exacerbation resolves spontaneously. Since more than half of exacerbations may be noneosinophilic (usually neutrophilic), the efficacy may be wrongly attributed to the combination treatment. This can only be resolved if the effect of an antiinflammatory therapy is evaluated using direct measurements of airway inflammation, such as sputum cell counts. Further, in the same patient, the nature of inflammation may vary with each exacerbation depending on the cause of the exacerbation. Second, the regular and excessive use of $\beta_2$-agonists is not without side effects. It is, therefore, prudent not to recommend them for all patients with asthma until it is possible to identify the responders and nonresponders, and the patients who are likely to be adversely affected with excessive use of $\beta_2$-agonists. Also, it is necessary to identify whether it is the corticosteroid or the long-acting $\beta_2$-agonist in the combination that can be credited with the clinical efficacy.

Asthma is a heterogeneous disease. Various components of the disease such as airflow limitation, airway hyperresponsiveness, and airway inflammation of different types and causes, in different combinations, may contribute to symptoms. Individualized therapy is thus necessary for optimal disease management. Currently, sputum cell counts are only used for clinical practice in a few academic centers. Thus, this “tailored” therapy may seem impractical. However, the measurements are practical, and when they become properly remunerated and automated, they will become more widely available and utilized. Before a single therapy is recommended by all specialists and general practitioners, even need to consider separate guidelines for specialists and general practitioners.

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Coinfection in Exacerbations of COPD

A New Frontier

Investigations with modern investigative techniques have clarified considerably the role of bacteria and viruses in the pathogenesis of exacerbations of COPD. Application of polymerase chain reaction-based methods for detection has shown that viral nucleic acids are present in respiratory secretions in 30 to 50% of exacerbations. Furthermore, these studies used sputum samples, rather than nasopharyngeal samples, as was done in previous studies, providing us with confidence that direct viral infection of the tracheobronchial tree is responsible for the exacerbation. Application of molecular epidemiology has demonstrated that acquisition of new strains of bacteria is critical to the pathogenesis of bacterial exacerbations. Other investigations have shown that specific immune responses and a neutrophilic inflammatory process accompany bacterial exacerbations. Typical and atypical bacterial pathogens are now implicated in up to 50% of exacerbations.

Though our knowledge of bacterial and viral exacerbation pathogenesis as sole agents has improved considerably, little is known about the consequences of coinfection with these infectious agents in COPD. In this issue of CHEST (see page 317), Wilkinson et al demonstrate that simultaneous identification of bacterial and viral pathogens in sputum at the time of exacerbation is associated with enhanced airway inflammation, increased bacterial load and symptoms, and a larger decrement in lung function.

Their findings are interesting and valuable. However, this study has important limitations that should be considered in its interpretation. The only virus actively identified in this study was the rhinovirus. Identification of other viruses would have been useful; instead, cold symptoms were used as a surrogate. However, it is unclear how specific cold symptoms are for viral infection, as allergic and environmental stimuli can induce similar symptoms. Sera obtained before and after the exacerbation were available to the investigators. Demonstration of a serological response to viral antigens would have enhanced the pathogenic significance of the rhinovirus identified. It is difficult to draw conclusions regarding the pathogenic significance of bacterial pathogens isolated from sputum in the study. Specifically, the investigators did not attempt strain identification by molecular methods to distinguish between colonizing strains antedating the exacerbation and new acquisitions at the time of exacerbation. Demonstration of a serologic response to the infecting bacterial strain would have also been important.

Bacterial-viral interaction in the lower respiratory tract is best understood in the context of influenza and the development of secondary bacterial pneumonia. Similar mechanisms may exist in COPD exacerbations, including viral infection related impairment of innate and adaptive immune mechanisms as well as increased bacterial adherence to host cells. Mechanisms that are peculiar to COPD are also likely. The deleterious effects of viral infection of an already compromised mucociliary clearance could allow retention of secretions and bacterial overgrowth. Inflammation induced by the viral infection in an already inflamed airway could impair lung defense mechanisms, allowing establishment of bacterial infection. Mechanisms of bacterial-viral interaction are poorly understood in the context of COPD and warrant further investigation. Furthermore, most bacterial-viral interaction research has focused on the influenza virus, whereas in COPD, rhinovirus and respiratory syncytial virus infections are equally important.

The conventional paradigm is that an acute viral infection precedes and predisposes to the development of bacterial infection in the respiratory tract. However, an alternative paradigm may exist in COPD, in which bacterial infection may facilitate viral infection. Chronic bacterial infection of the lower airways in COPD is an inflammatory stimulus, and a chronically inflamed airway is likely to be more hospitable to viral pathogens. In fact, increased levels of baseline airway inflammation in COPD are associated with more frequent exacerbations.

In this study, a higher airway bacterial load as measured in sputum was seen in coinfections and during exacerbations as compared to stable state. Several issues surround the measurement of bacterial load: its significance and its interpretation. Two methods are used by investigators to assess airway bacterial load. In the first method, as in this study, all bacterial colonies isolated, pathogens and nonpathogenic species, are counted as contributing to the bacterial load. This method assumes that all bacteria isolated in sputum are coming from the lower respiratory tract. That is unlikely because some extent of...