EDITORIAL

Systemic Markers of Exacerbated Chronic Obstructive Pulmonary Disease: How They Can Help With the Decision of Whether or Not to Prescribe Antibiotics

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The natural history of chronic obstructive pulmonary disease (COPD) is characterized by recurrent exacerbations that manifest as changes in the patient's usual clinical situation, with an increase in respiratory symptoms. Although there is no clear definition of COPD exacerbation, we know that a wide range of factors trigger them. Most are caused by infectious agents, such as viruses or bacteria, although unknown environmental agents are sometimes involved. Though experience has shown that both corticosteroids and antibiotics have a beneficial effect in the standard treatment of COPD exacerbations, there are no known clinical or biological parameters that are able to accurately determine the etiology of exacerbations.

In recent years, ever increasing attention has been given to studying the role played by systemic markers of the inflammatory response mechanisms observed in COPD exacerbation. The description of such circulating biomarkers is of vital importance since they may ultimately be the key to detecting exacerbations whose cause requires specific treatment. The practical utility of such markers is related to the important clinical decision of whether or not to administer antibiotic treatment in exacerbations.[1]

An epidemiological survey carried out in 360 US hospitals, involving 69 820 COPD patients hospitalized for exacerbations, showed that 85% received antibiotic treatment.[2] A similar survey in Spain, France, the United Kingdom, and Italy of a cohort of 600 patients hospitalized for exacerbations of COPD showed that more than 80% were finally treated with antibiotics (unpublished data). Information from these surveys indicates that the use of antibiotics in treating patients hospitalized with exacerbations is common practice. However, though the prescription of antibiotics for exacerbated COPD is almost universal, there is no clear evidence of their efficacy in all cases: some controlled studies show antibiotics to be beneficial, whereas others conclude they are of little benefit. It is well known that uncontrolled use of antibiotics in this context raises health care costs and has negative repercussions on bacterial resistance rates.[3] The latter factor is especially problematic in elderly patients who present more severely reduced lung function, have other concomitant diseases, or suffer frequent exacerbations that often require hospitalization.

A recent meta-analysis that systematically reviewed the results of 11 randomized placebo-controlled trials carried out between 1966 and 2005 concluded that the use of antibiotics had a clearly beneficial effect on COPD exacerbations characterized by increased sputum volume and purulence.[4] In such cases the use of antibiotics reduced the risk of short-term mortality by 77% and the rate of treatment failure by 53%. In general, antibiotics were seen to benefit patients with moderate to severe COPD and, as expected, patients who required hospitalization. Such results, however, should be interpreted with caution since the meta-analysis included studies with notable differences in patient selection criteria and choice of antibiotic. In summary, to date no appropriately designed clinical trial has evaluated the benefits of withholding antibiotics in cases of nonpurulent exacerbation of COPD, despite the fact that patients with such exacerbations are a significant group among those requiring hospitalization.

Determining the infectious etiology of COPD exacerbations has become an ever-present challenge for researchers in this field since most studies evaluating the relation between exacerbation and infectious bacteria are based on sputum sample cultures—a cost-effective technique, but one that is often omitted when evaluating a patient with COPD owing to the difficulty of differentiating between bacterial infection and colonization. With this limitation in mind, some authors have reported that the presence of purulent sputum is significantly correlated with the isolation of pathogenic bacteria in these patients. This finding underlines the importance of using simple clinical criteria that are clearly associated with respiratory infection.[5,6] Along the same line, a recent study of patients with exacerbated COPD who required hospitalization showed that the criterion "purulence" reported by the patient on admission is a good predictor

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(sensitivity, 89.5%; specificity, 76.2%; negative predictive value, 88.9%) of bacterial infection.[7]

Recent clinical studies have also explored the role of certain systemic markers in determining the etiology of exacerbations and in deciding whether or not to prescribe an antibiotic.[8,9] These authors have reported that the use of such markers seemed to contribute to establishing the prognosis in exacerbations in terms of length of hospital stay, treatment failure, and mortality.

In general, an ideal marker of bacterial infection should enable a correct diagnosis, provide information on the course of disease and prognosis, and facilitate treatment decision-making. In recent years, the C-reactive protein (CRP) level has provided a reliable indicator of bacterial infection: some authors have reported CRP levels to be significantly elevated in patients with exacerbations of COPD and purulent sputum.[5,10] Such findings suggest that CRP would be a useful marker in decision-making on whether to prescribe antibiotics for exacerbations of COPD with sputum purulence. However, a meta-analysis designed to assess the diagnostic accuracy of serum CRP and procalcitonin in patients hospitalized for suspected bacterial infection showed that procalcitonin is clearly more sensitive and specific than CRP for differentiating bacterial infection from other causes of systemic inflammation.[11]

Peptides known as hormokines, such as procalcitonin, copeptin, and proadrenomedullin, seem to meet the profile of the ideal biomarker better than other more commonly used candidates. Levels of circulating procalcitonin are markedly higher in bacterial infection than in viral infection or noninfectious inflammatory disease, an observation that has shown procalcitonin to be an effective marker of systemic infection, such that it has been used as a criterion for antibiotic treatment of lower airway infections.[1] In January 2007, Stolz et al[12] reported the results of a study in which 208 patients who required hospitalization for exacerbations of COPD were randomized to receive antibiotic treatment at admission either in accordance with standard clinical criteria or in relation to serum concentrations of procalcitonin at admission. Their study showed that basing the therapeutic strategy on procalcitonin concentrations (procalcitonic guidance) decreased the prescription of antibiotics to 40% (in contrast to the 72% treated with antibiotics according to standard clinical criteria). Moreover, the group of patients whose treatment was guided by procalcitonin level were prescribed less antibiotic medication during the 6 months following the COPD exacerbation. During the 6-month follow-up of the cohort, however, no differences between the 2 groups were noted regarding forced expiratory volume in 1 second expressed as a percentage of the reference value (FEV_1%), the number of readmissions, or the time elapsed before the next exacerbation. Though the results of Stolz and coworkers seem to show that procalcitonin level may be useful when considering how to treat an exacerbation of COPD, regardless of other factors, their study has limitations that prevent the widespread use of this biomarker at this time. When the patients' sputum was analyzed, no significant association was observed between purulence (present in 58% of the samples) and an elevation in serum procalcitonin. Likewise, though the study did not include exhaustive microbiological tests, no correlation was found between isolation of bacteria from sputum and elevation of serum procalcitonin. Furthermore this study, like others of similar design in this line of research, had 2 potential limitations that could prevent the generalization of findings to all patients with COPD.[13] First, most patients with exacerbations of COPD have serum procalcitonin levels of less than 0.1 µg/mL, indicating the absence of bacterial infection, or they have concentrations between 0.1 µg/mL and 0.25 µg/mL, meaning that antibiotic treatment would have to proceed according to clinical criteria.[12] Secondly, initiating a treatment plan as soon as possible means that serum concentrations of procalcitonin and other homokines should be measured within the first or second hour after the patient's arrival at the emergency department—a circumstance that would limit the use of this biomarker in patients who are hospitalized with moderate or severe exacerbations and for those with milder exacerbations treated at home.

In light of these findings, further studies are needed to determine the utility of antibiotic treatment for patients with nonpurulent exacerbations of COPD in order to establish explicit definitions of exacerbation criteria as well as useful measures for assessing clinical course and prognosis following exercerbation. Priorities for this line of research should be the evaluation of simple criteria that would enable combining clinical markers of infection (eg, purulent sputum) and systemic markers (eg, CRP, procalcitonin, or other circulating hormokines, such as copeptin or proadrenomedullin).

REFERENCES

1. Christ-Crain M, Müller B. Biomarkers in respiratory infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J. 2007;30:556-73.
2. Lindenauer PK, Pekow P, Gao S, Crawford AS, Gutiérrez B, Benjamin EM. Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 2006;114:894-903.
3. Nseir S, di Pompeo C, Cavestri B, Jozefowicz E, Nyunga M, Soubrier S, et al. Multidrug resistant bacteria in patients with acute severe exacerbations of chronic obstructive pulmonary disease: prevalence, risk factors and outcomes. Am J Respir Crit Care Med. 2006;34:2959-66.
4. Ram F, Rodríguez Roisin R, Granados Navarrete A, García-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Acute Respiratory Infections Group. Cochrane Database Syst Rev. 2006;(2):CD004403.
5. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest. 2000;117:1638-45.
6. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C, Hendrix R. Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease. Clin Infect Dis. 2004;39:980-6.
7. Soler N, Agustí C, Angrill J, Puig de la Bellacasa J, Torres A. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease (COPD). Thorax. 2007;62:29-35.
8. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, et al. Co-peptin, C-reactive protein and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest. 2007;131:1058-67.

9. Stolz D, Christ-Crain M, Morgenthaler NG, Miedinger D, Leuppi J, Müller C, et al. Plasma pro-adrenomedullin but not pro-endothelin predicts survival in exacerbations of COPD. Chest. At press 2008.
10. Weis N, Almdal T. C-reactive protein – can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? Eur J Intern Med. 2004;17:88-91.
11. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39:206-17.
12. Stoltz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonic-guidance with standard therapy. Chest. 2007;131:9-19.
13. Müller B, Morgenthaler N, Stolz D, Schuetz P, Muller C, Bingisser R, et al. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. Eur J Clin Invest. 2007;37:145-52.