Bronchodilators in COPD
To the Max

Is the approach to bronchodilator therapy for COPD patients about to change course? The last decade has witnessed a transformation in asthma therapy with more intensive use of inhaled bronchodilators. A number of recent studies in COPD patients suggest that single drug therapy can achieve maximal bronchodilation without necessitating a polypharmacy regimen. However, single drug bronchodilator therapy is not universally accepted. A number of factors, specific both to the patients we study, as well as to our methods of assessment, may account for these differences of opinion.

Studies in stable outpatients with COPD demonstrate that, with adequate dosing and delivery, an inhaled bronchodilator (either a beta agonist or an antimuscarinic) can result in complete bronchodilation (as measured by FEV₁). In these studies, addition of a second agent did not result in further spirometric improvement. These findings were independent of the class of agent used, beta agonist or anti-muscarinic; in the dose regimens studied, both types of bronchodilators were equally effective. The study by Karpel et al in this issue (see page 871) is consistent with these findings. Additionally, this trial extends the conclusions to include treatment in both the acute and chronic settings.

The results of other studies conflict with these conclusions. In the study of Gross and Skorodin, the addition of an inhaled antimuscarinic to initial beta agonist therapy resulted in further bronchodilation. Differences in study design (study population, particular drug, route, dosage, site of deposition) as well as patient factors (receptor down regulation, basal airway state, airways inflammation) may account in part for these disparate conclusions regarding effects of multidrug therapy.

Apart from patient considerations, the experimental methods for determining bronchodilation also may affect study results. If we are to contend that a particular bronchodilator can provide maximal airway dilation, we must be very clear regarding the definition of maximum bronchodilation. Most clinical studies use an improvement in flow (typically the FEV₁) as that endpoint. While this may be the best overall discriminator for a significant bronchodilator re-

sponses, other indicators (FEF25-75, FVC) may be more sensitive in certain individuals.

Other difficulties are inherent in the analysis of a maximal response. Patients acutely ill with an exacerbation of COPD or even in a chronic "stable" state, show lability in their airway dynamics; these patients present a moving target for our assessments of drug response. In the companion investigations of Karpel et al, the same patients, studied short- and long-term, reached their endpoints of "maximal bronchodilation." However, in the chronic state, patients had a pre-therapy FEV₁ about equal to their post-therapy maximums under acute conditions. We may not be intuitively surprised by these results, but they highlight the point that "maximum bronchodilation" is a relative term, not an absolute one. Other factors (patient variables, airway inflammation) may modulate airway responses to produce differing "maximum" endpoints.

While the answer—single or multidrug bronchodilator therapy in COPD—is not yet in, we are learning how to pose the question. Although we may eventually be able to agree on methodology and therapeutic endpoints, many clinical factors govern bronchodilator responsiveness. Therefore, in some patients, we must still consider the addition of other medications (anti-inflammatories, alternate bronchodilator) if we are to take the COPD patient's bronchodilator response "to the max."

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The Role of Chest CT in Evaluation of the Febrile Bone Marrow Transplant Recipient

Bone marrow transplantation is used as treatment for a growing number of disorders including acute and chronic leukemia, aplastic anemia, lymphoma, and breast cancer. Many factors determine the survival of patients undergoing bone marrow transplantation. In the immediate post-transplantation period prior to successful marrow engraftment, infection remains one of the major causes of morbidity and mortality. Most infections during this period are bacterial and fungal, with the risk of invasive fungal disease increasing proportionally to the depth and duration of granulocytopenia. After successful marrow engraftment, viral infections, particularly those due to cytomegalovirus, become an increasing problem.

Improved survival of patients undergoing bone marrow transplantation depends critically on early detection and appropriate treatment of opportunistic infections that occur during the aplastic period. Unfortunately, early recognition and definitive diagnosis of such infections, including pulmonary infections, are difficult and often elusive. The most common clinical problem is the profoundly neutropenic patient with persistent fever despite broad spectrum antibiotics. Localizing pulmonary symptoms such as cough or pleuritic chest pain may or may not be present. Many of the plain film findings of early lung infection are subtle and nonspecific. Opportunistic fungal and viral organisms are fastidious and difficult to isolate. Sputum cultures are frequently negative early in the course of infection and may not become positive until long after the culture was obtained. The significance of positive cultures obtained noninvasively from the upper respiratory tract is also controversial as to whether isolated organisms represent true infection or merely colonization. Invasive biopsy procedures which might otherwise provide a definitive diagnosis are often prohibited in such patients because of their compromised respiratory status and severe thrombocytopenia. Yields on attempted biopsies are often disappointingly low. Although the routine use of broad-spectrum antibiotics has decreased mortality from bacterial infections, empiric treatment of invasive fungal disease with amphotericin B is not without complications, particularly nephrotoxicity. Thus, substantiating evidence to support a clinical suspicion of invasive fungal infection is often desired before an aggressive course of high-dose antifungal therapy is begun. A rapid, noninvasive technique which could facilitate early detection and characterization of pulmonary infection in the bone marrow transplant recipient might be expected to improve survival from opportunistic pulmonary infection.

The article by Barloon et al appearing this month (see page 925) adds to a growing body of evidence to suggest that computed tomography (CT) has become an important noninvasive tool for the evaluation of the febrile patient following bone marrow transplantation. Their work, along with others, underscores the potential role of CT in the aggressive management of opportunistic lung infection through early detection, characterization of pulmonary infiltrates, and determination of disease extent and response to therapy.

Many questions still remain. Is CT more sensitive than conventional chest films in detecting early infection in the patient undergoing bone marrow transplantation? In the study by Barloon et al, CT failed to provide statistically significant additional information in patients with normal chest radiographs, but the study was not designed as a prospective comparison of serial chest films and serial CT examinations in their respective abilities to detect early lung infection. Circumstantial evidence provided from work on other pulmonary diseases would suggest that CT might be more sensitive in detecting at least certain types of lung infection in this patient population. CT has clearly been shown to be more sensitive than conventional radiographs in the detection of pulmonary nodules and metastases. It would not be surprising, therefore, if CT were found to be more sensitive than conventional plain films in detecting early invasive pulmonary aspergillosis, since the earliest pulmonary lesions in this infection are small inflammatory nodules. In addition, conventional radiographs of the chest are often limited in the acutely ill patient by poor inspiratory effort, portable technique, and respiratory motion. Advances in CT technology and decreases in scan acquisition times have contributed greatly to both the speed and quality of CT examination, particularly in the immunocompromised host with pulmonary infection. One second and second CT scan times are now available on many state-of-the-art CT scanners, eliminating many of the earlier problems of respiratory artifacts in the acutely ill patient and allowing diagnostic examinations of the chest to be performed in 10 minutes or less. High-