spironolactone. This drug is thought to work through the inhibition of aldosterone, not by its overall diuretic effect, although the exact mechanism of action of spironolactone in CHF is not yet clear. Thus, higher doses are not necessarily better for patients, nor were the results of higher doses studied. Yet we have observed a number of patients with electrolyte abnormalities associated with high-dose spironolactone therapy. Indeed, with the extensive publicity this study received this past summer and the enthusiasm with which spironolactone therapy has been embraced, we have observed that many patients are receiving this drug despite not being represented in the trial. We are seeing patients with NYHA class I or II symptoms, patients not on ACE inhibitors, and patients with CHF associated with preserved left ventricular systolic function receiving spironolactone treatment.

An additional concern we have is the lack of treatment with β-blockers of NYHA class III patients in RALES (who comprised two thirds of the study population). The authors of the RALES report note that their patients were at higher risk than those in the β-blocker trials available at the time, but additional evidence demonstrating the effectiveness of β-blockers for CHF treatment continues to accumulate. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), over half of the patient population in the study had NYHA class III symptoms at the time of enrollment.7 Like other β-blockade clinical trials, MERIT-HF also demonstrated improved survival, improved NYHA functional class, and reduced need for hospitalization due to worsening CHF for those patients receiving β-blocker therapy compared with those patients receiving placebo. There is also accumulating evidence that favors treatment of patients with NYHA class IV symptoms with β-blockers.8 In summary, we agree with the recommendations of Califf and O’Connor9 that all patients with a left ventricular ejection fraction ≤ 40% and no contraindication to β-blocker therapy should have treatment initiated with one of these drugs. The findings of RALES, though impressive, do not release clinicians from the duty they have to attempt β-blockade treatment of their CHF patients, a treatment that has a far larger body of evidence justifying its use.

In conclusion, we are glad that RALES has demonstrated that spironolactone may benefit patients with severe CHF symptoms. We recommend its use for patients with NYHA class III or IV symptoms who are already receiving regimens of optimal loop diuretics, ACE inhibitors, and β-blockers. Clinicians should start patients at a dose of 25 mg po qd, and they should check electrolytes 1 week after initiation. A dose increase to 50 mg po qd can be considered for patients with progressive CHF symptoms while receiving the lower dose; electrolytes should be checked shortly after the dose increase and periodically thereafter. We believe that adverse events of spironolactone therapy will be as rare in “real world” practice as in the RALES trial if patients are carefully chosen for spironolactone therapy and if they receive close follow-up.

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Acute Exacerbation of Chronic Bronchitis

What Is the Clinical Significance of Pathogenic Bacteria in Sputum Cultures?

Acute exacerbation of chronic bronchitis (AECB) in patients with COPD is an important disease affecting millions of Americans. The use of antibiot-
ics in such patients is controversial, as the etiology of AECB is complex, including inhalation of environmental irritants, discontinuation of medications, deviation from diet, viral infections, atypical bacterial infections, especially *Chlamydia pneumoniae*, and pyogenic bacterial infections.\(^1\)–\(^3\) Although the use of antibiotics in patients with AECB has been reported to be beneficial,\(^4\),\(^5\) it is clear that not every episode of AECB needs antimicrobial therapy. Furthermore, injudicious use of antibiotics has led to increasing bacterial resistance, resulting in ineffectiveness of commonly used antibiotics.\(^5\)

The role of pathogenic bacteria in sputum cultures from patients with AECB is controversial, since these bacteria may be present in COPD patients with stable chronic bronchitis. In other words, do these bacteria represent colonization or infectious agents causing AECB in these COPD patients?\(^7\)

In this issue of CHEST (see page 1557), a group of experienced investigators used a new line of inquiry into the clinical significance of *Haemophilus influenzae* and *Moraxella catarrhalis* cultured from sputum of COPD patients with AECB. They studied a group of COPD patients who were followed prospectively at regular intervals and when symptoms were suggestive of AECB in a study clinic of Veterans Affairs Medical Center. They cultured sputum, expectorated or induced, from patients who had clinical evidence of AECB. At the same time, the sputum specimens were assayed for interleukin (IL)-8, tumor necrosis factor (TNF)-\(\alpha\), and neutrophil elastase (NE), which were used as surrogates for neutrophilic inflammatory response to acute bacterial infection of the airways. They found that AECB sputum specimens that grew *H influenzae* were associated with significantly higher sputum IL-8, TNF-\(\alpha\), and NE, and that *M catarrhalis* in sputum cultures was associated with significantly higher sputum TNF and NE when compared to sputum specimens that grew normal oropharyngeal flora. The interpretation of these results was that the presence of *H influenzae* or *M catarrhalis* in sputum cultures was associated with significant higher sputum TNF and NE when compared to sputum specimens that grew normal oropharyngeal flora. The clinical significance of *S pneumoniae*, other Gram-negative bacilli, and multiple bacterial pathogens in sputum cultures of COPD patients with AECB should similarly be studied in the future. Perhaps studies can also be done involving atypical bacteria by substituting serologic studies for sputum cultures. This may lead to the more rational use of antibiotics in COPD patients with AECB, thereby reducing the occurrence of antibiotic resistance, which is currently a major public health problem. “Emerging Antibiotic Resistance” was the first-ever Clinical Theme in the 2000 Annual Session of the American College of Physicians-American Society of Internal Medicine.\(^6\)

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Home Mechanical Ventilation in COPD

Do We Know When and How To Use It?

In the end stage of COPD, chronic respiratory failure is usually present and most patients are prescribed long-term oxygen therapy. However, significant hypercapnia often develops with oxygen administration, particularly at night, even when oxygen flow has been adjusted. Alternatives to oxygen therapy are scarce, but one promising candidate, noninvasive ventilation (NIV), can theoretically provide benefits by compensating for nighttime hypoventilation, allowing respiratory muscles to rest, improving nocturnal gas exchange, and resetting central respiratory control in response to PaCO₂ concentration. Sleep quality should thereby improve, as should arterial blood gas measures and perhaps daytime symptoms and patient survival.

Solid clinical evidence of the usefulness of NIV in COPD patients is lacking, yet the technique is being applied with mixed results, as shown by discrepant reports in literature. In a randomized crossover study by Strumpf et al., in which NIV was compared to conventional treatment of 19 patients over 3 months, compliance was poor (only 7 patients completed the study) and no changes in pulmonary function, gas exchange, sleep quality, exercise tolerance, or neurophysiologic variables were observed with either treatment. The authors therefore concluded that NIV provides no apparent clinical benefit. Meecham Jones et al. then reported strikingly different results after a similarly designed study of 18 patients with chronic respiratory hypercapnic failure due to COPD. NIV plus oxygen therapy was compared to oxygen therapy alone. Significant improvements in daytime gas exchange, overnight PaCO₂, sleep efficiency, and quality-of-life scores were observed in the NIV group. Moreover, improved daytime gas exchange correlated with changes in overnight PaCO₂, suggesting that improved ventilation during the night (reduced PaCO₂) accounted for the response to NIV. Other studies of NIV are also inconclusive, particularly as they feature methodologic shortcomings such as a short clinical follow-up, a small number of patients, or only retrospective analysis. At present, we therefore have no adequate analyses of the impact of home mechanical ventilation on the survival of COPD patients.

In this issue of CHEST (see page 1582), Casanova et al present the most ambitious study published to date, with the largest number of patients and the longest period of follow-up (1 year), thus making a valuable contribution toward clarifying the possible usefulness of NIV. In this randomized, controlled trial enrolling 52 patients with severe COPD, standard treatment alone was compared to nasal NIV plus standard treatment. Most patients in both treatment groups also received domiciliary oxygen therapy. No statistically significant differences in respiratory lung function or survival were found, although the authors did not analyze important variables such as quality of life or sleep.

What might account for such mixed results from the application of home mechanical ventilation of stable COPD patients? It may be that differences in enrollment criteria from study to study are responsible for the disparity. Thus, it may be relevant that a favorable outcome was seen in patients with high initial PaCO₂ in the study by Meecham Jones et al., while patients with nearly normocapnia at the beginning of another trial received no benefit. Hypercapnic patients can be assumed to have developed high nocturnal hypoventilation and, therefore, to respond better to nocturnal ventilation, as was in fact observed by Meecham Jones et al.. A decrease in daytime PaCO₂ would then undoubtedly lead to some alleviation of symptoms. Nocturnal hypoventilation analysis may therefore be needed to explain the clinical results in trials such as these, above all when oxygen is administered. The studies by Meecham Jones et al. and Sivasothy et al. are the only ones that analyzed this factor, demonstrated that patients with greater alteration of nighttime ventilation are those who show a greater response to NIV, and it may well be that studies reporting little or no benefit from NIV were those enrolling patients without meaningful nocturnal hypoventilation. A second likely source of discrepant results may lie in the differences in adjustment of NIV parameters and, above all, the monitoring of response to NIV therapy. In the study by Strumpf et al., ventilation was adjusted when patients were ambulatory, making it impossible to confidently assess response to NIV. Only Meecham Jones et al. and Sivasothy et al. adjusted NIV parameters to monitor changes in