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INSIDE

Financial Disclosure: *Critical Care Alert*'s Editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson, MD, report no financial relationships related to this field of study.

Fluid Management Strategies in ARDS

ABSTRACT & COMMENTARY

By Uday Nanavaty, MD

Pulmonary and Critical Care Medicine, Rockville, MD

Dr. Nanavaty reports no financial relationships related to this field of study.

Synopsis: *In a large randomized trial of two fluid management strategies in patients with ALI or ARDS, investigators found no difference in mortality between liberal or conservative fluid strategies. In spite of arguments about early liberation from the ventilator and shorter ICU stays, the benefits of the rather complex "conservative" fluid management strategy remain unclear.*

Source: The ARDS Net Investigators. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564-2575.

Proper fluid management of patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) is important. Although the pulmonary edema in ARDS patients is not due to increased hydrostatic pressures, it is believed that there is more fluid leakage at higher pressures. Further, if fluid administration results in lower blood oncotic pressure, it may result in an increased tendency towards edema formation. Whether restricting intravenous fluids or early diuresis can improve mortality in patients with ALI or ARDS is not clear, so the investigators conducted a randomized, controlled, clinical trial of a liberal fluid strategy (which might be considered usual practice) compared to a conservative strategy (the experimental strategy for this trial). Participants of this trial were additionally randomized to receive either a central venous catheter (CVC) or a pulmonary artery catheter (PAC) to further direct the fluid management. Since the outcomes were the same whether the patients received a PAC or a CVC, in the analysis the fluid management strategy was used to group the patients irrespective of which catheter was used.

Over 4 years, more than 11,000 patients were screened, and 1001 patients were enrolled in the study. Patients were of similar age and severity of illness. Within 48 hours of development of ALI or

ARDS, patients were randomized to a conservative (503 patients) or liberal (497 patients) fluid management strategy with fluid management being directed by a predetermined protocol. For patients in shock, liberal fluid use was allowed in the conservative strategy, and for patients with high oxygen requirements, fluid boluses were somewhat restricted at adequate filling pressures in the liberal strategy. The details of this fluid management strategy are beyond the scope of this review. The ventilator management was per ARDS Network protocol of lung protective ventilation.

At 60 days, there was no difference in mortality rate between the conservative management (25.5 ± 1.9%) or liberal management (28.4 ± 2.0%) strategies. The conservative strategy patients had more ventilator-free days, days free of central nervous system failure, and ICU-free days, during the first 28 days. There were no significant differences in the number of failure-free days for other organs during the first 28 days, although there was a small increase in the number of cardiovascular-failure free days during the first 7 days with the liberal strategy. Black patients seem to have experienced a higher mortality rate, but that difference was not significant once adjustment for co-morbidities was made. The numbers of patients needing renal replacement therapies were similar in the two groups.

Critical Care Alert, ISSN 1067-9502, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Critical Care Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issues date.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robert.kimball@thomson.com

World Wide Web: http://www.ahcpub.com

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $289

(Student/Resident rate: $120)

Multiple Copies

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COMMENTARY

In my honest opinion, this massive study proves nothing. When 11,000 patients are screened and only 10% are eligible or enrolled in a trial, generalization of the study's findings is impossible. The protocol seems tedious and almost unrealistic in clinical application. Although the authors have gone to great lengths to suggest that ventilator-free days and days out of the ICU were statistically significantly better with the conservative (experimental) strategy, those conclusions seem just statistics and are unlikely to change practice very much. The authors have tried to dig hard into the database to come up with some positive conclusion of this massive clinical exercise but have come up really empty handed.

The original ARDS network protocol looked at mortality at 30 days and showed the difference in mortality then. The protocol here had to be stretched to 60 days and yet they could not show a mortality difference. The ventilator-free days and ICU-free days are calculated at 28 days, hence the differences reach statistical significance. Let's stretch them to 45 or 60 days or look at 7 days (when study protocol ended) and there would be no differences, I presume.

The preachers of the low tidal volume strategy did not practice their teaching. At the time of randomization, about 48 hours into the ALI/ARDS, tidal volumes were close to 7.4 mL/kg of predicted body weight. That would mean that they either do not start the ALI-ARDS protocol early enough or do not believe in their own results.

There is an alternative explanation in my opinion about the reason why the ventilator-free days were increased in the conservative-strategy patients. I presume that this group of patients was developing contraction alkalosis. With a significantly high number of patients with metabolic alkalosis, it is possible that they tolerated higher arterial CO_2 levels and hence were breathing at a slightly lower minute ventilation, and hence were able to come off the ventilator a little bit early.

The authors did not describe the problems of hypokalemia as well. With frequent use of diuretics, I suspect that a large number of the conservative strategy patients needed frequent potassium checks and/or replacement. The hemodynamic parameters also are not usual standard practice, as far as other studies are concerned. Previous studies of "dry lungs equal happy lungs" have failed to show truth as far as mortality rates are concerned, and this massive expenditure of our tax dollars joins that list in my mind. Conservative or liberal, keep doing the right things, doctor. ■

How Common is Pulmonary Embolism in Patients with COPD Exacerbations?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In a selected population of patients with known COPD who were hospitalized with acute worsening of respiratory symptoms but did not have usual signs of an infection or other specific process, 25% were found to have pulmonary embolism.*

Source: Tillie-Leblond I, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med*. 2006;144:390-396.

In this study from the University Hospital A Calmette in Lille, France, patients with known COPD who were admitted because of acute respiratory deterioration were evaluated for inclusion in a prospective investigation of the prevalence and risk factors for pulmonary thromboembolism (PE) in this setting. Patients who required intubation were excluded, as were all who had purulent sputum, a history of cold or sore throat, a discrepancy between radiographic findings and the clinical picture, severe hypoxemia, pneumothorax, or "iatrogenic intervention" (not further defined). Patients who had none of these exclusionary features underwent spiral computed tomography angiography and venous ultrasonography, and if either of these was positive the patient was classified as having PE. The investigators recorded demographic and clinical data and calculated the probability of PE using the Geneva score. This score correlates the risk of PE with age, previous PE or deep-vein thrombosis, recent surgery, heart rate, arterial PO_2 and PCO_2, and selected findings on chest radiograph.[1]

During the 45-month study, 211 patients met the entry criteria, of whom 197 had complete data and form the basis of the article. Two-thirds of them were admitted from the emergency department and one-third were already in the hospital at the time of referral. One hundred-sixty of 197 patients had had pulmonary function tests within 3 months prior to admission, and their mean FEV_1 was 1.56 L (52% of predicted). Mean admission arterial PO_2 and PCO_2 values off supplemental oxygen were 62 and 42 mm Hg, respectively; 29% of the patients had known underlying malignancy.

Forty nine of the 197 patients (25%) met the diagnostic criteria for PE. Clinical factors associated with a statistically significant increased risk for PE were prior PE (risk ratio, 2.43), malignant disease (RR, 1.82), and a decrease in admission PCO_2 of at least 5 mm Hg compared with previous measurements (RR, 2.10). Among the 197 patients, 9.2% who had a low Geneva score, indicating a low probability of PE, turned out to have PE (95% confidence interval, 4.7%-15.9%). The authors calculated the likelihood of PE substituting malignant disease for recent surgery in the Geneva score, and postulated that this might increase its predictive ability.

COMMENTARY

One-fourth of the COPD patients in this study who were admitted with a severe exacerbation without another obvious cause were found to have PE. The diagnosis of PE was more likely to be made among patients with previous thrombosis, underlying malignancy, or an admission PCO_2 at least 5 mm Hg below their baseline value. What can these findings tell us about the likelihood of PE among the patients we manage with COPD exacerbations, or whether we should include a CT angiogram or Doppler study in our admission evaluation of such patients? In my opinion, the answer is "that depends."

From a clinician's perspective there are some unfortunate omissions in this paper. We are not told how many patients were admitted to the authors' unit with COPD exacerbations during the study period, or what proportion of them were considered not to have an infection or other specific cause and were thus referred for possible inclusion. Most COPD patients presenting with an exacerbation have features suggesting infection, and such patients were not included in this study. In fact, the widely used Anthonisen criteria[2] for determining whether a severe exacerbation is present rely on sputum volume and purulence in addition to an increase in dyspnea for the definition. The study also excluded the most severely ill patients, those requiring intubation and mechanical ventilation. Thus, the patients in this study may have represented a minority of the COPD exacerbations seen at the authors' institution during the study period.

These patients were also not the "end-stage" patients in whom many exacerbations occur. Most of them would be classified as Stage II or III by the GOLD criteria, based on their baseline FEV_1 values. Their exacerbations would not have been judged severe by blood gas criteria: arterial pH values are not provided, but mean admission PCO_2 42 mm Hg and PO_2 62 mm Hg breath-

ing room air would not be expected in many patients presenting with severe exacerbations. In addition, the paper does not include hospital length-of-stay or mortality data on the patients. Thus, clinicians attempting to apply this study's findings to their own practices need to be aware of the selected nature of the patients who were included.

For me, the take-home message of this study is that when patients with known COPD present with an acute clinical deterioration and do not have the usual features of a severe exacerbation, PE should be considered-especially if they have a known malignancy, a history of thrombosis, or an arterial PCO_2 lower rather than higher than expected. The prevalence of PE in the general population of COPD patients presenting with an exacerbation cannot be determined from this study. ■

References

1. Wicki J, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med.* 2001;161:92-97.
2. Anthonisen NR, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106:196-204.

Special Feature

Update on COPD Exacerbations: Part I — Overview and Patient Assessment

By David J. Pierson, MD

EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) are an important cause of morbidity and mortality, and have substantial economic consequences. Patients with COPD exacerbations account for a substantial proportion of ICU admissions. Despite the frequency with which they are encountered by intensivists and other clinicians, however, and a large number of available studies and published guidelines on different aspects of their management, COPD exacerbations are often managed suboptimally, and poor outcomes are frequent.

This article reviews some of the evidence underlying current guideline recommendations for the assessment and management of patients with severe COPD exacerbations, and attempts to place such recommendations into practical clinical perspective. The definition, pathogenesis, and etiologies of exacerbations are covered this month, along with an algorithmic scheme for patient assessment. How best to approach the use of bronchodilators, corticosteroids, antibiotics, oxygen, and noninvasive and invasive mechanical ventilation in managing patients with COPD exacerbations will be discussed in the second installment.

What Are Exacerbations and Why Are They Important?

An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variation and acute in onset, generally coming on over 1 to 3 days.[1,2] The term should not be applied to an acute respiratory deterioration due to another specific process, such as pneumonia or pneumothorax, or to the sudden episodes of respiratory distress to which patients with very severe obstruction are prone when faced with emotional upset, unaccustomed exertion, or prolonged coughing. The widely used term "acute exacerbation" is technically redundant, since COPD exacerbations are acute by definition.

Exacerbations are important both at the time they occur and in a larger sense because of their influence on the natural course of COPD. Although outcomes vary somewhat by health system and national context, about 10% of patients admitted to US hospitals because of COPD exacerbations die during that hospitalization.[3] Having been admitted because of an exacerbation is a marker of increased mortality thereafter. Mortality is as high as 40% during the succeeding year among patients who survive, and the likelihood of dying during that period increases with increasing age.[2,3] Exacerbations—especially those requiring hospitalization—account for about 70% of the direct medical costs of COPD.[4]

Much of our current understanding about the causes and effects of exacerbations[5-7] comes from the East London COPD Study, a cohort study carried out during the 1990s. Patients in that study completed daily diary cards on their symptoms, activities, and treatment, and also monitored their pulmonary function at home. The findings of the various arms of the study include the following:

- Exacerbations are more common than previously thought (median, 2.5-3.0 per year), and about half of them are not brought to the attention of the clinicians caring for the patient.[8]
- Patients with more frequent exacerbations have worse quality of life.[9]
- Both functional and symptomatic recovery to the patient's baseline status following an exacerbation

may take longer than previously appreciated. After one-fourth of exacerbations, patients were not back to their baseline peak flow one month later.[9]
- Patients who experience more frequent exacerbations have a more rapid overall decline in lung function over time, as measured by forced expiratory flow in the first second (FEV_1).[10]
- Early therapy of exacerbations both hastens functional and symptomatic recovery and is associated with improved quality of life.[11]

What Causes COPD Exacerbations?

In addition to increased dyspnea and cough, exacerbations are typically associated with an increase in the amount and overt purulence of sputum. Increased amounts of various markers for airway inflammation—such as tumor necrosis factor alpha and interleukins 6 and 8—can be demonstrated at such times.[5,6] Studies have demonstrated that the majority of exacerbations are associated with (and presumably caused by) acute airway infection.

From one-third to one-half of all exacerbations are caused by viruses,[12] of which the most common by far appears to be rhinovirus. Other viruses that may be isolated from the sputum of patients with COPD exacerbations include coronavirus, influenza virus, parainfluenza virus, adenovirus, and respiratory syncytial virus. One recent study of 107 COPD exacerbations requiring invasive mechanical ventilation found that 64% of these had a probable infectious etiology, with viruses isolated in 43% and a viral infection the presumed sole infection in 33%.[13] Patients with viral infection could not be distinguished from the others in the study by any of the clinical or laboratory features examined.

The lower airways of as many as one-third of patients—particularly those with very severe airflow obstruction and those who continue to smoke—are chronically colonized with bacteria, chiefly *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.[5,14] However, despite the frequent presence of airway colonization at baseline, the weight of evidence supports the concept that these bacteria increase in numbers and are responsible for most non-viral infectious exacerbations.[15] In addition, patients may acquire new strains of these or other common airway bacteria, and that this event can be associated with severe exacerbations.[16]

Other causes of COPD exacerbations include atypical organisms such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, and exposure to pollutants such as ozone, particulates, sulphur dioxide, and nitrogen dioxide. The latter agents account for most episodes that are not caused by infection. Some patients experiencing exacerbations without features suggesting infection or environmental exposure (a distinct minority of cases) have acute pulmonary embolism,[17] as discussed elsewhere in this issue of *Critical Care Alert*. "Patient noncompliance," with prescribed medications and other therapy, is frequently offered as an explanation for exacerbations, and likely does sometimes precipitate acute clinical deterioration, although this etiology should never be assumed without first excluding other, much more common mechanisms.

How Should Patients Be Assessed?

The initial clinical assessment of a patient presenting with a presumed COPD exacerbation should answer 3 questions:
- Is this a COPD exacerbation, or something else?
- Should the patient be admitted to the hospital?
- Should the patient be admitted to the ICU?

Answering these most urgent questions requires a careful history and physical examination, along with judicious and stepwise application of laboratory and imaging studies. It would be an unjustifiable use of medical resources to obtain arterial blood gases, com-

Table 1

Indications for Obtaining Arterial Blood Gases, Complete Blood Count, and Chest Radiograph in Evaluating a Patient with COPD Exacerbation

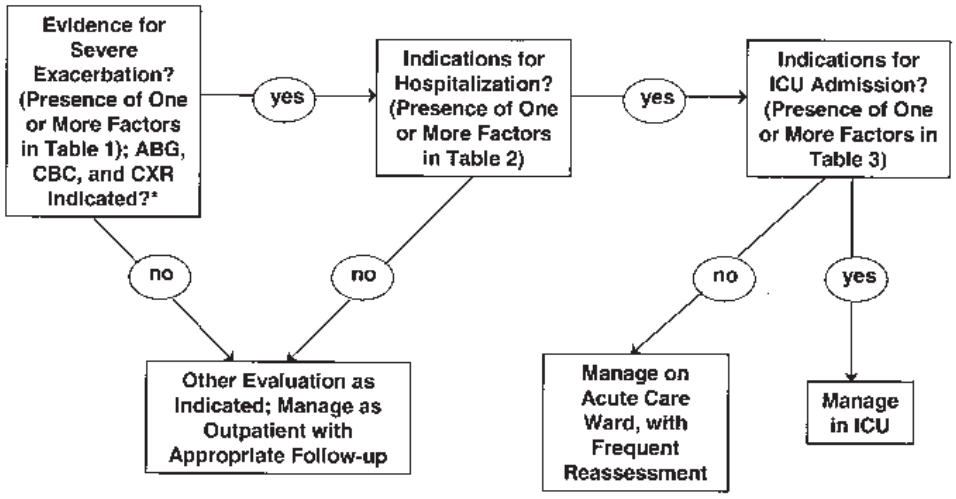
• Recent hospitalization, treatment for exacerbation, or other acute respiratory problem
• Known very severe COPD (GOLD Stage IV*)
• Patient on continuous oxygen at home
• Respiratory symptoms that are new for this patient
• Marked, sustained increase in patient's usual degree of dyspnea
• Inability to speak in complete sentences
• Pleuritic chest pain
• Onset of respiratory distress sudden rather than over several hours or days
• Hemoptysis
• Altered mental status (new confusion; somnolence or obtundation)
• Sustained tachypnea (RR > 30 breaths/min)
• Sustained tachycardia (HR >100 beats/min)
• Oximetry saturation < 90% on room air or patient's usual supplemental oxygen
• Fever (T > 38.3°C)
• Hypotension (systolic BP < 100 mm Hg or 20% lower than patient's usual)
• Arrhythmias (new for this patient, or worse, or different pattern)
• New or markedly worsened edema
• Sustained use of accessory muscles of respiration at rest
• Paradoxical chest and abdominal wall motion on breathing

*GOLD, Global Initiative for Chronic Obstructive Lung Disease[3]; Stage IV = $FEV_1/FVC < 0.70$ and $FEV_1 < 30\%$ of predicted, or presence of chronic respiratory failure

All Tables and Figure Source: Pierson DJ.

Figure 1

Algorithm for Evaluating a Patient with Suspected COPD Exacerbation



*ECG and other studies should also be considered as indicated

plete blood count, a chest X-ray, sputum gram stain and culture, and other studies on every patient with known or suspected COPD who presents with increased symptoms. Current guidelines[2,3,18] and a substantial body of experimental evidence indicate that such studies can be applied selectively, depending on the urgency of the situation and the findings on initial assessment (*see Figure 1 and Table 1*).

Not everyone presenting with respiratory distress and a long smoking history has COPD. The discussion in this article applies to patients who meet the diagnostic criteria for COPD, and these rely heavily on the presence of airflow obstruction.[20] Many patients who carry the diagnosis of COPD have never had spirometry, and a substantial number of these individuals do not have airflow obstruction—and thus have something other than COPD—despite a suggestive history. All current guidelines rely on pulmonary function testing (primarily the forced expiratory volume in the first second [FEV_1] and its relation to the vital capacity), both for diagnosing COPD and for tailoring management to disease severity.[20] It may not be technically feasible to obtain spirometry during initial management of acute illness, but the clinician should make a mental note to have this done as soon as possible when the patient improves.

Nearly 20 years ago Anthonisen and colleagues[19] classified COPD exacerbations into 3 levels of severity based on just 3 symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence. Exacerbations in patients with all 3 of these symptoms were categorized as Type 1 (most severe). A Type 2 exacerbation (intermediate severity) was present if only 2 of the symptoms were present. If there was only 1 of the symptoms, plus the presence of cough, wheeze, or symptoms of an upper respiratory tract infection, the exacerbation was Type 3 (least severe). This widely accepted clinical classification scheme was modified slightly in the East London COPD Study: an exacerbation was diagnosed if 2 new respiratory symptoms were present for 2 days, with at least one of them one of the 3 major symptoms in the Anthonisen classification.[6]

These modified Anthonisen criteria permit the clinical diagnosis of a COPD exacerbation in many cases without the need for further investigation. However, current guidelines agree that there are clinical features suggesting a potentially life-threatening exacerbation or the presence of a serious complicating process. Table 1 lists these features. If one or more of the findings in the table are present, evaluation beyond the history and physical should be done, and in most instances this should include an arterial blood gas (not just pulse oximetry), a complete blood count, and a chest radiograph. Patients with chest pain, arrhythmias, or signs of heart failure should also have an electrocardiogram. The rapid measurement of B-type natriuretic peptide (BNP) in the emergency department has been shown to be both clinically helpful and cost-effective in cases of diagnostic uncertainty when evaluating patients with acute dyspnea, particularly when the differential is between congestive heart failure and COPD exacerbation (see *Critical Care Alert*, July 2006, pp 28-29).

Sputum purulence does not necessarily mean infection. The green color of sputum is due to the action of leukocyte myeloperoxidase, particularly in the presence of stasis, and is not a very reliable indicator of bacterial

Table 2

Indications for Admission to the Hospital

• Persistence of symptoms and signs in Table 1 despite initial treatment
• Respiratory acidosis (eg, hypercapnia with pH < 7.35) uncorrected with initial treatment
• Presence of a complicating acute respiratory process (eg, pneumonia, pneumothorax)
• Diagnostic uncertainty
• Presence of significant comorbidities
• Severe impairment of activities of daily living
• Significant recent deterioration in overall condition
• Inability to eat or sleep because of respiratory symptoms
• Older age
• Need for therapy that cannot be provided in the home
• Insufficient home support

Table 3

Indications for Admission to the ICU*

• Need for NPPV, especially in initial hours of management
• Need for invasive ventilatory support
• Persistence of severe dyspnea, tachypnea, or tachycardia despite initial therapy
• Persistence of confusion, somnolence, or obtundation such that bronchodilators and other needed therapy cannot be delivered optimally
• Persistent or worsening hypoxemia (eg, requirement for more than 40% oxygen)
• Persistent or worsening acute respiratory acidosis (eg, hypercapnia with pH < 7.30)

*These depend in part on bed availability, ward staffing and other local resources. NPPV, noninvasive positive-pressure ventilation

infection. Most exacerbations in ambulatory patients are managed without staining or culturing the sputum. Current guidelines do not recommend the latter as routine.[2,3,18] Gram stain and culture of sputum are more likely to be helpful in patients with severe exacerbations requiring admission to the hospital.[18]

Table 2 lists criteria for hospitalizing the patient with a COPD exacerbation. These criteria are agreed upon by current guidelines, and are intended to assure that patients at risk for developing acute respiratory failure or other life-threatening complications are appropriately managed, while avoiding unnecessary use of hospital resources.

Because of the huge impact of hospitalization on the patient's quality of life as well as on health care costs, interest has recently focused on "hospital at home," whereby inpatient admission can be avoided in selected patients. This approach has mainly been applied in Europe, but a recent study has demonstrated its feasibility in the United States as well.[21] A Cochrane Review found that patients managed for exacerbations with "hospital at home" had acute outcomes and rates of hospital readmission that were equivalent to those of inpatient management, with patient and caregiver preference for the former.[22] Management of severe exacerbations without admission to the hospital requires a complex, coordinated application of resources, as well as carefully selected patients, and this approach is not yet widely feasible in this country.

Which Patients with COPD Exacerbations Should Be Admitted to the ICU?

The risk of dying during a COPD exacerbation is associated with the development of acute respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support. The likelihood of successful management depends on rapid and accurate diagnosis and early and appropriate intervention. Although all the elements of critical care, including assessment, monitoring, and intensive therapy, can be achieved on a respiratory ward, this demands an outlay of material and personnel resources not generally available in US hospitals. Thus, the more severely ill the patient, the more rapidly his or her condition is changing, and the more uncertainty there is about what is going on, the greater is the need for admission to the ICU.

Table 3 lists criteria for ICU admission taken both from current guidelines[2,3,18] and from my own experience in managing patients with potentially life-threatening COPD exacerbations. Bed availability and other local factors must be taken into account but, generally speaking, even a brief stay in the ICU is preferable to the chance that the severity of the episode will be underestimated or important signs of deterioration missed on the ward.

Acute respiratory acidosis (initial arterial pH < 7.25) that does not respond to initial therapy, particularly in patients with very severe COPD (GOLD Stage IV), those on home oxygen, and those with severe comorbidities, should prompt admission to the ICU. Because hypoxemia in COPD is typically due to alveolar hypoventilation and ventilation-perfusion mismatching—physiologic processes that respond readily to administration of supplemental oxygen—a requirement for a high inspired oxygen fraction (eg, more than 0.40 or 0.50) suggests that something beyond the usual exacerbation may be going on, and should prompt consideration for admission to the ICU for closer observation than can be achieved on the floor. Abnormal mental status is an especially worrisome finding in a patient with a COPD exacerbation, suggesting the presence of a coexisting process, making administration of appropriate treatments problematic, and increasing the likeli-

hood that intubation will be necessary.

Unless the intention is to provide comfort-care only, patients who have declared their wishes not to be resuscitated (DNAR) and/or not to be intubated (DNI) may nonetheless benefit from admission to the ICU. As many as half of such patients may respond to noninvasive positive-pressure ventilation and aggressive pharmacologic management and survive to hospital discharge, often to what is for them an acceptable quality of life. ■

References

1. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl.* 2003;41:46s-53s.
2. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax*. 2004;59 (Suppl 1):1-232. www.thorax.bmjjournals.com/content/vol59/suppl_1/
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.com
4. Sullivan SD, et al. The economic burden of COPD. *Chest.* 2000;117(2 Suppl):5S-9S.
5. Wedzicha JA. Exacerbations: etiology and pathophysiologic mechanisms. *Chest*. 2002;121(5 Suppl):136S-141S.
6. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care.* 2003;48:1204-1213.
7. Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax*. 2006;61:250-258.
8. Seemungal TA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1418-1422.
9. Seemungal TA, et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161:1608-1613.
10. Donaldson GC, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2000;57:847-852.
11. Wilkinson TM, et al. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169:1298-1303.
12. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2004;1:115-120.
13. Cameron RJ, et al. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med.* 2006;32:1022-1029.
14. Hurst JR, Wedzicha JA. Chronic obstructive pulmonary disease: the clinical management of an acute exacerbation. *Postgrad Med J.* 2004;80:497-505.
15. Anthonisen NR. Bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 2002;347:526-527.
16. Sethi S, et al. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002;347:465-471.
17. Tillie-Leblond I, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med.* 2006;144: 390-396.
18. American Thoracic Society/European Respiratory Society Task Force. Standards for the Diagnosis and Management of Patients with COPD. http://www-test.thoracic.org/copd/.
19. Anthonisen NR, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106:196-204.
20. Pierson DJ. Clinical practice guidelines for chronic obstructive pulmonary disease: A review and comparison of current resources. *Respir Care*. 2006;51:277-288.
21. Leff B, et al. Hospital at home: feasibility and outcomes of a program to provide hospital-level care at home for acutely ill older patients. *Ann Intern Med.* 2005;143:798-808.
22. Ram FS, et al. Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003;(4):CD003573.

CME Questions

19. The ARDS Network study of a liberal vs a conservative fluid management strategy for patients with acute lung injury or ARDS had which of the following findings?

a. A higher mortality with the conservative management strategy
b. A lower mortality with the conservative management strategy
c. No difference in mortality with the two fluid-management strategies
d. A lower incidence of the need for dialysis in the liberal fluid management strategy
e. Both c and d

20. Based on the study of Tillie-Leblond et al, the prevalence of pulmonary embolism among all patients hospitalized with severe exacerbations of COPD:

a. is less than 15%.
b. is 25%.
c. is at least 30%.
d. cannot be determined.
e. None of the above

21. Which of the following increased the likelihood of pulmonary embolism among patients hospitalized with a COPD exacerbation?

a. a PCO_2 higher than expected
b. underlying malignancy
c. a previous episode of thrombosis
d. all of the above
e. b and c but not a

Answers: 19 (c); 20 (d); 21 (e)

In Future Issues: Managing Patients with COPD with Exacerbations, Part II

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Safety of Long-Acting Beta Agonist Inhalers

Do long-acting beta agonist inhalers increase the severity of asthma? Yes, according to the results from a large meta-analysis recently published in the *Annals of Internal Medicine*. Pooled data from 19 trials with nearly 34,000 participants found that the long-acting beta agonists salmeterol, formoterol, and eformoterol were associated with higher rates of asthma exacerbations, requiring hospitalization, (odds ratio 2.6 [95% CI, 1.6-4.3]) and life-threatening exacerbations (odds ratio 1.8 [CI, 1.1-2.9]), compared to placebo. In subgroup analyses, the odds ratio for hospitalizations was 1.7 for salmeterol and 3.2 for formoterol. The risk of hospitalization was especially high in children on long-acting beta agonists (odds ratio 3.5 [CI, 1.3-9.3]). The odds ratio for adults was 2.0 (CI 1.1-3.9). Although the rate of death was low, the odds ratio for asthma-related death was 3.5 (CI, 1.3-9.3).

In the largest of the studies included in the meta-analysis, the Salmeterol Multicenter Asthma Research Trial (SMART), in which 26,000 patients were followed for 6 months on salmeterol or placebo, there was a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma related deaths. The authors conclude that long-acting beta agonist use increases the risk of hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. The authors also conclude that inhaled corticosteroids cannot adequately protect against the adverse effects of these drugs (*Ann Int Med*. 2006;144:904-912).

An accompanying editorial suggests that physicians should follow current guidelines which emphasize use of inhaled corticosteroids as the first-line treatment for patients with mild-to-moderate persistent asthma. Only after maximal corticosteroid doses have been reached should long-acting beta agonist be considered (*Ann Int Med*. 2006;144:936-937).

The FDA met one year ago to discuss long-acting beta agonist and required black box warnings on the labeling for these drugs; however, there usage has changed very little in the ensuing year.

Treating Chronic Primary Insomnia

Cognitive behavioral therapy is more effective than zopiclone for the treatment of chronic primary insomnia in older adults, according to a new study from Norway. In a randomized, double-blind, placebo-controlled trial, 46 adults (mean age, 60.8; 22 women) with chronic primary insomnia were randomized to cognitive behavioral therapy, sleep medication with zopiclone 7.5 mg each night, or placebo for 6 weeks. The cognitive behavioral therapy consisted of 6 weekly sessions lasting 50 minutes that covered sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques. The main outcome was

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polysomnographic data and sleep diaries, which were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep.

Cognitive behavioral therapy (CBT) resulted in improved short-term and long-term outcomes compared with zopiclone on 3 of 4 outcome measures. CBT improved sleep efficiency from 81.4% to 90.1% at 6-month follow-up compared to a decrease from 82.3% to 81.9% with zopiclone. CBT resulted in better sleep architecture and less time awake during the night. Total sleep time was similar in all 3 treatment groups but, at 6 months, patients receiving CBT had better sleep efficiency than those taking zopiclone. The authors conclude that cognitive behavioral therapy is superior to zopiclone for management of insomnia, both in the short term and long-term. For most outcomes, zopiclone did not differ from placebo (*JAMA*. 2006;295:2851-2858).

Zopiclone is a new generation sleep medication available in Europe. The active isomer of zopiclone has been available in the United States since April 2005 (eszopiclone - Lunesta).

New Breakthrough in Smoking Cessation?

Varenicline, Pfizer's new smoking cessation drug, is the subject of 3 articles in the July 5 issue of *JAMA*. The drug, which is a partial agonist of the 4 2 nicotinic receptor, blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Two of the 3 articles compared varenicline to bupropion and placebo in combination with behavioral counseling over 12 weeks of treatment. In both studies, varenicline was significantly more effective than placebo or bupropion (*JAMA*. 2006;296:47-55, 56-63). In the third study, 12 more weeks of varenicline was found to be significantly more effective than placebo in maintaining abstinence. This study also found that after 24 weeks of treatment, the benefit of the drug was maintained up to one year (*JAMA*. 2006;296:64-71). An accompanying editorial points out that while the studies of varenicline are promising and the drug represents a new agent with a different mechanism of action, it is not a panacea for smoking cessation, with quit rates still under 50% in these studies (*JAMA*. 2006;296:94-95). These studies could not come at a better time for Pfizer, as the company plans to market the drug within the next few months under the trade name Chantix.

FDA Actions

The FDA has given Biogen-Idec approval to resume marketing natalizumab (Tysabri) for the treatment of relapsing forms of multiple sclerosis. The monoclonal antibody was initially marketed in November 2004, but was withdrawn four months later, after three patients developed progressive multifocal leukoencephalopathy (PML) in clinical trials. Subsequent trials have not shown any additional cases of PML, but the drug is limited to use in patients who have failed or have not tolerated alternative therapies for multiple sclerosis. The re-approval is a restricted distribution program which includes registration of patients, prescribers, infusion centers, and pharmacies and includes patient education materials. Patients are also required to have a brain MRI prior to initiation of therapy. More information is available at: www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Duramed Pharmaceuticals have received approval to market a new 91 day birth control regimen consisting of 84 days of levonorgestrel 0.15 mg with ethinyl estradiol 0.03 mg, and seven days of ethinyl estradiol 0.01 mg (Seasonique). This product differs from the company's other 91 day birth control regimen (Seasonale) in that it incorporates estradiol rather than placebo for the last seven days in order to reduce bloating and breakthrough bleeding. Both products result in four menstrual periods per year.

The FDA has approved Genentech's ranibizumab (Lucentis) for the treatment of neovascular (wet) age-related macular degeneration (AMD). The drug, which is injected intraocularly, inhibits vascular endothelial growth factor A which is thought to contribute to proliferation, vascular leakage, and angiogenesis. Many ophthalmologists have been using Genentech's other anti-angiogenesis drug bevacizumab (Avastin) for the treatment of AMD, although it is not approved for this indication. Compounded bevacizumab injected intraocularly is approximately $17 per dose. Ranibizumab marketed as Lucentis is projected to cost approximately $2000 per dose.

Two former blockbuster drugs are making the switch to generics. Sertraline (Zoloft- Pfizer) will be available later this year in both generic pill and liquid form. In 2005, Zoloft was the most popular antidepressant in the US. The FDA has also approved a generic form of simvastatin (Zocor) Merck & Co.'s enormously popular statin for the treatment of hypercholesterolemia. Generic simvastatin is currently available 5, 10, 20, 40, and 80 mg strengths. ■