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A monthly update of developments in critical care and intensive care medicine

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INSIDE

Special Feature: *Update on COPD exacerbations: Part II—Management* ***page 43***

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Putting Therapeutic Hypothermia into Practice

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Synopsis: *This retrospective 'real-life' single-center study found that therapeutic hypothermia could be readily implemented and that it improved outcomes in patients with out-of-hospital cardiac arrest.*

Source: Oddo M, et al. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med*. 2006;34:1865-1873.

PREVIOUS LARGE, RANDOMIZED STUDIES HAVE DEMONSTRATED improved neurological outcome in comatose patients with out-of-hospital cardiac arrest due to ventricular fibrillation (VF) who are managed with therapeutic hypothermia (TH): those with other arrhythmias or shock were excluded.[1,2] General acceptance and implementation of TH however have been slow to occur.[3] Oddo et al performed a retrospective, single-center trial to assess ease of implementation of TH and its impact on outcomes in patients with out-of-hospital cardiac arrest of all etiologies. At a Swiss medical intensive care unit, consecutive patients with coma after out-of-hospital cardiac arrest were enrolled over an approximately 2-year period during which TH was being used: data were also collected on a similar number of historical controls. Standard resuscitation and care were provided to all patients. TH consisted of external cooling (ice bags and cooling mattress, started in the emergency department) to 33º for 24 hours, followed by passive rewarming. Outcome was determined by blinded review of patients' neurological examination at the time of discharge. 'Good' outcome was defined as 1 or 2 on the Glasgow-Pittsburgh Cerebral Performance categories: 1 is total recovery and 2 is moderate disability but able to work part-time and be independent in activities of daily living. Standard statistical methods were used.

The study included 109 patients, 55 treated with TH and 54 historical controls. The groups were similar in terms of demographics,

comorbidities, time from collapse to return of pulse, and initial arterial pH. A similar number of patients in each group had an initial rhythm other than VF: these patients had longer time to return of pulse, lower initial pH, and more shock. Goal temperature of 33º was achieved in a median time of 5 hours, and this time interval decreased with experience. There was no relationship between time-to-goal temperature and outcome. Of the patients with cardiac arrest due to VF, good outcome was noted in 55.8% of those managed with TH vs 25.6% of controls. The numbers of patients with other initial arrhythmias were small and their outcomes extremely poor (mortality > 80%) thus it was difficult to comment on impact of TH. In contrast, those patients with shock at presentation also had high mortality.

TH did appear to improve outcomes compared to standard care alone. In comparing the treatment groups, the authors noted that patients receiving TH had greater fluid resuscitation and use of vasopressors and higher mean arterial pressures. Multivariate analysis using these and other predictors defined *a priori* revealed that these differences did not appear to account for the improved outcomes in the TH group. Only time to return of spontaneous circulation (< 30 minutes) was significant. Finally, incidence of infections or new arrhythmias was no different between the 2 groups.

COMMENTARY

Oddo et al's work provides further support for what has thus far been published about TH in out-of-hospital cardiac arrest. That is, TH is an effective means of significantly improving neurological outcome in patients who suffer out-of-hospital cardiac arrest due to VF.[1,2] This study shows that TH can be applied safely to all patients (rather than just to a specially selected, screened population as was done in the larger randomized trials). Using simple and universally available methods of external cooling, goal temperatures were able to be achieved in a short period of time (≤ 5 hours) and maintained for 24 hours: we see that this is something any hospital could do.

The authors observed rates of improved outcomes with TH that were similar to those in previously published large randomized trials. (There was an approximately 2-fold difference between the TH group and the control group.) As in prior studies, the time to return of spontaneous circulation related to outcome even in those patients receiving TH. These authors added to our knowledge by observing the impact of TH on patient populations excluded from prior large studies of TH: they demonstrated that TH may be beneficial in patients with persistent shock after cardiac arrest. Their results also suggest that TH may not add much to the care of those with cardiac arrest due to arrhythmias other than VF. This is at least partly because those patients have extremely high mortality: perhaps studies to assess earlier interventions (eg, cooling in the field) in these populations are warranted.

This study has several limitations which the authors acknowledge. It is a single-center study with somewhat small numbers and this may limit its generalizability. It is non-randomized and retrospective and it relies on historical controls. All of these factors make it likely that some bias is introduced and that there may be significant unmeasured differences between the 2 comparison groups. Thus, although the study's findings offer limited support for the already-available strong evidence for TH and suggest new hypotheses for areas not well-investigated (such as TH for out-of-hospital cardiac arrest with prolonged shock), they do not in themselves provide substantial new scientific information.

I suggest to you that the importance of this study should not be measured by its ability or inability to prove the benefits of TH: that has already been done by prior large randomized trials.[1,2] Rather, this work is valuable because it clearly and completely meets its pri-

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mary objective: it demonstrates that what was accomplished in large, randomized clinical trials can be readily reproduced in our own institutions. If we can absorb this and follow Oddo et al's example, we will significantly improve outcomes for our patients with out-of-hospital cardiac arrest. ■

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Special Feature

Update on COPD Exacerbations: Part II—Management

By David J. Pierson, MD, Editor

A RECENTLY PUBLISHED STUDY USING A LARGE national administrative database found that only two-thirds of patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD) received care that was consistent with current guidelines of the American College of Physicians and the American College of Chest Physicians.[1] In addition, the investigators found that 45% of the 70,000 patients in the study received at least one form of therapy that was considered ineffective (that is, not supported by acceptable evidence) and thus was not recommended by the guidelines. With this kind of performance record, considering that each year some 750,000 patients are hospitalized because of COPD exacerbations in the United States, a review of currently recommended management seems like a good idea.

Part I of this Special Feature, published last month,[2] discussed the definition and clinical importance of COPD exacerbations. It outlined an approach for diagnosing exacerbations, assessing clinical severity, and deciding which patients should be admitted to the hospital and to the ICU. This month's concluding segment is devoted to the different components of therapy: how best to use bronchodilators, corticosteroids, antibiotics, and other drugs; how to administer supplemental oxygen effectively and safely; when to use noninvasive positive-pressure ventilation (NPPV); and when intubation and invasive mechanical ventilation are most likely to be required. In summarizing these topics I will refer to the best available evidence, wherever possible from the Cochrane database (www.thecochranelibrary.com) or from other systematic reviews, as well as to the recommendations of the major clinical practice guidelines on managing COPD.[3-5]

Bronchodilators

Despite the fact that airflow obstruction in patients with COPD tends to be mostly irreversible, inhaled bronchodilator therapy remains a cornerstone of management during exacerbations. Increased airway inflammation may worsen obstruction acutely, and this may respond to bronchodilators. In addition, respiratory distress and the physiologic consequences of acute hyperinflation—as a phenomenon separate from airflow obstruction per se—may be amenable to more rapid resolution with aggressive bronchodilator therapy. Management of exacerbations mainly involves intensifying the use of the same drugs as used for chronic therapy, rather than adding new agents.

Most available evidence on the effectiveness and administration of bronchodilators comes from studies on acute asthma, and fewer investigations have been done in patients with COPD exacerbations. However, the available database in this area is large, and it permits the following conclusions to be drawn:

1) Albuterol and other short-acting beta agonists should be administered by inhalation, not parenterally. Aerosol delivery produces at least as much therapeutic effect, with considerably less tachycardia, tremor, and other adverse effects.
2) Beta agonists should be given at higher doses and greater frequency during an exacerbation—at least in initial management—than with long-term administration.
3) When this is done, there is no evidence that anticholinergics such as ipratropium provide greater benefit than beta agonists.[6]
4) Although both beta agonists and anticholinergics are commonly given together during exacerbations, meta-analysis of controlled trials comparing the combination to the effects of single-agent therapy shows no added benefit.[6]

5) Administration via metered-dose inhaler plus spacer is therapeutically equivalent to nebulization[7] and costs less.

Studies comparing metered-dose inhalers to dry-powder inhalers for delivery of drugs to patients with COPD have shown these to be equivalent in stable patients, but similar studies in exacerbations have not been published. At present there is no way to deliver dry-powder aerosols effectively to intubated patients, and it is doubtful whether non-intubated patients who are too ill to use dry-powder inhalers according to the manufacturer's instructions can benefit from them.

Continuous nebulization is sometimes used for bronchodilator therapy in treating acute asthma in the emergency department. However, studies have failed to demonstrate that this is superior to conventional, intermittent therapy in terms of outcome, and the use of continuous nebulization for more than 2 or 3 hours should probably be avoided. Albuterol or another short-acting agent should be used for intensive beta-agonist therapy, and long-acting bronchodilators such as salmeterol and formoterol should not be used more frequently than recommended for long-term therapy.

Corticosteroids

While aggressive administration of inhaled bronchodilators may have a more immediate effect on airway function, the true mainstay of pharmacotherapy for COPD exacerbations is systemic corticosteroids. Although no randomized, controlled trials have been carried out exclusively in patients admitted to the ICU, strong support for the use of corticosteroids comes from numerous well-designed studies on hospitalized patients. A Cochrane review by Wood-Baker et al identified 10 such studies (951 patients) published through 2005 that met specified criteria.[8] Based on high-quality evidence, the conclusions of this review are as follows with respect to the use of systemic corticosteroids vs placebo:

- Fewer treatment failures (odds ratio, 0.48; hazard ratio, 0.78; one treatment failure prevented for every 9 patients treated)
- More rapid improvement in FEV_1 (weighted mean difference, 140 mL at 72 h)
- Significantly improved breathlessness and arterial blood gas values
- No difference in mortality
- Increased adverse effects (odds ratio, 2.29; one extra adverse reaction for every 6 people treated), primarily hyperglycemia

In addition, studies suggest that corticosteroid treatment prolongs the interval between exacerbations in patients who have them frequently.

Hospitalized patients have traditionally been treated with intravenous methylprednisolone, most often at a dose of 0.5 mg/kg every 6 hours. However, there is no compelling evidence that intravenous administration is more effective than oral, that it is beneficial to give the agent more often than once a day, or that the smaller doses recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] and other guidelines (eg, 40 mg prednisone once daily for 10 to 14 days) are any less effective. Higher doses cause more adverse effects—especially hyperglycemia—and studies have shown no advantage of continuing therapy beyond 14 days. Guidelines recommend that patients receiving prolonged or frequent courses of systemic corticosteroids for exacerbations receive prophylaxis against osteoporosis.[5]

Maltais and associates[9] carried out a multicenter, randomized, controlled trial of high-dose inhaled corticosteroid (budesonide) every 6 hours, as compared to oral prednisolone twice daily, and placebo, in 199 COPD patients with exacerbations. FEV_1 improved more in 72 h in the 2 steroid groups than in patients treated with placebo; the improvement in FEV_1 was somewhat less (but not significantly so) in the budesonide group. Because of the greater expense (for both drug and labor), and the fact that the patients in this trial had only relatively mild exacerbations (normal pH; minimal hypoxemia), treatment of ICU patients with inhaled corticosteroids cannot be recommended.

Antibiotics

Meta-analyses of the considerable literature on antibiotics show that they are effective in severe exacerbations and conclude that they should be used.[10,11] The most recent review, an evaluation of 10 trials (917 patients) by Ram et al,[10] found that antibiotic therapy, regardless of which agent was used:

- Reduced mortality (relative risk, 0.23; number needed to treat = 8)
- Decreased treatment failure (relative risk 0.47; number needed to treat = 3)
- Reduced sputum purulence (relative risk 0.56; number needed to treat = 8)

In this meta-analysis, there was no significant effect of antibiotics on arterial blood gases or peak flow, but there was an increase in the incidence of diarrhea (relative risk, 2.86) among patients who received antibiotics.

The classic randomized trial by Anthonisen and colleagues during the 1980s[12] showed benefit from antibi-

otic therapy only in patients who had at least 2 of the 3 cardinal symptoms of increased dyspnea, increased sputum volume, and increased sputum purulence. Thus, while those with mild exacerbations may not be helped by antibiotics, patients who are ill enough to be admitted to the hospital (and especially to the ICU) should receive them.

Which antibiotic should be used? Studies comparing one antibiotic to another are numerous in the literature, but much less robust than those using placebo controls and included in the meta-analyses just cited. The value of sputum Gram stains and cultures in patients with COPD exacerbations has been difficult to demonstrate, even knowing that such patients may have recently acquired new strains of bacterial pathogens. Because patients with COPD are commonly colonized with bacteria (most often *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*), finding these organisms in the sputum does not ensure that the exacerbation is bacterial in origin or that the recovered species are responsible.

Knowledge of local antibiotic resistance patterns is important, although the choice of antimicrobial agent remains largely empirical.[13,14] Traditional recommendations have been for inexpensive agents—trimethoprim-sulfamethoxazole, amoxicillin, or a tetracycline, for example—that cost far less than whatever heavily marketed oral agent has most recently been approved for this indication, especially for less severe exacerbations. I still use these old standbys for outpatient treatment. Fluoroquinolones and macrolides are increasingly used when patients are admitted to the hospital, and a good case can be made for this. When patients have evidence for pneumonia, *Pseudomonas* infection, or sepsis, or have already been taking antibiotics when admitted, more extensive bacteriologic investigation and broader antimicrobial coverage are probably indicated.

Other Medications

Methylxanthines. A generation ago, intravenous aminophylline was a therapeutic mainstay in managing COPD exacerbations. However, although its use was supported by several hypothetical benefits—bronchodilation, an inotropic effect on the diaphragm, stimulation of ventilatory drive, diuresis—when subjected to current standards for therapeutic evidence, aminophylline and other methylxanthines have been found wanting. A recent Cochrane review of clinical trials comparing aminophylline to placebo in COPD exacerbations found no clinically important differences in lung function either immediately or after 3 days, no symptomatic benefit, an increase in nausea and vomiting, and a greater likelihood of relapse at 1 week.[15] These drugs have a narrow therapeutic window, and unlike the inhaled bronchodilators they have the substantial potential for serious or even fatal adverse effects (eg, arrhythmias, seizures) during acute administration. Current guidelines either advise against their use in exacerbations,[1] or caution that serum levels be monitored closely because of the danger of side effects.[3]

Sedatives. Although patients with COPD exacerbations are often restless and anxious, the use of benzodiazepines, opioids, and other agents with sedating effects in managing them is difficult and dangerous. Respiratory distress is the result of an increase in the work of breathing, and treatment aims to ameliorate the former by reducing the latter. Blunting the patient's perception or manifestation of distress without improving the mechanical situation runs the risk of worsening hypercapnia and academia, and thus of precipitating the need for intubation. Although small doses of lorazepam or other benzodiazepine may sometimes succeed in calming an agitated patient without overtly depressing ventilation, such therapy must be used with extreme caution, given that intubation is associated with increased mortality, more complications, and increased lengths of stay in the ICU and the hospital. The skillful use of noninvasive positive-pressure ventilation (NPPV), as discussed below, allows a reduction in the patient's work of breathing that is usually manifested by reduced distress and less potential need for sedation.

Mucolytics and respiratory stimulants have traditionally been used more often in Europe and some other regions than in the United States. Neither category of drug is recommended by the current international guidelines for use in exacerbations.[3-5]

Supplemental Oxygen

Hypoxia is the greatest immediate threat to life in patients with severe COPD exacerbations, yet generations of clinicians have been hesitant to treat it aggressively for fear of acutely worsening hypercapnia. As a result, patients are sometimes allowed to remain dangerously hypoxemic, even after admission to the hospital. The traditional teaching is that such patients may be "running entirely on their hypoxic drive," and that blunting the latter with too much oxygen will precipitate CO_2 narcosis and frank ventilatory failure. Several studies over the last 25 years have shown that this fear is unnecessarily exaggerated, but also that the mechanism of hypercapnia is more complicated than originally believed.

Robinson et al studied 22 patients with severe COPD

(baseline FEV_1 30% of predicted) who were admitted to the hospital with exacerbations.[16] They measured arterial blood gases, cardiac output, and ventilation-perfusion distribution using the multiple-inert-gas elimination technique, while the patients breathed ambient air and again after 20 minutes breathing 100% oxygen. None of the patients went into frank ventilatory failure, although arterial PCO_2 rose by more than 3 mm Hg in 12 of them. Compared to the other 10 patients, these 12 "retainers" had lower overall minute ventilation, but also had greater perturbation of ventilation-perfusion matching and an increase in physiological dead space. Thus, administering too much oxygen to patients with COPD exacerbations can indeed cause acute hypercapnia, but the mechanism is more complex than simply depressing their ventilatory drive.

How often hyperoxia-induced hypercapnia is a clinically important problem when over-oxygenation is avoided was evaluated by Moloney et al, who studied 24 consecutive patients presenting to the emergency department with COPD exacerbations.[17] The patients had very severe underlying COPD, and initial mean arterial PO_2 and PCO_2 values breathing room air were 46 and 56 mm Hg, respectively. These authors carefully titrated the administration of supplemental oxygen, raising SpO_2 above 90% but keeping it always below 92%, and re-checked arterial blood gases after 2 hours. Using this approach, only 3 of the 24 patients experienced a rise in PCO_2 of more than 7.5 mm Hg, and arterial pH fell below 7.25 in only 1 of them. No patient required intubation, and none experienced a worsening of PCO_2 or pH beyond 2 hours. In keeping with the findings of other studies, patients with the highest initial PCO_2 values tended to have greater increases with supplemental oxygen.

The bottom line, consistent with the recommendations of all current guidelines,[3-5] is that SpO_2 should be raised above 90% (corresponding to a PO_2 > 60 mm Hg) in all patients, and that clinically important CO_2 retention is unlikely if SpO_2 is kept in the low 90s. Patients with more severe initial hypercapnia should be monitored closely during initial oxygen administration.

Should oxygen be given by nasal cannulae or by Venturi mask? The delivered oxygen concentration is known and constant with the latter—but actually only in the mask itself, since there is always some entrainment of room air when the patient inspires. Nasal prongs are more likely to remain on the patient, and do not have to be removed when talking, expectorating, taking medications, or eating. The theoretical risk that the inspired oxygen concentration may increase if the patient hypoventilates while the nasal oxygen flow remains constant can be mitigated by continuous SpO_2 monitoring and titration of the liter flow to maintain the target value of 90-92%. Either administration technique can be used effectively, but I prefer the nasal cannula.

Noninvasive Ventilation

The most important advance in the management of COPD exacerbations during the last 15 years has been the emergence and validation of NPPV as the standard of care for patients with acute-on-chronic ventilatory insufficiency. Several previous *Critical Care Alert* special features have dealt with the practical application of NPPV in this and other settings, and I will not discuss the technical aspects of this therapy here. However, a brief review of the evidence supporting NPPV is warranted.

The database on the efficacy of NPPV in COPD exacerbations is extensive. It includes 14 randomized controlled trials (758 patients) meeting criteria for a recent systematic review by Ram et al.[18] These authors drew the following conclusions from their analysis:

- NPPV reduces mortality (relative risk, 0.52; number needed to treat = 10)
- It decreases the need for intubation (relative risk, 0.41; number needed to treat = 4)
- It reduces treatment failure (relative risk, 0.48; number needed to treat = 5)
- Tachypnea, arterial pH, and PCO_2 improve more rapidly with NPPV
- It decreases treatment-associated complications (relative risk, 0.38)
- It shortens hospital length-of-stay (weighted mean difference, 3.24 fewer days)

Simply stated, the use of NPPV in 10 patients with COPD exacerbations can be expected to save 1 life, compared with not using NPPV, all other aspects of management being the same. At least 2 of those 10 patients will avoid intubation who would otherwise require invasive mechanical ventilation. The risk of complications associated with their care would be reduced by 62%. And, based on the available literature, if managed with NPPV those 10 patients would have an aggregate hospital stay of more than a month less than they would otherwise.

Not all patients are appropriate for NPPV. Based on currently available evidence, as well as on the recommendations of leading guidelines, Tables 1 and 2 list the indications and contraindications for NPPV in patients with COPD exacerbations.

Confalonieri and associates[19] have recently developed and validated a chart for predicting NPPV failure

Table 1

Patient Selection for Noninvasive Ventilation

- Respiratory distress: tachypnea (rate > 25 breaths/min); use of accessory muscles; paradoxical abdominal motion
- Ventilatory failure rather than hypoxemic respiratory failure (elevated PCO_2 with arterial pH 7.35 or less; Hypoxemia correctable with 50% oxygen or less)
- Secretions moderate in amount; patient able to clear them spontaneously
- Cardiovascular stability (no hypotension, acute ischemia, or serious arrhythmias)
- Intact bulbar function (ability to protect lower airway)
- Patient alert and cooperative
- Availability of experienced staff and appropriate ICU setting

Table 2

Exclusion Criteria for Noninvasive Ventilation

- Respiratory arrest
- Cardiovascular instability (hypotension, myocardial infarction, serious arrhythmias)
- Impaired mental status (obtundation, severe confusion, uncontrollable agitation)
- Uncooperative patient
- High aspiration risk
- Copious or viscous secretions
- Nasopharyngeal abnormalities
- Recent facial trauma or surgery
- Extreme obesity

Table 3

Criteria for Intubation and Invasive Mechanical Ventilation

- Respiratory arrest
- Obtundation; increasing somnolence; uncooperativeness
- Failure of noninvasive ventilation
- Sustained tachypnea (eg, rate > 35 breaths/min)
- Severe hypoxemia (eg, arterial PO_2 < 40 mm Hg, or PaO_2/FIO_2 < 200)
- Worsening acidemia (eg, pH < 7.25) and hypercapnia (eg, PCO_2 > 60 mm Hg) despite aggressive initial therapy
- Cardiovascular complications (hypotension; heart failure; myocardial infarction)
- Other comorbidities or complications (pneumonia; sepsis; pulmonary embolism; pneumothorax; massive pleural effusion; metabolic acidosis)

in patients with COPD exacerbations. They used a series of 1,033 consecutive patients, 797 of whom were successfully managed with NPPV, in developing the chart, which uses the APACHE II score and the Glasgow Coma Scale score as well as the patient's respiratory rate and arterial pH initially and after 2 hours of therapy, to predict the likelihood of NPPV failure. They then validated the chart prospectively in an additional 145 patients. To identify patients in whom NPPV was more likely to fail than to succeed, the chart had sensitivities and specificities of 33% and 97% on admission and of 53% and 94% after 2 hours of NPPV, respectively. Whether use of this chart will prove to be beneficial beyond the circumstances of this study remains to be established.

Patients with COPD exacerbations who do not meet the criteria listed in Table 1 may be less likely to benefit from NPPV. Keenan et al recently published an evaluation of NPPV vs usual care in a cohort of 25 patients with milder exacerbations than included in most series.[20] They found that only about half of the patients tolerated the therapy, and that there were no significant differences in length of stay or other outcomes in the NPPV and usual-care groups.

Invasive Mechanical Ventilation

Even when patient assessment is performed appropriately, and NPPV is applied when and as it should be, some patients require intubation and invasive mechanical ventilation. Table 3 lists the findings and circumstances in which intubation is indicated.

How to ventilate patients once they are intubated is beyond the scope of this article. However, the goals of mechanical ventilation are to unload the respiratory muscles so that they can recover from the overload that led to ventilatory failure; to provide adequate oxygenation; to improve acid-base status without disrupting any underlying compensation and causing alkalemia; to avoid dynamic hyperinflation and auto-PEEP; and to make the period of intubation as short as possible. Realizing these goals is not easy, and the frequency and severity of complications of invasive mechanical ventilation in patients with severe COPD underscore the importance of making every effort to avoid it. The guidelines summarized in this article may assist in this effort. ■

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CME Questions

22. In implementing therapeutic hypothermia, Oddo et al noted that:
a. external cooling was ineffective
b time to achieving goal temperature correlated with outcome
c. nursing and other ancillary staff were opposed to cooling
d. emergency room physicians were opposed to cooling
e. goal temperature was readily achieved by a median time of 5 hours

23. Which of the following statements about the use of systemic corticosteroids in COPD exacerbations is true?
a. It decreases mortality
b. It decreases complications
c. It has no effect on the rate of improvement in air flow
d. Parenteral administration has been shown to be more effective than oral
e. None of the above

24. Which of the following is a contraindication to noninvasive ventilation?
a. Recent facial or nasal surgery
b. Extreme obesity
c. Acute myocardial infarction
d. Copious respiratory secretions
e. All of the above

Answers: 22 (e); 23 (e); 24 (e)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:
- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues: **Enhancing Patient Safety During Hand-Offs**

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.

Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

The Truth About Multivitamins

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

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supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin B_6 was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin B_{12} has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■