CRITICAL CARE ALERT®

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INSIDE

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Lung-Protective Ventilation Saves Lives, But We Don't Use It

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Even at an ARDSNet-participating academic medical center and well after publication of that study's findings that low-tidal-volume ventilation saved lives, only a minority of patients with acute lung injury were receiving tidal volumes of 7.5 mL/kg predicted body weight or less.*

Source: Kalhan R, et al. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med*. 2006;34:300-306.

KALHAN AND COLLEAGUES AT THE HOSPITAL OF THE UNIVERSITY of Pennsylvania (a participating ARDSNet investigation site) performed a prospective observational cohort study of patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) managed in their ICUs during a 22-month period beginning after publication of the initial ARDSNet study.[1] The investigators determined the proportion of patients for whom tidal volume on days 2, 4, and 7 of ALI/ARDS was 7.5 mL/kg predicted body weight (PBW) or less (as used in 95% of the patients in the low-tidal-volume group in the original ARDSNet study). In a sensitivity analysis, they also determined how many patients were receiving not more than 6.5 mL/kg PBW and 8.5 mL/kg PBW at those same times.

Of 175 patients with ALI/ARDS screened during the study period, half were excluded for a priori reasons, so that the study population comprised 88 patients. These 88 patients were ventilated with an assortment of modes, per the managing teams: 25% with volume assist-control, 31% with volume intermittent mandatory ventilation, 33% with pressure support, and 11% with pressure control. However, only 39% of them were on tidal volumes not more than 7.5 mL/kg PBW by the end of the second day after ALI/ARDS diagnostic criteria were met. The proportions on day 4 and day 7 were 49% and 56%, respectively. About half of all patients with ALI/ARDS (49%) were receiving tidal volumes exceeding 8.5

mL/kg PBW on day 2, 30% on day 4, and 24% on day 7. Patients with lower arterial PO_2 values and lower values for total respiratory system static compliance tended to be on low tidal volumes more often. Thus, this study demonstrates that, even at a participating ARDSNet study hospital, physicians managing patients with ALI/ARDS used lung-protective ventilation in only a minority of instances.

COMMENTARY

The number needed to treat in the original ARDSNet low-tidal-volume study[1] was 11. This means that for every 11 patients managed with tidal volumes of 6 mL/kg instead of 12 mL/kg PBW in that study, one life was saved. There has been a great deal of debate about the design of that study, with some people claiming that 12 mL/kg was a tidal volume no longer used in actual patient management, rendering the findings irrelevant, and others providing evidence that, in fact, tidal volumes in that range are still very commonly used, especially when tied to PBW rather than to actual body weight. The fact is that there are few interventions in critical care that have been demonstrated so convincingly to save lives as simply using lower tidal volumes and end-inspiratory plateau pressures during mechanical ventilation. And yet several studies have shown that even at participating ARDSNet centers, where the staff certainly ought to know how to perform it, lung-protective ventilation is not in fact used in managing most patients with ALI/ARDS. Why not? At these same institutions, therapies whose benefits are supported by far less compelling evidence have been put into wide usage.

This study is not the first to show a low rate of use of lung-protective ventilation. The accompanying editorial by Young[2] lists several others, including studies from other ARDSNet centers, that have demonstrated similar findings. Measuring height in order to calculate PBW is still not done in many ICUs, and in the ARDSNet study[1] actual body weight was on average 20% greater than PBW. Studies have shown that, despite internationally standardized criteria, ALI/ARDS remains a grossly underdiagnosed condition. A survey of ICU nurses and respiratory therapists by Rubenfeld et al[3] found that physicians were often concerned about patient discomfort from low-tidal-volume ventilation, and also frequently felt that this management approach was medically contraindicated for their patients. In addition, lung-protective ventilation is a form of protocolized patient management, a concept still resisted by some despite bountiful evidence that it improves care.

Whether a tidal volume of 6 mL/kg PBW and an end-inspiratory plateau pressure less than 30 cm H_2O are optimally lung-protective are unproven to the satisfaction of some, and are likely to remain so for awhile. However, given the findings of the ARDSNet study[1] and others[4] that low tidal volumes and distending pressures improve outcomes, the onus in 2006 is on any clinician who does not manage ALI/ARDS patients this way to demonstrate otherwise. Unawareness of current standards, and failure to recognize ALI/ARDS when it is present in one's patients, is hard to defend when lives are at stake. ■

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New Trick for Liberation from Mechanical Ventilation?

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Dr. Akhtar does research for Eli Lilly.

Synopsis: *This prospective observational study suggests that a successful spontaneous breathing trial with pressure support immediately after a failed T-piece trial may predict and allow successful liberation from the ventilator.*

Source: Ezingeard E, et al. Weaning from mechanical ventilation with pressure support in patients failing a T-tube trial of spontaneous breathing. *Intensive Care Med*. 2006;32:165-169.

SOME STUDIES HAVE SHOWN THAT BREATHING through an endotracheal tube imposes a small but measurable excess respiratory workload. Although randomized, controlled studies have found no difference between T-piece and pressure support (PS) spontaneous breathing trials (SBTs) as predictors of readiness for extubation, the authors suggest that perhaps the excess respiratory workload may be an issue for specific patients. They aimed to evaluate the utility of a PS SBT following a failed T-piece SBT. Their primary outcome was extubation failure rate within 48 hours.

A prospective observational study was performed in 2 French medical-surgical intensive care units between 2003 and 2004. Over a 17-month-period, all patients requiring mechanical ventilation for > 24 hours and ready for a SBT were eligible. Patients with tracheostomies and those with pending decisions about goals of care were excluded. Patients underwent a 30-minute T-piece SBT with extubation if successful. A successful trial was defined as absence of signs of respiratory distress (eg, retractions or agitation), oxygen saturations ≥ 90% on ≤ 50% oxygen, respiratory rate ≤ 35 per minute and absence of a 20% variation in respiratory rate or blood pressure. If patients failed a T-piece SBT, they were immediately placed on a PS of 7 cm H_2O for 30 minutes. If they met the noted criteria of success, they were extubated. Standard statistical methods were used to compare groups.

A total of 118 consecutive patients were enrolled. Of these, 87 were extubated after a 30-minute T-piece SBT. Of the remaining 31 patients, 21 (68%, or 18% of the original cohort) were extubated following a PS SBT. Reintubation rates at 48 hours were not significantly different (13% for T-piece group and 19% for those undergoing PS SBT after T-piece). Patients in the 2 groups were similar in terms of age, chronic medical problems, acute diagnoses, endotracheal tube size, duration of mechanical ventilation and death. The only difference was in percentage of patients with decompensated COPD in each group: 13% of those successfully liberated from the ventilator after T-piece SBT had decompensated COPD compared to 38% of those successfully liberated after PS SBT. The authors note that they adjusted sensitivity and pressurization slope individually for each patient undergoing a PS SBT: they suggest that this allowed for improved patient-ventilator synchronization and thus a successful SBT particularly in those patients with COPD.

COMMENTARY

Well designed, large, randomized trials have previously compared weaning strategies (time to extubation and success rates measured by reintubation at 48 hours) and found no significant difference between T-piece and PS SBTs.[1] Although there may be reasons to think that respiratory failure in patients with COPD differs from respiratory failure in other settings, some studies have even compared these weaning strategies specifically in patients with COPD and found no difference.[2]

Ezingeard and colleagues' work may appear to put these findings into question. However, a direct comparison is difficult since this study assesses immediately consecutive weaning trials (rather than delayed, daily weaning trials). The study is clearly limited by lack of randomization and the number of patients (total and with decompensated COPD): would immediately following up a failed PS SBT with a T-piece SBT lead to similar results? Would this study have revealed more or less striking results in a large group of patients with COPD?

Another concern is that the authors' defined criteria for failure of a SBT may not be those used by other intensivists (a 20% variation in respiratory rate or blood pressure was used but without specific thresholds; respiratory rate > 35 per minute may be too low).[3] This is an important issue as the majority of patients considered to fail their T-piece SBT did so based on only 1 of the several criteria: the results may have been greatly altered had the criteria varied or failure been defined by not meeting 2 or more of the criteria. Finally, as with many other studies of weaning, criteria for reintubation and failed extubation are not clearly defined, adding considerable potential bias to the primary outcome.

It is essential to continue to evaluate our approach to weaning and to work to avoid unnecessary days on the ventilator. I hope that despite the limitations of this study, Ezingeard et al follow up their interesting hypothesis with a larger randomized trial. Until then, we must continue to consider T-piece and PS SBTs as equals. ■

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Simulation Training Beats Problem-Based Approach

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, RN, PhD

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

Dr. Hoffman reports no financial relationship to this field of study.

Synopsis: *For fourth-year medical students, simulation-based learning was superior to problem-based learning in teaching assessment and management skills.*

Source: Steadman RH, et al. Simulation-based training is superior to problem-based learning for the acquisition of critical assessment and management skills. *Crit Care Med*. 2006;34:151-157.

Despite favorable reviews, limited evidence supports the benefit of high fidelity human simulation (HFHS) in preference to more traditional forms of health care provider education. Steadman and colleagues compared the performance of 31 fourth-year medical students who were randomized to receive HFHS training or problem-based learning (PBL). On Day 1, all participants underwent a simulation-based assessment designed to evaluate their critical care skills. The assessment was conducted by 2 instructors blinded to group using a standardized 35-item checklist. The PBL group learned about assessment and management of dyspnea in a standard PBL format and the simulation group using HFHS. To equalize simulator education time, the PBL group received instruction about assessment and management of abdominal pain using the simulator, whereas the HFHS group was taught using the PBL format. During the final day of the course, both groups were evaluated on the assessment and management of dyspnea on the simulator. During these sessions, the "patient" presented with a chief complaint of shortness of breath from various etiologies, eg, asthma, COPD, anaphylaxis, pneumothorax, pulmonary edema, expanding neck hematoma. Each student was responsible for independently managing the "patient" and scored using the same 35-item checklist.

Scores were equivalent at baseline ($P = .64$) for the 2 groups. The HFHS group performed better ($P < .0001$) than the PBL group on the final assessment. When each participant's change in score (% correct on the final assessment minus % correct on the initial assessment) was compared, the HFHS group also performed better. The mean improvement for the HFHS group was 25 percentage points vs 8 percentage points for the PBL group ($P < .04$).

■ COMMENTARY

In the critical care setting, practitioners must be able to quickly assess and appropriately manage critical events. Training to acquire these skills is challenging because patient well-being must supersede opportunity for skill acquisition. Exposure to suitable patients cannot be standardized and emergent events are often handled by practitioners with more experience, which limits student participation.

HFHS training offers the potential to overcome these obstacles by providing exposure to frequent, emergent, or rare events in a setting that facilitates evaluation of actions, decisions, and time to accomplish these. However, evidence supporting benefits of HFHS training remains limited. In this study, the authors were careful to match the training of both groups. Before the intervention, all participants attended the same didactic lectures on the test topic (dyspnea) and control topic (abdominal pain). During the intervention, the same instructors taught all PBL or HFHS sessions. Equivalent information and teaching time were provided to both groups and the rating format was identical for the initial and final assessment. The goal was to learn the skills needed to accomplish a primary and secondary survey and initiate appropriate critical care management. The

primary difference was the more realistic simulation environment which consisted of actual equipment, monitors that modeled physiologic changes, and the presence of individuals who modeled actions of the critical care nurse and other health care personnel.

In the opinion of the authors, the simulation environment evoked a distinctly different, more engaged learning atmosphere versus the more reflective response elicited by the PBL-based case studies. Study findings suggest that HFHS led to improved performance, a finding that was especially impressive given the brief duration of the teaching session (< 15 minutes per student). Of note, the study did not attempt to evaluate skills in the critical care setting. Therefore, whether improved performance in the simulation laboratory translates to improved performance under real life conditions remains to be determined. ■

ARDS in Catastrophic Antiphospholipid Syndrome

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this study of a registry of patients with catastrophic antiphospholipid antibody syndrome, 21% developed ARDS. Patients with ARDS did not differ otherwise from the other patients in the registry, and the mortality was the same.*

Source: Bucciarelli S, et al. The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients. *Ann Rheum Dis*. 2006;65:81-86.

Using a website-based international registry of patients with catastrophic antiphospholipid syndrome (CAPS), Bucciarelli et al sought to determine how often ARDS occurred as a complication. There were 220 patients with CAPS in the registry, reported by physicians in 20 different countries. Patients had a mean age of 38 years, and 70% were female. Of the 220 patients, 48% had primary antiphospholipid syndrome, 40% had systemic lupus erythematosus, and the remainder had a variety of other primary diseases. ARDS was diagnosed by the patients' managing physicians, using a definition of bilateral infiltrates on chest radiograph, PaO_2/FIO_2 < 200 mm Hg, and the absence of clinical evidence of cardiogenic pulmonary edema.

Some pulmonary involvement was present in 68% (150/220) of the CAPS patients in the registry. Forty-seven patients (21%) were diagnosed as having ARDS, of whom 19 (40%) died. There were no differences in age, sex, precipitating factors, clinical manifestations, or mortality among patients with CAPS and ARDS as compared with patients with CAPS who did not develop ARDS.

COMMENTARY

Catastrophic antiphospholipid syndrome is characterized by multiple vascular occlusive events, usually affecting small vessels, occurring over a short period of time in the presence of antiphospholipid antibodies. Many patients who develop the syndrome have lupus, although it occurs in other diseases and also as an apparently isolated phenomenon. Specific diagnostic criteria for CAPS, also called Asherson's syndrome, are evidence of involvement of 3 or more organs, systems, or tissues; development of these manifestations simultaneously or within a one-week period; biopsy confirmation of small-vessel occlusion from at least one site; and laboratory confirmation of antiphospholipid antibodies.

Because the diagnosis of ARDS in this study was assigned by each patient's managing physician, and because the website from which the data for this study were taken is no longer available at the URL provided in the article, the validity of the incidence figures cited by Bucciarelli et al is uncertain. Although the number of ARDS cases reported was relatively small, there did not appear to be any differences among CAPS patients who did and did not develop the syndrome. It is noteworthy that mortality was not increased among patients who developed ARDS. However, it seems clear that the development of ARDS is a frequent and serious phenomenon among patients with CAPS. ■

Special Feature

The Emerging Nightmare of *C. difficile* in the ICU

By Uday Nanavaty, MD

Pulmonary and Critical Care Medicine, Rockville, MD

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

Nosocomial infections are unfortunately common in intensive care units all across the United States. Although a wide variety of guidelines and treatment options exist for common types of nosocomial infections, such as catheter-related bloodstream

infections or the ventilator-associated pneumonia, much less importance is given in critical care to *Clostridium difficile* infections. Although infection with this organism is not necessarily nosocomial, it is more often acquired during hospitalization. Several reports of severe *C. difficile*-associated disease (CDAD) due to a hyper-virulent strain have appeared recently,[1-3] including the report from Canada in which CDAD was associated with high short- and long-term mortality and approximately 10 extra days of hospitalization per case.[4] Therefore, I review the literature on this "existing" infection as I am certain that the readers of this publication are much more likely to see and treat a case of severe CDAD in their ICU in the future than any of the "emerging" infections that we hear about from the scientific and lay press.

The Organism

C. difficile is a Gram-positive bacillus that can form spores. Although it is uncommon to find the organism in the stool of healthy adults (< 3%), carriage rates increase with increasing age, with antibiotic therapy, and with hospitalization or hematological malignancies. The organism can live in spore form in the hospital room for weeks to months after the infected patient has been discharged. It produces toxins that cause severe inflammation and cell death in the colonic mucosa. Although the organism was first described in 1930s, its pathogenic role in pseudomembranous colitis was established only in the 1970s.

The organism is difficult to culture, hence the name "difficile." Enzyme assay to detect *C. difficile*'s toxin A or toxin B is the most rapid way to make a clinical diagnosis. The assays have high sensitivity and specificity although a negative test does not necessarily rule out an infection. Care must be taken to submit the specimen within 2 hours of collection as the toxin rapidly degenerates at room temperature giving rise to a false-negative test. Tests based on *C. difficile*'s ability to induce cytotoxicity are very specific but take longer time and hence are not routinely used in clinical practice.

Spores of this organism are ingested and when bowel flora is altered in susceptible individuals, the organism assumes a vegetative form in the colonic mucosa. The organism can exist in both forms in the colonic mucosa. In recurrent CDAD, it is often difficult to assess if the organism grew from the colonic mucosa (relapse) or if a new organism was acquired (recurrence).

The Epidemiology

Antibiotic exposure is clearly the most important factor in the development of CDAD. Although practically any antibiotic can cause CDAD, cases and outbreaks have been reported more frequently after clindamycin, third-generation cephalosporins, broad-spectrum penicillins, and fluoroquinolone use. CDAD accounts for approximately 15-25% of antibiotic-associated diarrhea, and the majority of cases of pseudomembranous colitis.

The incidence of CDAD is clearly on the rise. As estimated by the Centers for Disease Control and Prevention,[1] CDAD as a diagnosis during hospital stay was reported at the estimated rate of 31 cases per 100,000 population in 1996, which subsequently doubled to an estimated rate of 61/100,000. The highest rate of infection occurs in the age group older than 65 years. This age group tends to get affected about 7 times as much as the next age group of 45-64 years. Thus age seems to be an important risk factor in development of CDAD. The majority of cases occur in patients who have received antibiotics, although cases have been reported as long as 3 months after stopping antibiotics. Hematological malignancy and prolonged hospital stay are also associated with increased risk of CDAD.

CDAD is associated with variable mortality. In one of the largest outbreaks reported from Quebec, Pepin et al reported a mortality rate of 23% at 30 days in patients who had CDAD compared to 7% among matched controls.[3] In the most severe cases where surgery is considered an option, mortality may be as high as 50%. It is estimated that each case of nosocomial CDAD caused 10.7 additional days of hospitalization. It is estimated that CDAD costs $1.1 billion dollars in annual healthcare costs in the United States alone.

The Clinical Spectrum of CDAD in Critical Care

In most cases, CDAD presents as mild diarrhea. In the majority of the cases that I have seen personally in critical care settings, patients present with severe watery diarrhea associated with a peculiar smell and dehydration. Abdominal pain is not typical unless colonic perforation develops. Abdominal distension is often seen in patients presenting to the critical care units with CDAD. Diarrhea may be absent and patients may present with toxic megacolon or an ileus-type picture. Sepsis and septic shock are often the presenting diagnosis; sometimes developing before the obvious diarrhea that raises suspicion for CDAD. Laboratory tests are characterized by elevated leukocyte counts, often in the leukemoid range. Renal failure develops in the severe cases. Abdominal exam should be carefully followed in the ICU as patients may develop toxic megacolon or colonic perforation days after starting appropriate treatment.

The clinical diagnosis is often suspected with the peculiar smell of CDAD and the previous history of antibiotic therapy. A freshly collected stool specimen should be sent for *C. difficile* toxin assay. Bedside sigmoidoscopy or colonoscopy is also often helpful, especially if the toxin assay is negative, as it can demonstrate the pseudomembrane formation and show patchy necrosis or colitis. Rarely, only the right side of the colon may be involved. If this is suspected, a more complete endoscopic examination may be necessary. CT scan often demonstrates thickened bowel wall and colonic dilatation and can help rule out perforation or alternative diagnosis.

Treatment of CDAD[4]

Patients with severe CDAD in the critical care setting require rapid volume resuscitation for severe dehydration. Septic shock may require vasopressor therapy. If patients are on antibiotics, careful attention needs to be given to limiting the duration of antibiotics as much as possible. Stopping of the offending agent(s) is one of the first steps toward improving the chances of clearing this organism. Patients who continue to stay on the antibiotics that resulted in CDAD have higher chances of developing recurrence and severe CDAD.

Most cases of CDAD respond initially to antibiotic therapy. Oral metronidazole, in a dose of 250 to 500 mg every 8 hours for 10 to 14 days, is the most preferred therapy. If the patient is unable to take this agent (eg, pregnancy) or to tolerate it, oral vancomycin is equally effective at 125 mg 4 times a day dosing. Increasing the dose of oral vancomycin does not offer any additional advantage and in general the cost of this drug is substantially higher than that of metronidazole. I am not aware of any randomized controlled trial of the combination of vancomycin and metronidazole. The intravenous form of metronidazole has been shown to be effective. However, vancomycin is not very well secreted in colonic mucosa to be effective via the intravenous route.

A novel concept, especially in patients with recurrent or relapsing CDAD, is to use pulse doses of oral vancomycin or metronidazole. The antibiotic is given in usual doses but at increasing interval with the hope that as the interval of antibiotic administration increases, the remaining spores will germinate and be killed by the next dose. Such regimens are continued for up to 3 weeks.[4]

Additional antibiotics have been tried but are not commonly used. Teicoplanin, fusidic acid and bacitracin have been tried in one or more randomized studies. Rifampicin has been reported to help patients with recurrent or relapsing CDAD but only in a total of 8 patients in the literature. Similarly, very limited case series data exist for use of intravenous gamma globulin (IVIg), a very expensive and limited resource, in CDAD.

Patients with CDAD should be isolated to prevent the spread of the organisms. Gloves should be worn while touching the patient or any surface in the patient's room as they may have the spores of organism on them. If close contact with the patient's bed is expected, gowns should be worn as well. Although an alcohol hand wash is often adequate, if the institution is experiencing a high rate of CDAD, hand washing is often recommended after taking care of CDAD patient as the spores may not be eradicated with alcohol-based hand sanitizers.

Probiotics are cultures of microorganisms that are administered orally to populate the colonic mucosa to reduce the severity or prevent development of CDAD. *Saccharomyces boulardii* and *Lactobacillus* species have been used, more often for prevention of CDAD.[5] The role of probiotics in severe CDAD is not clear but in my opinion, they are worth trying. Rare case series have reported use of human stool enemas to populate the colonic mucosa as a treatment of severe CDAD. Severe cases may require total parenteral nutrition to provide nutritional support until resolution of diarrhea. In the reported literature, diarrhea due to recurrence or relapse can last for as many as 55 days.

Role of Surgery in Severe CDAD

If the patient presents with an acute abdomen or develops toxic megacolon, or has refractory diarrhea and does not seem to respond in 4-5 days of conservative treatment, total colectomy with ileostomy may be a life saving option. In one of the largest reported series, Longo et al reported 67 cases from a Department of Veterans Affairs database that required colectomy as therapy of CDAD.[6] Of these cases, 54% had acquired CDAD in the hospital whereas 46% had acquired it in community settings. 37% of the cases did not have diarrhea, and 64% presented as a surgical abdomen. 18% of the cases had negative stool studies for C difficile, but all had pathological changes of CDAD in colon. Perforation and infarction were found in 58 out of 67 cases. Overall mortality was 48% in this case series. Thus surgery is often the last resort in the most severe cases of CDAD.

Conclusion

Overall, severe CDAD is a life threatening nosoco-

mial infection that requires careful contact isolation, judicious use of antibiotics and close monitoring for development of complications. Although there are not many reports of severe CDAD in the critical care literature, mortality is high, especially if complications develop that require surgical intervention. As more and more care gets bundled, careful unbundling of the broad spectrum antibiotics will be required to reduce the incidence and to prevent further spread of this fastidious organism. ■

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CME / CE Questions

1. **According to the findings of the ARDSNet, the number needed to treat in order to save one life when ventilating patients with ALI/ARDS with tidal volumes of 6 vs 12 mL/kg predicted body weight is:**
   a. 11.
   b. 22.
   c. 44.
   d. 88.
   e. 132.

2. **Which of the following have been proposed as possible reasons why clinicians do not use lung-protective ventilation in managing patients with ALI/ARDS?**
   a. Concerns about patient discomfort
   b. Failure to diagnose ALI/ARDS
   c. Belief that it is medically contraindicated for many patients
   d. All of the above
   e. None of the above

3. **In the Kalhan study of ventilator management for patients with ALI/ARDS, what percentage of patients were on tidal volumes of 7.5 mL/kg PBW or less at day 2?**
   a. 22%
   b. 39%
   c. 49%
   d. 56%
   e. 77%

4. **In Ezingeard et al's study, patients who failed a T-piece spontaneous breathing trial:**
   a. rested for 30 minutes before a spontaneous breathing trial with pressure support.
   b. immediately went onto a 30-minute spontaneous breathing trial with pressure support.
   c. rested for 24 hours and then had a repeat T-piece trial.
   d. were immediately extubated.
   e. immediately went onto weaning by gradual reduction in SIMV rate.

5. **Compared to problem-based learning, medical students who were taught using simulation:**
   a. scored lower in the dyspnea scenario.
   b. scored lower in the abdominal pain scenario.
   c. took longer to complete the history of present illness.
   d. performed better on all aspects of the evaluation.
   e. had less favorable perceptions of learning.

Answers: 1 (a); 2 (d); 3 (b); 4 (b); 5 (d)

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:

Sildenafil in Pulmonary Embolism

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.

Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

Treatment of Benign Prostatic Hyperplasia

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

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commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■