CRITICAL CARE ALERT®

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

Thomson American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com; CE for Nurses—http://www.ceweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Recruitment Maneuvers Still Controversial in ALI/ARDS

ABSTRACT & COMMENTARY

Synopsis: *In patients with ALI/ARDS from pulmonary and extrapulmonary causes, receiving mechanical ventilation with low tidal volumes and high PEEP, short-term effects of recruitment maneuvers as conducted in this study are variable.*

Source: ARDS Clinical Trials Network. *Crit Care Med*. 2003;31: 2592-2597.

One of the most controversial issues in managing patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) is whether (or how) special maneuvers to fully inflate the lung and open atelectatic areas (recruitment) should be used. The objectives of this study were to assess a) the magnitude of the immediate effects of recruitment on arterial oxygenation; b) the duration of the effects of recruitment maneuvers on requirements for FIO_2 and positive end-expiratory pressure (PEEP); and c) the immediate effects of recruitment maneuvers on hemodynamics and barotrauma. The study was conducted in ALI or ARDS patients who were enrolled in a multicenter clinical trial designed to compare outcomes with 2 approaches to managing PEEP: a traditional PEEP strategy vs a strategy using higher PEEP levels. All patients received mechanical ventilation with small tidal volumes (6 mL/kg predicted body weight). This ancillary study of recruitment maneuvers was conducted only in patients randomized to the higher PEEP arm of the main trial.

This was a crossover study in which patients were randomized to receive single recruitment maneuvers on either the first and third or the second and fourth mornings after enrollment in the main ARDSnet trial. Recruitment maneuvers and sham recruitment maneuvers were not conducted if patients were in the process of being weaned from ventilatory support, if systolic blood pressure was < 100 mm Hg or > 200 mm Hg, or if heart rate was < 70/min or > 140/min. No additional sedatives or neuromuscular blocking agents were required. All patients were supported with volume-controlled ventilation.

Recruitment maneuvers were conducted by changing the ventila-

tor mode to continuous positive airway pressure (CPAP) and gradually raising the CPAP level over 5-10 seconds to 35 cm H_2O (40 cm H_2O if measured weight exceeded 150% predicted body weight). This level of CPAP was maintained for 30 seconds unless systolic blood pressure decreased to < 90 mm Hg or by > 30 mm Hg, heart rate increased to > 140/min or by > 20/min, SpO_2 was < 90% and had decreased by > 5%, or a cardiac dysrhythmia occurred. The CPAP level then was decreased over 5-10 seconds to the previous ventilator settings. Sham recruitment maneuvers were conducted by assigning an initial time in the morning and then recording respiratory, hemodynamic, and radiographic data while patients continued on mechanical ventilation without conducting a recruitment maneuver.

To assess immediate effects of recruitment maneuvers, the greatest increments in SpO_2 during the first 10 minutes after initiating recruitment maneuvers or sham recruitment maneuvers were compared. After the first 10 minutes, FIO_2 and PEEP were adjusted in discrete steps according to an explicit protocol (FIO_2/PEEP-step) to maintain SpO_2 of 88-95%. To assess duration of recruitment maneuver effects, changes in FIO_2/PEEP-step were recorded at 30 minutes and 1, 2, 4, and 8 hours after recruitment maneuvers or sham recruitment maneuvers (a decrease in FIO_2/PEEP-step is a favorable change).

There were 66 recruitment maneuvers and 70 sham recruitment maneuvers in 43 patients in whom at least 1 recruitment maneuver and 1 sham recruitment maneuver were conducted. Increments from baseline SpO_2 were greater within 10 minutes after recruitment maneuvers than after sham recruitment maneuvers (1.7 ± 0.2% vs 0.6 ± 0.3%; $P < 0.01$). The responses to recruitment maneuvers were highly variable. In 10 instances, SpO_2 increased by 5-9% during the first 10 min. However, in 14 instances, SpO_2 decreased by 1-4% after initiating the recruitment maneuvers and did not return to baseline SpO_2 levels within 10 minutes. None of the differences between the changes in adjusted FIO_2/PEEP-step after recruitment maneuvers and sham recruitment maneuvers were significant. The mean decrease in adjusted FIO_2/PEEP-step 2 hours after recruitment maneuvers was 0.19 ± 0.14 steps greater than the mean decrease in adjusted FIO_2/PEEP-step 2 hours after sham recruitment maneuvers ($P = 0.18$). This is equivalent to a difference in PEEP of 0.36 cm H_2O or a difference in FIO_2 of 0.018.

Decreases in systolic blood pressure were significantly greater after recruitment maneuvers than after sham recruitment maneuvers. Decreases in SpO_2 during the first 10 minutes were also significantly greater after recruitment maneuvers than after sham recruitment maneuvers. Recruitment maneuvers were terminated early in 3 instances because of hypotension or low SpO_2. There were no apparent sequelae from these events, which were transient and self-limited. New barotrauma was evident on the first chest radiographs after 1 recruitment maneuver and after 1 sham recruitment maneuver.

COMMENT BY DEAN HESS, PhD, RRT

When Amato and colleagues[1] published their paper on lung-protective ventilation for ALI/ARDS in 1998, it became clear that how the ventilator is set can affect patient-important outcomes like mortality. As part of their protective ventilation approach, Amato et al used pressure-controlled ventilation, limited the inspiratory pressure and tidal volume, used higher than conventional levels of PEEP, and applied recruitment maneuvers. Because so many interventions were applied simultaneously, it is not possible to know which of these was

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

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Glen Harris.

ASSISTANT MANAGING EDITOR: Robert Kimball.

SENIOR COPY EDITOR: Christie Messina Petrone.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

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@ahcpub.com

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

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $239

(Student/Resident rate: $120)

Multiple Copies

1-9 additional copies: $215 each; 10 or more copies: $191 each.

Canada

Add GST and $30 shipping.

Elsewhere

Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AHC is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. Provider approved by the California Board of Registered Nursing, Provider Number CEP 10864, for approximately 16 contact hours.

This CME activity is intended for the Critical Care Physician. It is in effect for 36 months from the date of the publication.

THOMSON AMERICAN HEALTH CONSULTANTS™

Questions & Comments

Please call **Rob Kimball,** Assistant Managing Editor, at (404) 262-5413 or e-mail at rob.kimball@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Ms. Ball serves as a consultant to Steris Corp, IC Medical, and AMT-Coherent (Canada), is a stockholder of Steris and SLT, and is on the speaker's bureau of AORN. Dr. Pierson is on the speaker's bureau of GlaxoSmithKline, Boehringer-Ingelheim, 3-M, Bayer, and Astra Zeneca. Dr. Rubenfeld is a consultant to Eli Lilly and is involved in research with the National Institutes of Health. Drs. Baigorri, Durbin, Hess, Hoffman, Johnson, and O'Keefe report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Drs. Crawford, Gladwin, Nanavaty, and Takezawa did not return a financial disclosure form. Thomson American Health Consultans accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

most important or if all are necessary to achieve the desired outcome. The use of recruitment maneuvers in the Amato study was initially overlooked by many. However, in his travels around the world promoting his approach, Amato championed the role of recruitment maneuvers. During a trip to Boston, my colleagues and I heard Amato describe his enthusiasm for recruitment maneuvers. Within hours after hearing this, we applied recruitment maneuvers to a patient with ARDS. The results were positive, and we quickly submitted a case report.[2]

After my initial enthusiasm for recruitment maneuvers, I have become less and less excited about their use. Despite the occasional dramatic responder (in terms of improved oxygenation), I have observed many times when the recruitment maneuver produced no effect on oxygenation and a few cases in which bad outcomes have resulted (eg, barotrauma or hemodynamic compromise). I guess it's a matter of human nature that I was anxious to publish our first positive experience with the use of recruitment maneuvers but have not published subsequent bad outcomes associated with recruitment maneuvers.

The accumulating evidence is marginally supportive of recruitment maneuvers. Villagra and associates[3] reported that recruitment maneuvers have no short-term benefit on oxygenation. Grasso and colleagues[4] reported that recruitment maneuvers were only useful to improve oxygenation in patients with early ARDS and those without an impairment in chest wall mechanics. Moreover, the benefit was short-lived in that study. In patients with brain injury, Bein and associates[5] reported that recruitment maneuvers marginally improved arterial oxygenation and adversely affected cerebral hemodynamics. Johannigman et al[6] reported that recruitment maneuvers only transiently improved gas exchange during low tidal volume ventilation. To date, there have been no studies of the effect of recruitment maneuvers on patient-important outcomes.

In this multi-center, randomized, crossover study to assess effects of recruitment maneuvers in patients with ALI/ARDS receiving a lung protective mechanical ventilation strategy, systolic blood pressure and SpO_2 decreased significantly after recruitment maneuvers. However, these effects were self-limited and without apparent long-term sequelae. SpO_2 increased significantly more within 10 minutes after recruitment maneuvers than after sham recruitment maneuvers. The initial SpO_2 responses were highly variable. There were small increases in mean SpO_2 at 1 hour after recruitment maneuvers but not at other time points. Effects of recruitment maneuvers on requirements for FIO_2/PEEP-step were not significant at any time point, and respiratory system compliance did not increase more after recruitment maneuvers than after sham recruitment maneuvers. These data are consistent with other studies suggesting that any physiologic benefit from recruitment maneuvers is short lived.

I'm certain that these data will be controversial. Proponents of recruitment maneuvers will argue that the study did not apply the recruitment maneuvers correctly or that a protocol allowing a PEEP decrease after the recruitment maneuver may have obviated any benefit from the recruitment maneuver. Nonetheless, the accumulating evidence from this and others studies suggests that recruitment maneuvers may not be all that we had hoped for. Unfortunately, the lungs of patients with ALI/ARDS do not appear to be as recruitable as the lungs of animals with experimentally induced lung injury. At this time, recruitment maneuvers cannot be considered a standard of care in patients with ALI/ARDS. We await further clinical study to establish the role for recruitment maneuvers. ■

References

1. Amato MB, et al. *N Engl J Med*. 1998;338:347-354.
2. Medoff BD, et al. *Crti Care Med*. 2000;28:1210-1216.
3. Villagra A, et al. *Am J Respir Crit Care Med*. 2002;165:165-170.
4. Grasso S, et al. *Anesthesiology*. 2002;96:795-802.
5. Bein T, et al. *Intensive Care Med*. 2002;28:554-558.
6. Johannigman JA, et al. *J Trauma*. 2003;54:320-325.

Use of Restraining Therapies in the ICU

ABSTRACT & COMMENTARY

Synopsis: *A consensus group making recommendations on the use of restraining therapies in the ICU emphasizes the inadequacy of the evidence base in this area and calls for studies to generate better data.*

Source: Maccioli GA, et al. *Crit Care Med*. 2003;31:2665-2676.

A MULTIDISCIPLINARY TASK FORCE WAS CONVENED from the memberships of the American Association of Critical Care Nurses, American College of Critical Care Medicine, and Society of Critical Care Medicine, to evaluate the use of restraints in the ICU and to develop practice guidelines for appropriate use

Table

Consensus Recommendations for the Use of Restraints in the ICU

1. ICU practitioners should create the least restrictive but safest environment with regard to the use of restraints.
2. Alternatives to restraint therapy should be considered.
3. Restraints should not be used routinely. They should be used only in clinically appropriate situations, and the risks of untoward effects should outweigh the ethical, psychological, and physical risks of their use.
4. The restraining therapy selected should be the least invasive option that optimizes patient safety, comfort, and dignity.
5. Rationale for restraint use must be documented. Orders should be limited to a 24-hour period. The potential to discontinue restraints should be considered every 8 hours.
6. Patients should be monitored at least every 4 hours or more frequently, for the development of complications from restraining therapies. These assessments should be documented.
7. Ongoing education should be given to patients and families regarding the need for and nature of restraining therapies.
8. Agents to mitigate the need for restraining therapies should be used: analgesics, sedatives, neuroleptics used for treatment of pain, anxiety, or psychiatric disturbances. These should not be overused as a method of chemical restraint.
9. Neuromuscular blocking agents should not be used as chemical restraints when not otherwise indicated by patient condition.

for both adult and pediatric patients. Consensus was derived from a review of published literature using Cochrane methodology and expert option. Consensus recommendations were developed, and the document was reviewed and approved by the Society of Critical Care Medicine Council. Nine recommendations were made by the task force with regard to the use of physical restraints and pharmacologic therapies to maintain patient safety in the ICU (*see Table*). The task force anticipates that the implementation of these guidelines will decrease the inappropriate use of restraints. It recommends that these guidelines serve as a benchmark for regulatory agencies in assessing appropriate use of restraining interventions in the ICU.

COMMENT BY KAREN JOHNSON, PhD, RN

These professional organizations should be applauded in their efforts to jointly tackle this practice issue that is laden with medical, ethical, and legal implications. It is also noteworthy that the task force included a broad range of critical care practitioners including representatives from medicine, nursing, respiratory therapy, and pharmacy. As clinicians, we struggle on a daily basis with the issue of whether to use restraints. There is constant tension (within us and between us) in our desire to use them to protect the patient and the patient's rights.

Practice guidelines should help clinicians make decisions in specific clinical circumstances. Do the 9 recommendations listed above do that? No. Quite frankly, most of these recommendations are already in place in many ICUs to meet external regulatory standards (eg, JCAHO). But don't blame the messenger (the task force). The real message here is that we don't know what to do because we don't have the evidence to back clinical practice. The task force acknowledged (and rightfully so) that the development of these recommendations was difficult due to the lack of carefully performed trials assessing the risks and benefits of restraining therapies in the ICU setting. The task force concluded that despite numerous questions about the benefits, risks, and practices of the use of restraints in critically ill people, there is little prospective information in the literature that can be used for evidence-based guidelines. The overwhelming majority of the studies reviewed were uncontrolled case series or case reports, graded as Cochrane level 4 and 5. The grade for each of these recommendations was a C.

Should ICU clinicians even bother reading the article in its entirety? Absolutely! The task force did address some fundamental questions about the use of restraints in the ICU and summarized some strategies that are clinically relevant and useful. Here are just of few of the questions addressed in the article: What defines restraining therapy? What are indications for the use of restraining therapies in the ICU? How do we determine which patients need restraining therapies? What alternatives to restraining therapies should be considered? How should restraining therapies be initiated? How frequently should patients be assessed with regard to their need for restraining therapies? How frequently should monitoring for complications be performed in patients subjected to restraining therapies? How should restraint use be documented in the medical record? These are questions we have all dealt with in developing our own ICU restraint policies and procedures. There are some excellent strategies identified and presented in table format that will guide clinical decision making on alternatives to restraining therapies, categories of physical restraints, and recommendations for initiation, monitoring, and documentation of physical restraints.

Areas in need of investigation to develop more evidence-based guidelines for the use of restraining therapies in critically ill patients were identified. These include a randomized, controlled trial to assess the: (1)

efficacy of various restraining therapies in reducing the incident of inadvertent device removal; (2) optimal methods for safely weaning or discontinuing restraining therapies ("release trial"); and (3) hypothesis that ICU staffing patterns affect the need for and implementation of restraining therapies. ■

Daily 'Sedation Vacation': Long-Term Adverse Effects?

ABSTRACT & COMMENTARY

Synopsis: *This single-center study reveals that, compared to continuous sedation, daily sedative interruption is not associated with adverse psychological effects after 6-21 months.*

Source: Kress JP, et al. *Am J Respir Crit Care Med*. 2003;168:1457-1461.

Effects of sedation on long-term psychological functioning of critically ill patients are not well described. Although there is good evidence that daily sedation interruption (the "sedation vacation") offers considerable short-term benefits when compared to continuous sedation,[1] there are concerns that this may negatively effect long-term psychological outcomes.[2] Kress and associates set out to find evidence that daily sedative interruption may be associated with long-term psychological harm. A secondary aim was to determine whether daily sedative interruption may instead be associated with improved long-term psychological outcomes.

The study was conducted at the University of Chicago medical ICU. Study subjects included participants from a prior randomized, controlled trial of daily sedative interruption (intervention) vs continuous sedation (control)[1] plus contemporaneous subjects on the same protocol but not in that study. Demographics, severity of illness, hospital and ICU lengths of stay, mechanical ventilation duration, new and prior diagnoses (including psychiatric), and related treatments were recorded. Patients were contacted at least 6 months after discharge. Those who agreed to participate were evaluated by clinical psychologists who were blinded to the sedation protocol used. Evaluation included a structured interview, the Impact of Events Scale (IES, measuring signs of post-traumatic stress disorder [PTSD]), consideration of PTSD diagnosis according to DSM-IV criteria, the Medical Outcomes Study 36 item short-form health survey (SF-36, assessing overall perception of health and well-being), standard anxiety and depression questionnaires (State-Trait Anxiety Inventory [STAI] and Beck Depression Inventory-2 [Beck]), and the Psychological Adjustment to Illness score (PAIS).

Of the patients who were screened, 105 survived to hospital discharge. Only 35 (30%) could be contacted, and of these, 32 (91%) agreed to participate. There were 19 control and 13 intervention subjects, evaluated at 6-21 months post-discharge. As expected, there was a trend toward decreased ICU and hospital lengths of stay in the intervention group but otherwise no significant differences in baseline characteristics. Most patients (69%) in both groups remembered being in the ICU; none in the intervention arm recalled awakening there. The intervention group had significantly better IES scores, and none had PTSD per DSM-IV criteria; 6 patients in the control arm had PTSD. There were no significant differences between the 2 groups in terms of SF-36, STAI, Beck, or PAIS scores, although in almost every case the trend was toward better scores in the intervention group.

Kress et al conclude that daily sedative interruption is not psychologically harmful to patients in the long term. They highlight the trend toward decreased PTSD in the intervention group and suggest that daily sedative interruption may improve some psychological outcomes.

■ COMMENT BY SAADIA R. AKHTAR, MD, MSc

Kress et al have produced a novel and valuable report on a topic that deserves much greater attention. This is a long-term follow-up of a small cohort of subjects from a randomized, controlled trial of 2 sedation protocols (continuous vs daily interruption) combined with non-randomized subjects on the same protocol. Kress et al are concise but thoughtful and complete in their presentation. They make reasonable attempts to address the inherent limitations of this study design and are quite clear and appropriately cautious in their discussion and conclusions. This is a well-done and well-written important pilot study.

The study has some limitations due to its size and methodology, as Kress et al point out nicely in their discussion. For instance, the lack of difference in psychological outcome between the control and intervention arms could be due to the small study sample size: this greatly limits the power of the study to detect differences. The differences in duration of mechanical ventilation and length of ICU stay, key and significant short-term outcomes in the original daily sedative interruption study, were not statistically significant in this smaller

cohort. Thus, we must also interpret psychological outcomes data with some caution. Furthermore, follow-up/recruitment was very low at 30%, and the final study patients are a mix of 2 separate cohorts (one from a randomized, controlled study). Kress et al did compare known baseline characteristics of the cohorts, as well as those of recruited subjects vs those deceased or lost to follow-up and did not find significant differences; however, considerable unmeasured differences may still exist and may greatly bias the results. For example, there are no available data on baseline psychiatric diagnoses, subsequent medical or psychiatric diagnoses and related treatments, or reason for death or loss to follow-up of the unavailable subjects.

Taking these issues into account, Kress et al's results still represent the first reasonable evidence of relative safety of daily sedative interruption with respect to long-term psychological outcomes. They have set the groundwork for this area of research.

However, it is not enough to stop at equivalence to current outcomes, as it is clear that mental health and quality of life post-ICU stay is quite poor for many patients.[3,4] For this reason, Kress et al's observations of fewer PTSD symptoms and diagnoses, as well as a trend toward improved results in other psychological measures in the intervention group, are particularly intriguing and require further study and clarification. Is daily sedative interruption actually better and less psychologically stressful for patients? If so, what is the underlying mechanism? Does it relate to the sedative agent or dose, the medical staff attention given in order to conduct daily sedative interruption, the reduced time of ventilation or ICU stay, the underlying disease processes leading to ICU admission, the differences in physiology of sleep that may occur with interrupted vs continuous sedation, changes in memory (conscious or unconscious) of the ICU experience, or other factors? Additional aspects of long-term mental health such as neuropsychological functioning also must be examined in future studies.[5]

With continued investigation, we may someday achieve the ultimate goal of providing truly adequate and appropriate sedation at the lowest-effective doses and without adverse outcomes for all patients. For now, we have some good evidence to guide us. All medical ICUs should be implementing daily sedative interruption with the knowledge that it improves short-term outcomes and appears to be equivalent to continuous sedation in terms of patients' long-term psychological functioning. ■

References

1. Kress JP, et al. *N Engl J Med*. 2000:342:1471-1477.
2. Heffner JE. *N Engl J Med*. 2000:342:520-1522.
3. Nelson BJ, et al. *Crit Care Med*. 2000:28:3626-3630.
4. Herridge MS, et al. *N Engl J Med*. 2003:348:683-693.
5. Jackson JC, et al. *Crit Care Med*. 2003:31:1226-1234.

High FIO_2 Deleterious in Acute Asthma

ABSTRACT & COMMENTARY

Synopsis: *Adult patients presenting with acute asthma without significant respiratory acidosis who were given 100% oxygen to breathe had slight increases in arterial PCO_2 and slight decreases in arterial pH and peak expiratory flow, as compared with patients who received only 28% oxygen.*

Source: Rodrigo GJ, et al. *Chest*. 2003;124(4): 1312-1317.

Supplemental oxygen is a mainstay of the treatment of acute severe asthma, although it has been postulated that breathing too high a concentration might induce or worsen respiratory acidosis. Rodrigo and colleagues conducted this study in 2 hospital emergency departments in Uruguay to investigate this hypothesis. Adult patients presenting with acute asthma uncomplicated by signs of infection or complicating illness were randomized to breathe 2 different concentrations of supplemental oxygen (28% and 100%) via mask prior to initiating bronchodilator therapy. Rodrigo et al assessed the severity of dyspnea, vital signs, arterial blood gases, and peak expiratory flow (PEF) before and after the 20-minute oxygen breathing periods.

Seventy-four patients with acute asthma (mean age, 38; initial PEF 41 ± 12% of predicted) completed the study. Initial values for PaO_2 and $PaCO_2$ while the patients breathed room air were 78 ± 13 and 36 ± 4 mm Hg, respectively; no patient had an initial PaO_2 < 58 mm Hg or an initial $PaCO_2$ > 46 mm Hg. Heart and respiratory rates did not change with oxygen therapy and were not different in the 2 groups; dyspnea and wheezing scores were similar before treatment and were not presented after oxygen administration.

Mean arterial PCO_2 was higher (38.0 vs 35.4 mm Hg; $P = 0.03$), and arterial pH lower (7.38 vs 7.41; $P = 0.01$), after 20 minutes of oxygen therapy in the 100% group as compared to the 28% group. Four patients in the 100% oxygen group experienced a rise in $PaCO_2$

from < 50 mm Hg to > 50 mm Hg. Patients receiving 100% oxygen had a slight decrease in PEF (24 L/min; 11%), whereas those receiving 28% oxygen has a slight increase (7.6 L/min; 3%), and this difference was statistically significant ($P = 0.001$). Based on their findings, Rodrigo et al recommend that supplemental oxygen therapy in acute asthma be titrated to an oxyhemoglobin saturation (measured by pulse oximetry) of 92% or more, rather than administered in some standardized, fixed concentration or liter flow.

COMMENT BY DAVID J. PIERSON, MD

This study of patients presenting with acute asthma who had not yet received bronchodilator therapy showed that, on average, patients given 100% oxygen to breathe had slightly higher $PaCO_2$ and slightly lower pH values after 20 minutes than those given 28% oxygen. Arterial PCO_2 decreased in about as many patients as it increased, but among those given 100% oxygen, 42% of the patients had increases in $PaCO_2$ of 2-14 mm Hg (mean, 5 mm Hg), and the change for the whole group was statistically significant in comparison with the 28% oxygen group.

It is important to point out several features of this study that could affect clinical practice. Although the study period was brief (less than an hour, counting the various measurements), Rodrigo et al withheld bronchodilator therapy until after it was completed. In clinical practice, aerosol therapy would be begun immediately, and whether the observed differences would have been present under such circumstances cannot be known. Either by design or because of the patient mix seen in the participating emergency departments, the study also included no patients with clinically important acute respiratory acidosis. One might worry that patients with more severe attacks might have even greater changes in PCO_2 and pH in response to high FIO_2 than those in this study, but that is unknown.

On the other hand, one can wonder whether any of the changes in these values documented in this study were clinically important. Whether administration of 100% oxygen would affect the clinical response to bronchodilator therapy or lead to more patients having to be intubated is unknown. Still, it makes sense, based on these findings, not to give patients with acute asthma any more oxygen than is necessary to adequately saturate their hemoglobin.

Although there was a slight, but statistically significant, fall in PEF among the patients who received 100% oxygen in comparison with values from those who got 28% oxygen, Rodrigo et al make no comment on this other than to correlate it with changes in $PaCO_2$ values, and no possible physiologic explanation is offered. I doubt whether the PEF differences are clinically (as opposed to statistically) significant, but I must confess that I cannot think of a reason why airflow limitation would be increased by a higher concentration of oxygen in the breathing mixture. Perhaps a reader can enlighten me.

Decision Analysis of Treatment Strategies for Ventilator-Associated Pneumonia

ABSTRACT & COMMENTARY

Synopsis: *In late-onset VAP, survival improved and costs decreased using initial coverage with 3 antibiotics. Mini-BAL did not improve survival but decreased costs and antibiotic usage.*

Source: Ost DE, et al. *Am J Respir Crit Care Med*. 2003;168:1060-1067.

The optimal strategy for managing ventilator-associated pneumonia (VAP) remains controversial. To clarify the tradeoffs, Ost and colleagues developed a decision-analysis model to simultaneously examine outcomes of 16 diagnostic and treatment strategies. The "subjects" were a cohort of immunocompetent critically ill patients with the following characteristics: 1) intubated for 7 days; 2) evidence of late-onset VAP based on Centers for Disease Control and Prevention (CDC) criteria of fever, purulent secretions, leukocytosis, and radiographic infiltrates; and 3) estimated mortality of 20%. Five assumptions were built into the model. First, antibiotics would be chosen based on American Thoracic Society guidelines adapted to local formularies and ICU pathways. Second, antibiotics would be given immediately after the patient met CDC criteria for VAP and continued until diagnostic test results returned. Third, antibiotics would be adjusted to cover any identified pathogens and unnecessary antibiotics discontinued. Fourth, if all cultures were negative and the patient had ongoing severe sepsis or was unstable, antibiotics would be continued. Fifth, if the patient was stable, antibiotics would be discontinued.

There were 4 treatment strategies (zero, 1, 2, or 3 antibiotics) and 4 diagnostic strategies: 1) no diagnostic testing; 2) endotracheal tube aspirate quantitative cul-

tures; 3) bronchoscopic cultures; or 4) nonbronchoscopic mini-BAL quantitative cultures. Initial coverage with 3 antibiotics was better than expectant management (zero antibiotics) or 1 or 2 antibiotics, leading to both improved survival (54% vs 66%) and decreased costs ($55,447 vs $41,483 per survivor). Testing with mini-BAL did not improve survival but did decrease costs ($41,483 vs $39,967) and antibiotic use (63 vs 39 antibiotic days per survivor). From the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was 3 antibiotics with mini-BAL.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

VAP frequently complicates the course of critically ill patients on mechanical ventilation and is associated with a high mortality. Survival is highly dependent on selecting the appropriate initial antibiotic. Although diagnostic tests often lead to a change in therapy, it requires time to obtain the results, and when they become available it may be too late to alter survival. Therefore, many advocate that high-risk populations be initially treated with broad-spectrum antibiotic therapy. The decision model that Ost et al used was developed from a literature search that returned 555 citations, later reduced to 111 articles based on search criteria. The final model analyzed multiple outcomes including survival, cost, cost per survivor, antibiotic use, antibiotic use per survivor, and the combined perspective of financial and antibiotic cost per survivor. From a combined perspective, a 3 antibiotic plus mini-BAL strategy was superior to all 1 and 2 antibiotic strategies, irrespective of diagnostic technique, in terms of minimizing antibiotic use and financial cost per additional survivor. Diagnostic testing alone had little effect on survival but was cost-effective because it decreased unnecessary antibiotic usage.

Often overlooked as a technique, decision analysis offers a useful perspective on complex management challenges, such as those presented by VAP. The technique allows simultaneous testing of more options than are possible in a clinical trial. It is ideally suited to situations with multiple clinical options, a large literature base, and continuing uncertainty about the best approach. Decision analysis is subject to accuracy of the basic assumptions used to build the analytic model and unable to project the consequences of future events, such as the emergence of antibiotic resistance and the consequence of this outcome. Given these limitations, it provides an interesting approach to the analysis of a very complex problem. ■

CME / CE Questions

26. In the ARDSnet study of recruitment maneuvers, it was reported that recruitment maneuvers:
a. increase survival in patients with ALI/ARDS.
b. are associated with a high rate of barotrauma.
c. decrease the PEEP requirement in mechanically ventilated patients with ALI/ARDS.
d. variably increase arterial oxygenation, with a short-lived effect.
e. are only useful if a low level of PEEP is applied.

27. Reported adverse effects of recruitment maneuvers in managing patients with ALI/ARDS include:
a. hypotension.
b. hypoxemia.
c. pneumothorax.
d. All of the above
e. a and b but not c

28. Which of the following statements is *false*?
a. ICU practitioners should use the least restrictive restraints.
b. Restraints should be used routinely in the ICU for patient safety.
c. The rationale for restraint use must be documented.
d. Neuromuscular blocking agents should not be used as chemical restraints.
e. None of the above

29. Which of the following Cochrane evidence grades applied to the evidence used for all 9 consensus recommendations on restraining therapies?
a. A (best evidence)
b. B
c. C
d. D (weakest evidence)
e. Decreased anxiety scores

Answer: 26 (d); 27 (d); 28 (b); 29 (c)

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: Critical Care Management of the Jehovah's Witness Patient

AMERICAN HEALTH CONSULTANTS®

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 9, NUMBER 3 PAGES 5-6 MARCH 2004

Prevention of Cardiovascular Events with Aspirin and Vitamin in Type 2 Diabetics

Source: Sacco M, et al *Diabetes Care.* 2003;26:3264-3272.

Pooled data (n = 50,000) on primary prevention of cardiovascular disease with aspirin (ASA) indicates as much as 28% reduction in coronary heart disease, albeit no demonstrable effects upon total mortality or stroke. Recent data from the Primary Prevention Project, a large scale trial of persons with known cardiovascular risk factors (n = 4495) have corroborated that low-dose ASA provides a 40% or greater risk reduction for cardiovascular death.

The benefits of primary prevention with ASA specifically in diabetics remains less certain though meta-analysis suggests substantially lower benefits for diabetics afforded by primary prevention (7%) than we have seen demonstrated for secondary prevention (25%).

Sacco and colleagues report on the diabetic cohort of the Primary Prevention Project trial (n = 1031) who were randomly assigned to low-dose ASA (100 mg/d) and vitamin E. Consonant with recently published major clinical trials (HOPE, Heart Protection Study), no perceptible benefit from vitamin E was found. Disappointingly, no statistically significant benefits of ASA in this diabetic population could be confirmed, as far as cardiovascular death, stroke, or MI (composite end point) or total cardiovascular events. Indeed, there was a trend toward increased cardiovascular deaths. It is postulated that non-platelet-related vasculopathic forces in diabetic patients may counterbalance beneficial platelet effects of ASA. ■

Cinnamon Improves Glucose and Lipids of Type 2 Diabetics

Source: Khan A, et al. *Diabetes Care.* 2003;26:3215-3218.

There is a strong connection between diet and diabetes, but "best diet" remains elusive. Choosing foods with favorable glycemic index (lesser rate of rise of glucose) has been shown to positively effect diabetic control. Some spices, for instance bay leaves, cinnamon, cloves, and turmeric have been noted improve insulin sensitivity in vitro.

Animal studies have provided intellectual fodder for a putative role of cinnamon (CINN) in enhanced insulin activity, favorably affecting glucose uptake, glycogen synthesis, and insulin receptor phosphorylation. The effects of CINN supplementation in humans has been heretofore unknown.

Finely ground CINN mixed with flour was packaged into 500 mg capsules and administered in doses of 1 g, 3 g, or 6 g daily for 60 days. Subjects continued their regular diet (and medication) otherwise unaltered.

CINN produced an 18-29% decrease in fasting glucose levels at 60 days, but no dose-response curve was seen (ie, all doses reduced glucose to a similarly favorable degree). Comparable reductions in total cholesterol (13-26%) and LDL cholesterol (10-24%) were also demonstrated. Favorable effects were seen at CINN ingestion levels from 1-6 g/d. Whether even lower levels might be beneficial remains to be determined. ■

Depression Care on Pain and Functional Outcomes Among Adults with Arthritis

Source: Lin EB, et al. *JAMA.* 2003;290:2428-2434.

Arthritis is the most commonplace cause of disability in the United States, with as many as one-third of persons older than age 65 manifesting osteoarthritis (OA) of the knee. It is not uncommon for this same population to suffer comorbid depression, magnifying dysfunction associated with OA. No previous trial has examined the impact of depression treatment upon pain or functional outcome in OA.

The population studied comprised subjects with both knee OA and non-suicidal unipolar depression (n = 1801). Patients were randomized to "usual care" or a program of antidepressant pharmacotherapy and 6-8 psychotherapy sessions.

OA pain intensity and its interference with daily activities were statistically significantly improved in the active treatment group. Scores on the Hopkins Symptom Checklist were much more likely to improve among intervention recipients than "usual care" (41% vs 18%).

Specifics about individual pharmacotherapies are not included in the study, for instance, we do not know which specific antidepressant agents were used. Antidepressants with norepinephrine reuptake inhibi-

tion activity have already demonstrated favorable effects in some pain syndromes. At any rate, successfully addressing depression in persons suffering pain from OA with counseling and pharmacotherapy has been shown to reduce OA-related morbidity. ■

Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

Source: Landolfi R, et al. *N Engl J Med*. 2004;350:114-124

The increased red cell mass diagnostic of polycythemia vera (PCV) results in blood hyperviscosity, which is associated with increased thrombotic events. Initial enthusiasm for the concept of ASA thromboprophylaxis in PCV was dampened by a 1986 trial of aspirin (ASA) at a dose of 900 mg/d, in which an unacceptably high incidence of major GI bleeding was seen. In non-PCV populations, low-dose ASA has been shown to provide effective thromboprophylaxis, with lesser risk of major GI bleeding.

Plasma thromboxane (a direct stimulator of platelet activation) levels are elevated as much as 10 fold in PCV, a situation parallel to that seen in acute coronary syndromes, in which ASA has been proven to provide dramatic risk reduction. Since even low-dose ASA results in substantially reduced platelet thromboxane production, but less GI bleeding, the potential merit of such a clinical trial is straightforward.

PCV patients lacking any other direct indication for ASA (eg, previous MI) were enrolled in a double-blind placebo-controlled randomized trial to compare 100 mg ASA with placebo (n = 518). The 2 primary end points of the study were: 1) nonfatal MI + nonfatal stroke + CV death; 2) nonfatal MI + nonfatal stroke + PE + DVT + CV death. Secondary end points included individual thrombotic components of the above.

After a mean followup of 3 years, ASA reduced the primary end point #2 by 60%; primary end point #1 was reduced 59%, but did not achieve statistical significance. The lower ASA dose (100 mg/d) demonstrated excellent safety, with no statistically significant increased risk of either major or minor bleeding compared to placebo. Landolfi and associates recommend consideration of low-dose ASA for thromboprophylaxis in PCV. ■

Coronary Artery Calcium Score Plus Framingham Score for Risk Prediction

Source: Greenland et al. *JAMA*. 2004;291:210-215

The Framingham risk score (FRS) is a commonly recommended tool for estimating risk of coronary events (CHD) in asymptomatic persons (asymptomatic for CHD, that is). It provides an assessment of the likelihood of experiencing a CHD event in the next 10 years. Despite inclusion of age, sex, smoking, BP, lipids, and glucose, the FRS is imperfect in identifying those at CV risk, especially for those determined to be at 'intermediate risk' (FRS = 10-19%). Another tool used for CHD risk stratification is coronary artery calcium scoring (CACS), as obtained by CT. The purpose of this trial was to ascertain whether combining the 2 enhances accuracy.

Asymptomatic persons older than 45 (n = 1461) with at least one CHD risk factor (but without prior MI or proven CAD) were enrolled. Diabetics were excluded because CACS has not proven effective in this population, who are by definition already recognized as high risk for CAD at presentation. Patients were followed up to 8.5 years (mean, 7 years).

For persons with a FRS of at least 10% (but < 20%), a CACS greater than 300 (highest quartile CHD risk) significantly modified risk prediction. For instance, a FRS 10-year risk prediction of 10% was increased to 13-19% when coupled with a CACS score > 300. Greenland and associates suggest that for low-risk (FRS < 10%) and high risk (FRS > 20%) individuals, CACS adds little. Prognostication about the intermediate risk group (FRS = 10-19%) is enhanced by combining the tools. ■

Intra-articular Hyaluronic Acid in the Treatment of Knee Osteoarthritis

Source: Lo GH, et al. *JAMA*. 2003; 290:3115-3121.

The use of hyaluronic acid (HUA) injection in human subjects began in 1997, following a history of similar treatment in veterinary medicine. HUA is a constituent of normal synovial fluid, and has been conceptualized as a 'joint lubricant.' Because of mixed efficacy responses in clinical trials, clinician acceptance of this treatment modality for osteoarthritis of the knee (OA) has been somewhat tepid.

This metaanalysis included 22 trials, with almost 3000 patients. To quantify treatment effects, an 'effect size' metric was used; 0.2-0.5 is a 'small' effect size, comparable to the advantage of NSAIDs over acetaminophen in OA treatment trials. Analysis included all recipients of HUA injection, but was further separated out into groups based upon whether subjects had received standard, or highest molecular weight HUA.

Overall, HUA was found to provide a modest benefit (effect size = 0.32); Lo and associates discuss that even this result may be overoptimistic, since publication bias was discerned amongst HUA injection trials. According to this analysis, whether highest molecular weight HUA is more advantageous than other configurations remains indeterminate. Lo et al call for further independent trials to provide greater clarification of HUA efficacy. ■

Clinical Briefs in Primary Care™ is published monthly by American Health Consultants. Copyright © 2004 Thomson American Health Consultants. **Vice President/Group Publisher:** Brenda Mooney. **Editorial Group Head:** Glen Harris. **Editor:** Stephen Brunton, MD. **Assistant Managing Editor:** Rob Kimball. **Senior Copy Editor:** Christie Messina This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: robert.kimball@ahcpub.com
World Wide Web: http://www.ahcpub.com
Address Correspondence to: American Health Consultants 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

THOMSON
AMERICAN HEALTH CONSULTANTS

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5413. E-mail: christie.petrone@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■