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INSIDE

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Can We Achieve Semirecumbency?

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Dr. Akhtar does research for Eli Lilly.

Synopsis: *This prospective multi-center randomized trial determined that the target head-of-bed elevation of 45° for ICU patients was difficult to achieve, and that lower levels (up to 28°) did not reduce rates of ventilator-associated pneumonia.*

Source: van Nieuwenhoven CA, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med*. 2006;34:396-402.

A PROSPECTIVE, MULTI-CENTER RANDOMIZED TRIAL WAS PERformed to determine the feasibility of the semirecumbent position (goal, head of bed elevation [HOB] 45°) and its impact on the incidence of ventilator-associated pneumonia (VAP). Four ICUs in the Netherlands participated. Over a 2-year period, all patients who were intubated within 24 hours of ICU admission anticipated to require > 48 hours of mechanical ventilatory support, and, without contraindication to positioning as per the study protocol, were eligible. Selective digestive decontamination and continuous subglottic aspiration were not used. Usual demographic, severity-of-illness and outcome data were collected. All patients received stress gastritis prophylaxis until initiation of enteral feeding (via nasogastric tube). Angle of HOB above horizontal was monitored by a continuous computerized recording system that measured every 60 seconds for the first week. Patient position was adjusted as needed by research nurses 2-3 times a day and bedside labels reminded all caretakers of goal position. Deviation from randomized position was defined as a change of > 5°. VAP was diagnosed by standard CDC criteria and confirmed with quantitative cultures of bronchoscopic lavage; blinded investigators reviewed data and classification of VAP. Appropriate power calculations, intent-to-treat analysis and other usual standard statistical methods were used.

The study enrolled 221 patients and there were no significant differences in baseline characteristics or outcomes between the 2 posi-

tioning groups. A similar number of patients in each group required ventilation < 48 hours; ICU and hospital length of stays and mortality were also comparable. Mean HOB elevation was 9.8-14.8° for the supine/standard care group and 23.1°-29.2° for the semirecumbent (goal 45°) group. The latter group had HOB <40° 85% of the time. There was no difference between the 2 groups in the number of patients with clinically suspected or microbiologically confirmed VAP; the latter occurred in 10.7% of the semirecumbent group and 6.5% of the supine/standard care group. There was also no difference within each group in VAP risk relative to the degree of HOB elevation. The authors found no associations between VAP and diagnosis, severity of illness, age, gender, enteral feeding or length of sedation but did find an association with presence of infection at admission and with specific hospital.

COMMENTARY

Aspiration of gastroesophageal contents may be one mechanism for development of VAP and it has been clearly shown that endotracheal aspiration of gastric contents is greater in the supine vs semirecumbent position.[1] The one and only randomized trial of semirecumbent (45°) vs supine (0°) patient positioning was a single center study that was stopped early for the marked (78%) reduction in VAP.[2] Since then, patient positioning has been an important part of the recommended strategies for prevention of VAP.[3,4] It is a cheap and, in theory, easily applicable measure with no apparent downsides.

van Nieuwenhoven et al's study questions the feasibility and value of semirecumbent positioning for VAP prevention. It differs significantly from Drakulovic et al's work.[2] The present authors defined 'supine' as usual care (found to be HOB elevation about 10°) vs. a predefined level (0° in the prior study). In addition, they used a computerized recording device to measure position continuously (as opposed to just once a day), providing more accurate and detailed data. Finally, it is important to note that their recorded rates of VAP are lower overall than in the prior study.

The issue of feasibility is what drew me to this study initially, as in my personal experience it continues to be a struggle to consistently maintain semirecumbency (45°) for patients in the ICU despite repeated education and clear protocols. The reasons are not entirely clear and were not detailed in this publication either: they may include disbelief in prior data, patient request (for those awake and able to communicate this), hemodynamic instability, the need to change position for nursing care/procedures/ therapies and then forgetting or neglecting to return to prior position, perceptions about patient comfort, concerns about skin care or other.

Some institutions have 'compromised' and set HOB ≥ 30° (instead of 45°) as the goal, with the assumption that there will be some benefit in terms of prevention of VAP even at this level. The current study suggests that although this level of HOB elevation may be achievable, it does not appear to reduce VAP incidence compared to usual care. This is a reminder of the important concept that in order to attain the benefits noted in a particular study, one must follow the study protocol. To paraphrase a former mentor: "If a well-designed study demonstrates that a triple chemotherapy combination regimen improves mortality, you aren't going to pick only 1 of those drugs to give to your patients—the same principle is true of any clinical study protocol."

What about the fact that the authors found no difference in VAP incidence in their supine and semirecumbent positioning groups? The study's findings may be interpreted in several ways, such as: any elevation of HOB above 0° may significantly reduce incidence of VAP (perhaps 10° is as good as 45°); a specific threshold difference in elevation of HOB may be needed before a reduction in VAP rate is seen (about 20° may not be enough); usual ICU care has changed enough in the past 5-10 years that VAP rates are already lower and a larger sample size would be needed to appreciate smaller differences.

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Questions & Comments

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

I suggest that because patient positioning continues to be a 'free' intervention that may have significant benefit, we should continue to try to implement Drakulovic and colleagues' work more exactly until a confirmatory study is completed. ■

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Partial Liquid Ventilation in ARDS

ABSTRACT & COMMENTARY

By David J. Pierson, Editor

Synopsis: *In this large-scale randomized clinical trial in adult patients with ARDS, partial liquid ventilation using two different strategies for administration resulted in a greater number of serious adverse outcomes and did not improve survival compared to conventional ventilatory support.*

Source: Kacmarek RM, et al. Partial liquid ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;173:882-889.

Partial liquid ventilation (PLV) with perfluorocarbon (PFC) has been demonstrated in animal models of acute lung injury to recruit dependent lung regions (the so-called "liquid PEEP" effect), to redistribute blood flow to better ventilated regions, to thus improve gas exchange compared with conventional ventilation, and also to facilitate the clearance of retained secretions. Further, preliminary studies demonstrated the clinical feasibility of PLV in humans, and post-hoc analysis of data from a phase II trial[1] suggested that mortality might be reduced and other outcomes improved with the use of PLV in patients with ARDS. Accordingly, the authors of this paper designed a large-scale, multi-center clinical trial of PLV—administered according to 2 different dosing strategies—compared to conventional ventilatory support in adult patients with the acute respiratory distress syndrome (ARDS).

At 56 centers throughout the United States and in 6 other countries, investigators recruited patients between the ages of 16 and 65 who had a known ARDS risk factor, bilateral radiographic infiltrates, and a PaO_2/FIO_2 of 300 mm Hg or less on an FIO_2 of 0.5 or more with positive end-expiratory pressure (PEEP) at least 13 cm H_2O. A relatively homogeneous population of patients with predominantly single-organ failure was sought via an extensive list of 28 exclusion criteria. The primary outcome was 28-day ventilator-free days; secondary outcomes were mortality, time to unassisted ventilation, percentage of patients alive and off ventilation at day 28 after randomization, and rate of ARDS resolution. Patients were randomized to conventional ventilation, low-dose PFC (10 mL/kg predicted body weight, PBW), or high-dose PFC (20 mL/kg PBW). A carefully controlled protocol governed the instillation and monitoring of PFC administration in the two treatment groups. All patients received PLV for at least 48 hours, and administration of PFC could continue for up to another 72 hours if the FIO_2 remained greater than 0.5.

Out of 3,817 patients screened for enrollment in the study, 311 were randomized to the 3 management groups. Ventilator-free days 28 days after randomization were 13.0 ± 9.3 in the conventional ventilation group, 7.4 ± 8.5 in the low-dose PLV group ($P < 0.001$), and 9.9 ± 9.1 in the high-dose PLV group ($P = 0.043$). The 28-day mortality in the 3 groups was 15%, 26%, and 19%, respectively (differences not statistically significant). There were more instances of pneumothorax, hypotension, and hypoxia in the PLV patients. The authors conclude that PLV at both the low- and high doses used in this study did not improve outcomes, and was associated with greater numbers of serious adverse outcomes compared to conventional mechanical ventilation, and that this approach to management is not indicated in adults with ARDS.

■ COMMENTARY

This was a carefully done study, as very thoroughly documented in this paper. The protocol was complicated, and many aspects of the use of PLV and the assessment of the patients had to be chosen more or less arbitrarily. The patients were enrolled between 1998 and 2000, prior to the publication of the ARDS Net low-tidal-volume study.[2] The tidal volumes (mean, 9 mL/kg PBW) and end-inspiratory plateau

pressures (mean, 30-32 cm H_2O) were higher than used by the ARDS Net, and the levels of PEEP employed were high. However, the 3 treatment groups were very well matched, and it is unlikely that these deviations from what is now standard practice in most centers affected the results.

As in most other negative randomized controlled trials involving interventions with positive effects in preliminary reports, the authors assert that PLV may yet prove useful and postulate a number of reasons why benefit that truly exists could not be demonstrated in the present trial. They cite aspects of the PFC administration and monitoring that might be improved, and ways in which patient selection and ventilator management in this trial could have affected the results. They caution that "it is still unclear how to optimally dose PFCs and adjust ventilator settings in patients receiving PLV. Therefore, the overall role, if any, of PFCs in ventilator management of ARDS remains to be determined despite this negative study."

Low-tidal-volume, low-plateau-pressure ventilation saves lives in patients with ARDS,[2,3] but the search continues for another specific intervention that does so. Put another way, although alternative ventilatory approaches such as HFOV, and management adjuncts such as surfactant, nitric oxide, and prone positioning have been the subjects of enthusiastic initial reports and continue to have strong advocates, none has been shown in a randomized controlled trial to improve outcomes in unselected patients with ARDS. We can now add PLV to that list, but with one important difference: its lack of availability to clinicians. Unlike the situation with prone positioning, inhaled nitric oxide, and HFOV, with PLV physicians will not have the dilemma of whether to try an unproven but still-advocated and readily available intervention in managing their patients with severe ARDS. ■

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Special Feature

Should I Prone My Patient with ARDS?

By Dean R. Hess, PhD, RRT

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Dr. Hess reports no financial relationship relating to this field of study.

In 1976, Piehl and Brown showed, in a retrospective study, that the prone position improved oxygenation in 5 patients with the acute respiratory distress syndrome (ARDS).[1] One year later, Douglas et al demonstrated, in a prospective study, that prone positioning could effectively improve oxygenation in ARDS.[2] Starting from these reports, interest in prone positioning in ARDS has increased over the years, culminating in several randomized controlled trials with survival as the primary outcome.

Does Prone Position Improve Oxygenation?

Pappert et al[3] evaluated 12 patients with severe ARDS before, during, and after a 2-h period of mechanical ventilation with the patient in the prone position. Prone position resulted in an overall increase of PaO_2 after 120 min (98.4 ± 50.3 to 146.2 ± 94.9 mm Hg). Although 8 patients had an improvement of PaO_2 > 10 mm Hg after 30 min in the prone position (responders), 4 patients had a deterioration of PaO_2 in the prone position (nonresponders).

Fridrich et al[4] evaluated 20 patients with ARDS after multiple trauma. Patients were turned to the prone position at noon and were turned back to the supine position at 8:00 AM on the next day. Immediately after the first turn from the supine to the prone position, the PaO_2 increased from 97 ± 4 to 152 ± 15 mm Hg. Most of this improvement was lost when the patients were turned supine, but could be reproduced when prone positioning was repeated after 4 h in the supine position.

Chatte et al[5] studied changes in oxygenation in 32 patients with ARDS who were turned to and from supine to prone position at 1- and 4-h intervals. Seven patients (22%) had no response (non-responders), and 25 (78%) had a positive response (responders). Among the 7 non-responders, 2 did not tolerate the prone position and were returned to supine before the end of the 4-h trial. In 10 of the 23 responders (43%), the PaO_2/FIO_2 returned to its starting value when patients

were repositioned to supine (response, but not persistent). The pattern of response could be categorized as a persistent response, not persistent response, or no response (*see Figure 1*).

These and other studies[6] suggest that arterial oxygenation is improved in many patients with ARDS who are turned from supine to prone position. In some patients, the response is maintained even after the patient is returned to a supine position (persistent responders). However, the response is not universal. About 20%-30% of patients do not improve their PaO_2 when turned to the prone position. Unfortunately, there is no reliable way of predicting which patients are likely to respond to prone position with an improvement in PaO_2.

What is the Mechanism of Action for Prone Position?

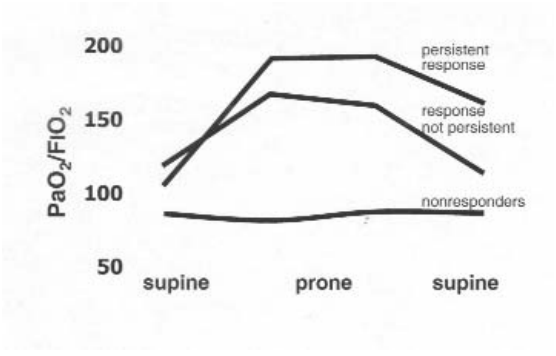
Changes in ventilation-perfusion (V/Q) relationships in the prone position most likely explain improvements in oxygenation when patients are turned to the prone position.[7] In ARDS, pulmonary blood flow is minimally affected by body position, and the prone position markedly increases the number of normal V/Q units compared with supine position. More uniform distribution of ventilation in the prone position may be largely responsible for the improvement in V/Q. In the supine position, gravity creates a pleural pressure gradient from the ventral (nondependent) to the dorsal (dependent) regions. The ventral regions are exposed to relatively more negative pleural pressure causing a higher regional transpulmonary pressure. The dorsal lung regions are exposed to a lower, relatively more positive, pleural pressure, so that transpulmonary pressure is less. Changing body position from supine to prone alters the ventral-dorsal pleural pressure gradient and regional transpulmonary pressure (*see Figure 2*) by altering gravitational forces and by reducing the compressive effects of the abdominal wall and the heart and mediastinal structures.

Other mechanisms may also contribute to an improvement in oxygenation in the prone position. Prone positioning facilitates drainage of secretions for the airways. There may be less compression of the lungs (particularly the left lung) by the heart.[8] There are also effects on the chest wall compliance.[9] The greatest improvement in PaO_2 when turned to prone may be in patients with a more compliant chest wall, and the greatest improvements in PaO_2 may in cases where the chest wall compliance decreases by the greatest degree in the prone position.

Does Prone Position Improve Patient Outcomes?

We know that many patients with ARDS have an improvement in their oxygenation when turned from supine to prone, and we have some idea of the mecha-

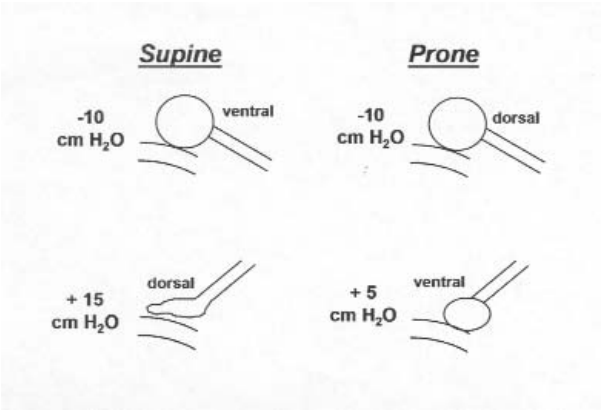
Figure 1



Patterns of response to prone position in patients with ARDS. Some patients respond with an increase in PaO_2/FIO_2, and that response persists when the patient is returned to supine. Others have an improvement in PaO_2/FIO_2 when turned prone, but the effect is lost when the patient is returned to supine position. Other patient have no improvement in their PaO_2/FIO_2 when turned prone.

Source: *Chatte G, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. Am J Respir Crit Care Med. 1997;155:473-478.*

Figure 2



Cartoon illustrating a proposed effect of prone positioning in ARDS, with a more uniform pleural pressure gradient in prone position. The effect of this is a lesser compression effect on dependent alveoli, improved ventilation of dependant alveoli, improved V/Q, and better oxygenation.

Source: *Dean R. Hess, PhD, RRT*

nism for this observation, but does this translate into improved patient outcomes? This has been explored in 4 randomized controlled trials.

Gattinoni et al[10] studied the effect on survival of prone position, compared with conventional treatment in the supine position, of patients with acute lung injury (ALI) or ARDS in a multicenter, randomized trial. There was a predefined strategy of placing patients in a prone position for ≥ 6 hrs/day for 10 days. The study enrolled 304 patients, 152 in each group. The relative risk of death in the prone group as compared with the supine group was 0.84 at the end of the study period (95% confidence interval, 0.56 to 1.27), 1.05 at the time of discharge from the intensive care unit (95% interval, 0.84 to 1.32), and 1.06 at 6 months (95% confidence interval, 0.88 to 1.28). During the study period, the increase in the PaO_2/FIO_2, measured each morning while patients were supine, was greater in the prone than the supine group. The incidence of complications related to positioning (such as pressure sores and accidental extubation) was similar in the 2 groups. The authors concluded that, although placing patients with acute respiratory failure in a prone position improves their oxygenation, it does not improve survival.

Guerin et al[11] determined whether prone positioning improves mortality in patients with acute respiratory failure in a multi-center randomized controlled trial of 791 patients. Patients were randomly assigned to prone position (n = 413), applied as early as possible for at least 8 hrs/day, or to supine position (n = 378). The 28-day mortality rate was 32.4% for the prone group and 31.5% for the supine group (relative risk, 0.97; 95% confidence interval, 0.79 to 1.19). Mortality at 90 days was 43.3% for the prone group and 42.2% for the supine group (relative risk, 0.98; 95% confidence interval, 0.84 to 1.13). The incidence of ventilator-associated pneumonia was 1.66 for the prone group vs 2.14 for the supine group, per 100-patients days of intubation ($P = 0.045$). Pressure sores, selective intubation, and endotracheal tube obstruction were higher in the prone group. This trial demonstrated no beneficial effect of prone positioning on mortality and some safety concerns associated with prone positioning. Prone position may lower the incidence of ventilator-associated pneumonia.

Curley et al[12] evaluated whether infants and children with ALI treated with prone positioning would have more ventilator-free days than those treated with supine positioning in a multi-center randomized controlled trial. Patients were randomized to either supine or prone positioning within 48 hrs of meeting acute lung injury criteria, with those patients in the prone group being positioned within 4 hours of randomization and remaining prone for 20 hrs/day for a maximum of 7 days. There were no differences in the number of ventilator-free days between the 2 groups. There were no differences in the secondary end points, including proportion alive and ventilator-free on day 28, mortality from all causes, the time to recovery of lung injury, organ-failure-free days, and cognitive impairment or overall functional health at hospital discharge or on day 28. The authors concluded that prone positioning does not reduce ventilator-free days or improve other clinical outcomes in pediatric patients with acute lung injury.

In the most recent study to examine patient outcomes with prone position, Mancebo et al[13] evaluated whether it is beneficial to administer prone ventilation early in the course of respiratory failure and for longer periods of time than previous studies. The study enrolled 136 patients within 48 hours of tracheal intubation for severe ARDS (60 to supine and 76 to prone). The prone group was targeted to be placed in this position 20 hrs/day. The ICU mortality was 58% in the patients ventilated supine and 43% in the patients ventilated prone ($P = 0.12$). A total of 718 turning procedures were done and prone position was applied for a mean of 17 hrs/day for a mean of 10 days. The authors concluded that prone ventilation is feasible and safe, and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day.

None of these 4 studies demonstrated a statistically significant reduction in mortality with prone position in patients with ALI and ARDS. There are several possible explanations for this disappointing finding. Perhaps prone position does not, in fact, affect important patient outcomes despite an improvement in oxygenation. Perhaps the timing or duration of prone position was not correct (wrong dose). Perhaps the studies were under-powered, although a meta-analysis pooling the results of the 4 randomized controlled trials demonstrates no benefit for prone position with respect to mortality (*see Figure 3*).

It might also be that patient outcomes are improved with prone position in selected subgroups of patients. For example, in post-hoc analysis, Gattinoni[10,14] has reported a survival benefit in patients with the highest risk ($PaO_2/FIO_2 \leq 88$ and SAPS II score > 49) and in patients who have a decrease in their $PaCO_2$ with prone position. However, the results of these post-hoc analyses need verification in properly designed randomized controlled trials.

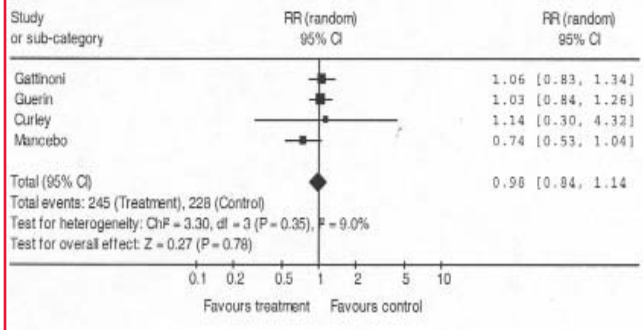
Is Prone Positioning Safe?

Turning a critically ill patient from supine to prone is not simple and descriptions for this procedure have been published.[7,15] Care must also be exercised to position the patient safely while in the prone position. Patients may have an increased need for sedation and paralysis related to turning to the prone position. Endotracheal tube obstruction has been reported while patients are in the prone position,[10,11] most likely related to drainage of airway secretions. Pressure sores (anterior chest wall, ventral shoulders, patellae, forehead) and facial edema are more prevalent when patients are in the prone position. Contraindications of prone positioning include increased intracranial pressure, fractures (facial, spinal, pelvic), open wounds on the ventral surface, and hemodynamic instability.

So What to Do?

Prone position in patients with ALI/ARDS is associated with an increase in PaO_2 in the majority of patients who receive this therapy. However, the improvement in oxygenation may not translate into a survival benefit. Based on the available evidence, prone position cannot be considered standard care in patients with ALI/ARDS. It is not wrong to use prone position in selected patients with ARDS, but it is also not wrong if prone is not used.[16] ■

Figure 3



Meta-analysis pooling the results of 4 randomized controlled trials of prone versus supine position, with mortality at the primary outcome variable. Note that the pooled relative risk of death is 0.98 (95% confidence interval 0.84 to 1.14; P = 0.80). This meta-analysis does not support a survival benefit for prone positioning.

Source: *Dean R. Hess, PhD, RRT*

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CME Questions

11. The new study differs from the prior randomized trial of semi-recumbent positioning and VAP incidence in the following way:
a. Selective digestive decontamination was used
b. Enteral feeding was not allowed
c. HOB of patients in the 'supine' arm was kept at 0°
d. A computerized system was used to record HOB position continuously
e. Quantitative cultures were not used to define VAP

12. van Nieuwenhoven et al found that patients in the semirecumbency group compared to supine/standard positioning:
a. had lower mortality.
b. had no difference in VAP incidence.
c. had longer ICU length of stay.
d. had shorter hospital length of stay.
e. were more less likely to be fed interally.

13. In the large-scale trial of Kacmarek et al, partial liquid ventilation in patients with ARDS was shown to have which of the following advantages over conventional ventilation?
a. Better survival
b. Shorter duration of mechanical ventilation
c. Fewer complications
d. Lower cost
e. None of the above

14. Prone positioning in patients with ALI/ARDS has been shown to:
a. decrease mortality.
b. increase oxygenation.
c. shorten duration of mechanical ventilation.
d. decrease risk of pressure sores.
e. increase need for hemodynamic support.

Answers: 11 (d); 12 (b); 13 (e); 14 (b)

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.

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Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■