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INSIDE



## Colloid or Crystalloid: Pick Your Poision

ABSTRACT & COMMENTARY

***Synopsis:*** *A large multicenter prospective randomized double-blind trial found no difference in 28-day outcomes for fluid resuscitation with normal saline vs 4% albumin for a heterogeneous ICU population.*

**Source:** The SAFE Study Investigators. *N Engl J Med*. 2004; 350(22):2247-2256.

IT IS UNKNOWN WHETHER THE CHOICE OF RESUSCITATION FLUID impacts outcomes of critically ill patients. This study hypothesized there would be no difference in 28-day mortality for patients resuscitated with normal saline (NS) vs 4% albumin.

A 20-month prospective, randomized, double-blind study designed to detect a 3% difference in absolute mortality was performed in 16 closed tertiary care ICUs in Australia and New Zealand. Patients older than age 18 and judged to require fluid resuscitation by the treating physician were eligible. Those admitted after cardiac surgery, liver transplantation or burn injuries were excluded. Patients were randomized to receive either NS or 4% albumin for all fluid resuscitation until death, discharge, or 28 days after randomization. Quantity and rate of study fluid administration and choice of other fluids (maintenance, nutrition, etc) and care were at the discretion of treating physicians. Data collected included demographics, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ-Failure Assessment (SOFA) scores, diagnostic criteria for severe sepsis, acute respiratory distress syndrome (ARDS) and traumatic brain injury, daily vital signs and infused fluid volumes, survival time, organ failures and duration of ventilation, renal-replacement therapy and hospital and ICU stays. Two interim analyses were planned. Intention-to-treat analysis and standard statistical techniques were used.

Seven thousand patients were randomized. The 2 study groups had similar baseline characteristics (mean age, 59 years; mean APACHE II score, 19; 43% surgical, 18% severe sepsis). A difference in total volume of study fluid administered was seen only in


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the first 3 days after randomization (ratio of volume for albumin group: NS group 1:1.3 to 1:1.6 per day). The albumin group also received more red blood cells (RBC) (mean, 71 mL) during this time and had slightly higher central venous pressures and serum albumin. There was, however, no difference in mean arterial pressure between the groups. There was no mortality difference at 28 days (absolute difference for albumin vs NS was -0.2%; 95% CI, -2.1-1.8%). Length of ventilation, renal-replacement, and ICU and hospital stays, number of organ failures and survival times were also the same. Analysis of mortality per subgroups defined a priori revealed a weak trend towards increased relative risk (RR) of mortality among trauma patients in the albumin group (RR, 1.36; 95% CI, 0.99-1.86): all of the increased risk was in the trauma patients with associated brain injury (RR 1.62; 95% CI, 1.12-2.34). There were no significant differences in mortality of patients with severe sepsis or ARDS receiving albumin vs NS; however, there was suggestion of a trend towards lower mortality in the severe sepsis group receiving albumin compared to those without severe sepsis (RR 0.87; $P$ = 0.06). The authors conclude that NS and 4% albumin are equivalent therapies for fluid resuscitation but suggest further studies in particular subgroups.

## COMMENT BY SAADIA R. AKHTAR, MD, MSC

The ideal choice of fluid for resuscitation has been a subject of discussion for decades. The primary debate focuses on whether colloid (usually albumin) or crystalloid (NS) is preferable. There are several reasons why albumin is theorized to have potential benefits. It may support colloid oncotic pressure and thus be superior for volume replacement. Furthermore, because low serum albumin is associated with increased mortality in a variety of acutely ill patients, albumin supplementation may improve outcomes.

Albumin appears to have benefit in patients with cirrhosis and spontaneous bacterial peritonitis (SBP); administration of a standard replacement on day 1 and 3, along with antibiotics and other supportive care, reduced mortality and risk of renal dysfunction in 1 randomized controlled trial.[1] There are multiple small studies (50-100 patients) showing trends towards both reduced and increased mortality with albumin for other indications. Meta-analyses of these suggest there is no role for albumin administration in general ICU populations. In 1998, the Cochrane Group reviewed 30 randomized studies (1419 patients) comparing albumin to placebo or NS or comparing differing levels of albumin supplementation in critically ill patients with hypovolemia (in the setting of trauma or surgery), burn injuries or hypoalbuminemia. There was an increased risk of mortality with albumin administration for all studies; this was persistent even when only studies with adequate blinding were analyzed (RR, 1.61; 95% CI, 1.09-2.38). The increased risk was seen particularly in patients with burn injuries or hypoalbuminemia as the indication for albumin administration.[2]

A 2000 updated Cochrane review reported the same results. In a similar analysis, Ferguson et al reviewed 24 trials (1204 patients) comparing albumin to no albumin or crystalloid in the same patient populations. No individual study "with a reasonable sample size" (not defined) suggested improved outcomes with albumin. The pooled relative risk of mortality was higher for patients receiving albumin (RR, 1.68; 95% CI, 1.07 to 2.23).[3] Finally, most recently, Wilkes and Navickis reviewed 55 trials including > 3500 patients; these compared albumin to placebo or crystalloid or other concentration of albumin for any indication in any patient population. There was a non-sta-

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tistically significant trend towards reduced mortality with albumin in trials with 2 of the following characteristics: adequate blinding, primary end point of mortality or no crossover. Pooled analysis revealed no difference in mortality between patients receiving albumin vs NS. The authors concluded that albumin was unlikely to be harmful but that is was unclear whether it added benefit.[4]

These reports have altered practice to some degree, but their findings remain controversial due to the inherent limitations of meta-analyses. The SAFE study, the largest and best-designed trial to date on this subject, finally provides more certain support for the assertion that albumin administration is equivalent to NS for fluid resuscitation for general ICU patients. I would extend this further to state that because of albumin's lack of benefit, associated increased RBC transfusion in this study, up to 30 to 40 fold higher cost and greatly limited supply (as a human blood product), it should simply not be used for fluid resuscitation for general ICU patients at this time. I suggest that its use be restricted to SBP (as defined by Sort et al,[1] until further investigated) and to large well-designed controlled trials for other specific indications. In addition, I wonder whether other products for volume replacement such as hypertonic saline with and without dextran, new starch products and novel blood substitutes may ultimately make albumin obsolete. ■

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# Antibacterial Effect of Oral Topical Chlorhexidine after Intubation

ABSTRACT & COMMENTARY


***Synopsis:*** *In surgical and trauma patients, a single oral application of 2 mL chlorhexidine gluconate was successful in reducing oral bacterial growth over a 72-hour period following intubation.*



**Source:** Grap MJ, et al. *Heart & Lung*. 2004;33:83-91.


THE PURPOSE OF THIS STUDY WAS TO DESCRIBE THE effects of a single early post-intubation oral application of chlorhexidine gluconate (CHG) on oral microbial flora. The study enrolled 34 patients who were admitted to a surgical trauma or neuroscience ICU, who were randomized to receive 2 mL of CHG by spray (n = 11), by swab (n = 12) or no CHG (n = 11). Oral cultures were obtained before administration of CHG, 12 hours after study admission, and every 24 hours for 72 hours or until extubation if this occurred before 72 hours.

No baseline differences were found for demographics, number of gastric residuals > 100 mL ($P = 0.99$), backrest elevation ($P = 0.60$) or number of mouth care interventions by nurses during the study ($P = 0.95$). Ten patients (3 swab, 3 spray, 4 control) had positive cultures during the study, including 5 positive cultures on admission. Two patients (1 swab, 1 spray) had a decrease in culture score (less growth). Culture growth did not decrease in control patients. At 72 hours, 100% of patients in the spray group had cultures with no growth, compared to 67% in the swab group and 50% in the control group. Due to small numbers and early extubation, no conclusions could be drawn in regard to effect of CHG on ventilator-associated pneumonia.

### ■ COMMENT BY LESLIE A. HOFFMAN, RN, PhD

In dentistry, chemical antimicrobial agents are used to prevent recolonization by periodontal pathogens following peridontal surgery. The efficacy of CHG, an example of this class of agents, as a bacteriostatic and bactericidal agent in dental plaque control has been recognized since the 1970s. The antiplaque activity of CHG appears to be mainly due to its capacity for strong absorption in multiple sites in the oral cavity, especially tooth surfaces. It has no known adverse effects beyond a tendency to enhance tooth staining and a bad taste. During the first 24 to 48 hours of critical illness, patients are typically unstable and oral care is not a priority. A simple, early intervention, such as that tested in this study, has the potential to decrease bacterial growth until the patient stabilizes and routine oral care can be substituted.

Before the study began, Grap and colleagues tested various doses of CHG (ranging from 1 to 20 mL) and found that 2 mL was adequate to cover all mouth surfaces when delivered as a spray using an atomizer (20 sprays) or by swabbing. Oral cultures were obtained at 3 time points: before administration of CHG, 12 hours later, and every 24 hours up to and including 72 hours after study enrollment. Only 12 subjects had complete data at all time points due to dropout from extubation. From the data obtained, CHG appeared to be effective in reducing bacterial growth as evaluated by trends in the data. Further statistical analysis was not performed

due to small group size. The study's primary limitation is its small sample size and the limited followup interval. Given the simplicity of the intervention and lack of significant adverse effects, use of CHG would seem to be an appropriate strategy for use in this early period following intubation with the goal of preventing ventilator-associated pneumonia. ■

# A New Approach to Predicting Extubation Failure?

ABSTRACT & COMMENTARY

***Synopsis:*** *This single-center prospective observational study reveals that the presence of 3 factors (low cough peak flow, high secretion volume, and poor neurologic score per a simple 4-task test) may be useful in predicting extubation failure.*

**Source:** Salam A, et al. *Intensive Care Med*. 2004; 30(7):1334-1339.

Though a spontaneous breathing trial (SBT) may demonstrate readiness for liberation from ventilator support, it does not provide information about continued need for an artificial airway. There are limited and conflicting data on the utility of assessment of cough, secretions and neurologic status (by Glasgow Coma Scale [GCS]) in predicting extubation outcome.[1,2] Salam and colleagues address whether combination of a different neurologic score with quantitative measures of cough strength and secretion volume may be useful in predicting extubation outcome.

An 11-month prospective observational study was performed in a Connecticut medical-cardiac intensive care unit (ICU). All patients receiving invasive mechanical ventilation were eligible after passing a 30-60 minute protocol-guided SBT. Patients with tracheostomies were excluded from the study. Extubations that were part of life-support withdrawal were also excluded. Demographics, APACHE II scores and a variety of respiratory variables were gathered for all study patients. Cough peak flow (CPF) was recorded using a pneumotachograph-calibrated Aztech peak flow meter placed in series with the endotracheal tube. Endotracheal secretions were suctioned and quantitated hourly for 2-3 hours before anticipated extubations. Finally, a simple 4-task neurologic score (1 point per task) was assigned by asking the patient to: open eyes, follow observer with eyes, grasp hand and stick out tongue. Patients' caregivers were blinded to the results of these tests. Decision to extubate was per the attending physician. Patients who remained extubated at 72 hours were classified as "successful extubations." Standard statistical analyses were employed.

Eighty eight patients (mean age, 62 years; mean APACHE II score, 24) with 100 extubations were enrolled. Median time of intubation was 4 days. Pneumonia was the most common reason for intubation. Fourteen (15.9%) patients failed the first extubation, with hypoxia and increased work of breathing being the most common reasons. There was no statistically significant difference in age, gender, duration of intubation or secretion volume between patients successfully extubated and those who failed. CPF and neurologic score were both significantly worse in patients with extubation failure. Neurologic score 0/4 was independently associated with extubation failure (RR, 3.2; CI, 1.6-6.1). Severity of illness was also significantly worse in patients with extubation failure (median APACHE II 28 vs 23). Patients with all 3 risk factors (CPF = 60L/min, secretions > 2.5 mL/hr, neurologic score 0/4) had a 100% extubation failure rate. There was no difference in results between analysis of first extubations vs both first and repeat extubations.

Salam and colleagues conclude that quantitative measures of cough strength and secretions may be more useful than qualitative ones in predicting extubation outcome. They also propose that a neurologic score such as theirs may be more predictive than GCS of extubation outcome. They suggest replication of their study in other centers and patient populations.

### ■ COMMENT BY SAADIA R. AKHTAR, MD, MSC

Intensivists clearly understand that in the daily care and assessment of intubated, mechanically ventilated ICU patients, the continued need for ventilator support should be considered separately from the continued need for an artificial airway. The best approach to the latter though remains unclear.

Salam et al's report adds some data to the limited literature on this topic and offers interesting new hypotheses that deserve to be explored further. Their overall results suggest that quantitative rather than qualitative measures of ability to protect the airway may have reasonable predictive value for extubation outcome. It is still quite surprising that such a small volume of secretions (> 2.5 mL/hr) would be significant, even in combination with other factors. Alone, the volume of secretions did not differ between patients successfully extubated and those who failed, suggesting this should not be a very impor-

tant or reliable predictor. Further study must follow to clarify this. One of the most intriguing observations from this report is that a neurologic score that is more specific for abilities required for airway protection may be more useful than a usual measure such as the GCS. Only reproduction of these findings in other studies will reveal whether Salam et al's 4-task score is adequate. Greater consideration may need to be given to what neurologic features are required for airway control and maintenance and how to measure them before concluding that this is not a valid predictor of extubation outcome.

Though some of the findings in this report conflict with those of prior studies, they do not detract from those data. The patient populations evaluated and the aims of the studies are quite different and simply cannot be directly compared. Coplin and colleagues described timing of extubation in patients with acute brain injury as well as the impact of delayed extubation on ICU and hospital lengths of stay and pneumonia incidence.[1] They examined GCS and airway issues only as secondary outcomes: they found neither had significant association with extubation result in their cohort. Namen and colleagues' aim was to evaluate a respiratory-therapy driven weaning protocol in neurosurgical patients.[2] Their findings were similar to those of Coplin et al: they observed significant extubation delays. Post-hoc analysis suggested that higher GCS was associated with increased likelihood of extubation success but this was not further assessed or independently validated. Both of these studies emphasize the fact that our current approaches to assessing readiness for extubation have considerable weaknesses and that relying on them may lead to unnecessary extubation delays. Neither, though, provides the ultimate solution.

I believe that all 3 of these publications present compelling hypotheses that, as a first step, must be confirmed in larger prospective studies of similar patient populations. The next step then will be to apply and validate the approach across other patient populations. Perhaps then we will have a tool for predicting extubation success that is at least equivalent to the SBT for liberation from mechanical ventilation: a tool with reasonably good (but far from 100%) negative and positive predictive value that must be accompanied by a disclaimer reminding us that a failed extubation rate of 0% means we may be delaying extubation unnecessarily and bringing harm to some of our patients. ■

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*Special Feature*

# Vasopressin in Septic Shock

*By Uday B. Nanavaty, MD*

SEPTIC SHOCK IS ONE OF THE COMMON CAUSES OF hypotension in the ICU. For decades, adrenergic agents with variable alpha- and beta-adrenergic activities have been the mainstay among vasopressor agents. Very few randomized controlled trials have been done that identify the efficacy or superiority of any one particular agent. Amongst the vasopressors in common use, norepinephrine (NE) and phenylephrine remain widely used, with dopamine losing favor over the last decade. Epinephrine is rarely used as the first vasopressor of choice.

Reviewing the available literature, it seems that NE is most commonly used as the vasopressor of choice in septic shock. However, it remains a common observation that in some patients NE is ineffective as a vasopressor. There are multiple potential pathophysiologic reasons for the failure of adrenergic vasopressors. Due to the lack of effectiveness of NE and other pressors in some patients with septic shock, as well as concern about toxicity at higher doses, alternatives have been sought. Vasopressin has become one alternative that is gaining increasing acceptance, although both the safety and efficacy of vasopressin in septic shock remain unproven. Here, I review the physiologic basis of using vasopressin in septic shock, as well as the available limited data about its safety and efficacy.[1,2]

## Vasopressin in Health

Vasopressin, also known as antidiuretic hormone (ADH), is a well-known peptide hormone that is formed primarily in the supraoptic and paraventricular nuclei of hypothalamus and secreted in the posterior pituitary gland. ADH is secreted in response to osmotic stimuli and plays a vital role in the reabsorption of water in the collecting tubules and ducts in the kidney. Absence of ADH leads to central diabetes insipidus, a condition characterized by large water losses. Resistance to actions of ADH on kidney tubules results in a similar condition called nephrogenic diabetes insipidus. The effects of ADH on water regulation are observed in response to osmotic stimuli and are observed at minute physiologic concentrations.

Aside from these effects on kidney function, higher concentrations of ADH are associated with arteriolar

vasoconstriction—hence the name vasopressin. Decreased blood volume and or a decrease in blood pressure exert their effects via dis-inhibition of atrial stretch receptors as well as decreased stretch of baroreceptors in the carotid, aortic and pulmonary vasculature.

The primary regulator of ADH secretion seems to be the osmolarity of extracellular fluids, with a 1% increase in osmolarity resulting in 7-fold increase in ADH secretion. Comparatively, more than a 10% decrease in blood volume is required before ADH secretion is affected. Besides osmolarity, blood pressure and blood volume, such diverse stimuli as hypoxia and nausea as well as wide variety of chemicals such as morphine, nicotine, and alcohol, as well as drugs such as cyclophosphamide and clonidine, affect ADH secretion. The vasoconstrictor effects are mediated through V1 vascular receptors, whereas the anti-diuretic effects are mediated through V2 renal receptors.

## Vasopressin Levels in Septic Shock[1,3,4]

Animal and human studies suggest that early on in septic shock, ADH levels are markedly elevated and after several hours of septic shock, levels of circulating ADH drop. ADH levels remain relatively low in patients who remain hypotensive after approximately 24 hours of therapy for septic shock. In patients with hemorrhagic shock, the levels of ADH are elevated initially, as would be expected based on physiological stimuli.

The precise mechanisms of low ADH levels in persistent septic shock are unclear. It is possible that the stores of vasopressin are exhausted in patients with persistent vasodilatory shock. It is also described that there may be autonomic dysfunction in baroreflexes. High levels of NE (endogenous or exogenously administered) are known to inhibit release of vasopressin, and nitric oxide overproduction in the posterior pituitary may have an inhibitory effect.

## Effects of Vasopressin Infusion in Patients with Septic Shock

Landry et al[3] first described their findings of using vasopressin infusion in vasodilatory shock and suggested a concept of "vasopressin hypersensitivity" as very low doses of vasopressin generated "pressor" responses. Since then, several investigators have evaluated the effects of vasopressin in small studies[5,6] or more often in form of case series and at times in retrospective fashion. The published literature is so scant that a meta-analysis would not be of significance but several similarities exist to draw the following conclusions.

## Is Vasopressin Effective as a Vasopressor in Septic Shock?[1,5,6]

It is clear that vasopressin, as an infusion, is associated with improvement in blood pressure and reduction in the doses of pressors required to maintain reasonable blood pressure in patients suffering from septic shock. It has been observed in several small studies that abrupt withdrawal of vasopressin will result in hypotension and re-institution of vasopressin results in prompt response with elevation of blood pressure. Similarly, it has been consistently noted that patients who receive vasopressin infusion with septic shock often demonstrate increased urine output. It is believed that this response may be simply due to increased renal perfusion pressure. As with other agents, failure to respond to pressor doses of vasopressin has been reported as well.

## What Dose of Vasopressin Is Safe in Treating Hypotension Associated with Septic Shock

The smallest possible dose of vasopressin should be used to achieve the mean arterial pressure goal. Although a wide variety of doses have been used, several different reports suggest that to avoid possible cardiac and other side effects, vasopressin should only be used in doses between 0.01 to 0.04 U/min. Effectiveness of vasopressin as a pressor agent has been demonstrated for the lower doses and at these small doses, very few if any side effects have been reported. Most of the studies that report few side effects have used vasopressin for 4 to 24 hours only. Two small studies have reported that even in small doses, vasopressin infusion can result in impaired gastric mucosal blood flow. This phenomenon of redistribution of blood flow may have potential harmful effects. Some of the studies have also reported a drop in cardiac index (CI). Most studies however have not reported any significant changes in lactate levels or other indices to suggested impaired systemic perfusion. Peripheral extravasation of vasopressin solution used for these low doses has been reported to induce skin necrosis.

## When Should One Use Vasopressin?

When vasopressin infusion should be initiated remains unclear. Unfortunately, various authors have used different doses of NE prior to starting the study of vasopressin. There is no study that compares vasopressin against NE as the first line treatment of

hypotension during septic shock. Based on the limited literature, vasopressin infusion should be used after volume resuscitation and failure of pharmacologic doses of NE or other vasoactive agents. If escalating doses of pressor agent fail, it would be reasonable to try vasopressin.

## Can Vasopressin Be Used To Replace Norepinephrine?

At least one study tried to replace NE with vasopressin. Klinzing et al[7] studied substitution of vasopressin for NE. They found that much higher dose of vasopressin (0.06-1.8 U/min) was needed to maintain blood pressure. They also observed that at these doses of vasopressin, CI tended to decrease, heart rate tended to decrease and although splanchnic blood flow was maintained, there was concern that mucosal blood flow may be reduced. Thus it seems reasonable to use vasopressin in low doses (0.01-0.04 U/min) enough to achieve the blood pressure goals when NE seems to be failing. Currently available studies suggest that replacing NE with vasopressin may have harmful effects.

## Does Vasopressin Infusion Improve Outcome in Septic Shock?

There are no studies that have looked at the effect of vasopressin infusion on the outcome of septic shock. It would be unwise to conclude that improvement in blood pressure will automatically result in improved outcome. We have seen the effects of nitric oxide inhibition with dramatic improvement in blood pressure in septic shock patients. Unfortunately, inhibiting nitric oxide resulted in higher mortality in a large randomized controlled study.

No significant change in creatinine clearance or dialysis requirement has been noted, and it is not possible at this point to draw any conclusions about improved renal function.

## When Should We Avoid Vasopressin?

Most authors have excluded any element of cardiogenic shock either by using invasive monitoring and excluding patients with low CI or by using echocardiographic assessment. Patients with unstable angina or recent myocardial infarction should be excluded as well.

## What Do We Know About Terlipressin in Septic Shock?

Terlipressin is a long acting analogue of vasopressin. There are some case reports that suggest that small doses of terlipressin administered every six hours result in improved blood pressure in patients with septic shock. Again, no randomized controlled studies have been performed to assess the safety or efficacy of intermittent dosing of terlipressin in septic shock.

## Conclusions

It seems safe to conclude that vasopressin acts as a pressor agent in the dose range of 0.01 to 0.04 U/min in septic shock-associated hypotension, especially if the patient remains hypotensive in spite of adequate fluid resuscitation and conventional pressor therapies. One should be careful in making sure that the patient does not have an underlying cardiac problem that can be exacerbated by vasopressin before starting this unproven therapy. Care should be taken to avoid complications such as skin necrosis. In view of lack of evidence to the benefit of using vasopressin in septic shock, extreme care should be taken in its use, at least until it is proven that the therapy does not harm the patient. Terlipressin, a vasopressin analog, may become valuable, if it can be shown to be effective and safe in treating septic shock-associated hypotension. ■

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# CME Questions

1. **Compared to critically ill patients receiving NS for fluid resuscitation, those receiving 4% albumin had:**
   a. Higher mortality.
   b. More red blood cells transfused.
   c. Longer hospital length of stay.
   d. Higher likelihood of requiring renal replacement therapy.
   e. Greater volume of fluid infused in the first 3 days.

2. **Patients with which of the following underlying conditions had a trend towards increased mortality when receiving 4% albumin instead of NS?**
   a. ARDS
   b. Shock
   c. Trauma
   d. Renal failure
   e. Severe sepsis

3. **In intubated patients who received chlorhexidine gluconate (CHG), oral cultures were most likely to be negative if:**
   a. backrest position was maintained at 45°.
   b. gastric residuals were < 100 mL.
   c. mouth care interventions were more frequent.
   d. the patient had dentures.
   e. CHG was applied by swab or spray.

4. **Topical oral application of chlorhexidine shortly following intubation has been shown to:**
   a. reduce the incidence of ventilator-associated pneumonia
   b. reduce the incidence of bacterial colonization of the lower respiratory tract
   c. both of the above
   d reduce bacterial growth in the mouth
   e. none of the above

5. **The use of topical oral application of chlorhexidine following intubation is an extension of a practice long-established in which of the following?**
   a. Tropical epidemiology
   b. Dairy microbiology
   c. Dentistry
   d. Enology
   e. Podiatry

6. **Which of the following factors was associated with extubation failure in the study of Salam et al?**
   a. Secretion volume > 10mL/hour
   b. Cough peak flow = 60L/minute
   c. GCS < 9
   d. Prior extubation failures
   e. Age > 62 years

7. **The rate of extubation failure for patients in the Salam study who had 3 risk factors (low cough peak flow, high secretion volume and poor neurologic score) was:**
   a. 18%
   b. 30%
   c. 62%
   d. 100%
   e. Not reported

8. **Vasopressin has been shown in small studies and case series/reports to be effective in management of septic or vasodilatory shock. All the following are safe assumptions except:**
   a. For vasodilatory shock, vasopressin should be used as 40 Unit bolus, administered via the intravenous route.
   b. For septic shock patients who do not respond to appropriate fluid challenges and norepinephrine, vasopressin can be used if there are no contraindications.
   c. Vasopressin should be avoided in patients with septic shock and patients who are also experiencing cardiac dysfunction (low ejection fraction or cardiac index).
   d. Vasopressin, in doses of 0.01 to 0.04 Units/min, has vasopressor effects in patients with septic shock.

9. **Under physiological conditions, vasopressin has multiple effects including anti-diuresis as well as some vasopressor effects. All of the following are true about effects of vasopressin in health and disease *except*:**
   a. Vasopressin mediates its anti-diuresis effects via V2 R receptors in the tubules of the kidneys.
   b. Vasopressin has vasoconstrictor effects both in health and in disease.
   c. In patients with septic shock, small doses of vasopressin (0.01 to 0.04 Units/min) have vasopressor effects.
   d. Vasopressin is effective as the primary therapy of septic shock by improving endothelial dysfunction commonly seen in septic shock.

**Answers:** 1 (b); 2 (c); 3 (e); 4 (d); 5 (c); 6 (b); 7 (d); 8 (a); 9 (d)

# CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

## In Future Issues:

**Intra-Hospital Transport of ICU Patients**

PHARMACOLOGY WATCH

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

# Linking COX-2 Inhibitors and Cardiovascular Event Risk

A new, and as of yet unpublished study, has raised increased concern about the relationship between rofecoxib (Vioxx), Merck's blockbuster COX-2 inhibitor, and cardiovascular events. The study, which was presented at a meeting in Bordeaux France, was financed by the FDA in collaboration with California's HMO giant Kaiser Permanente. The study was designed to determine if celecoxib, rofecoxib, ibuprofen, naproxen, or other NSAIDs increase the risk of acute myocardial infarction (AMI) or sudden cardiac death (SCD). Utilizing the 6-million member California database for Kaiser Permanente, all patients ages 18-84 who had taken a COX-2 inhibitor or nonselective NSAIDs between January 1999 and December 2001 were entered into the cohort. Controls were a risk-set match 4:1 on event date, birth year, gender, and health plan region. There were 8199 acute cardiac events within the study cohort (6675 AMI, 1524 SCD). The data revealed that rofecoxib use at > 25 mg per day increased the risk of acute cardiac events 3.15 fold (OR, 3.15 [1.14-8.75]). Rofecoxib at a dose < 25 mg resulted in an odds ratio of 1.29 (0.93-1.79), which was not statistically significant. When comparing low-dose rofecoxib to celecoxib (Celebrex), the risk of AMI and SCD was higher with rofecoxib ($P$= 0.04). Other NSAIDs, including naproxen, indomethacin, and possibly diclofenac, also increased the risk of AMI and SCD. These data will be presented in this country in October at the American College of Rheumatology. Concern about the relationship between rofecoxib and cardiac events was first raised with the publication of the VIGOR trial (*N Engl J Med.* 2000;343:1520-1528) which showed a relative risk of cardiac events associated with rofecoxib of 2.38 (95% CI, 1.39-4.00; $P$= .002). Dr. Eric Topol and colleagues from the Cleveland clinic subsequently reevaluated these data along with data from other studies and raised the concern of prothrombotic potential of COX-2 inhibitors, especially rofecoxib (*JAMA.* 2001;286:954-959). Their concern centered on the tendency for COX-2 inhibitors to block production of prostacyclin—thus blocking antiaggregatory and vasodilatory effects, while having no effect on thromboxane, which is responsible for platelet aggregation. Blockage of thomboxane is a COX-1 effect and accounts for the majority of the cardioprotective effects of aspirin and other NSAIDs. Rofecoxib, the most COX-2 specific of the drugs tested, may unbalance thromboxane and prostacycline accounting for the cardiovascular risk.

Some have considered a strategy of adding aspirin to a COX-2 inhibitor, but a new study suggests that aspirin negates the GI benefits of the COX-2 inhibitor, the primary benefit of COX-2 inhibitors over nonselective NSAIDs.

Researchers from USC performed a double-blind trial of rofecoxib, rofecoxib plus low-dose

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aspirin, ibuprofen, or placebo in patients without ulcers or erosive esophagitis. Endoscopies were performed at baseline, 6 weeks, and 12 weeks. At 12 weeks, the cumulative index of ulcers was placebo 5.8%, aspirin 7.3%, rofecoxib plus aspirin 16.1%, and ibuprofen 17.1% ($P < 0.001$ for rofecoxib plus aspirin and for ibuprofen vs each of placebo and aspirin). Over the same time, rofecoxib plus aspirin and ibuprofen both significantly increased the number of erosions (both $P < 0.001$ vs aspirin and placebo). The authors conclude that low-dose aspirin does not significantly increase ulcer recurrence, but that the addition of a COX-2 inhibitor with aspirin increases the rate of ulceration to a rate that is similar to a nonselective NSAIDs (*Gastroenterology.* 2004;127:395-402).

### Viagra: Maximum Capacity at High-Altitudes?

High-altitude hikers may soon be requesting sildenafil (Viagra) prescriptions based on the results of a new study. The drug, which is a phosphodiesterase-5 inhibitor, is known to cause pulmonary vasodilation. German researchers postulated that such an effect may increase exercise capacity during induced hypoxemia at low altitudes and at Mount Everest base camp. Fourteen healthy mountaineers and trekkers were assessed with measurements of systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximal exercise capacity on cycle ergometry while breathing a hypoxic gas mixture at low altitude, and retested at high-altitude at the Mount Everest base camp. Sildenafil 50 mg significantly increased arterial oxygen saturation during exercise ($P = 0.005$), reduced systolic pulmonary artery pressure at rest ($P < 0.001$), and during exercise ($P = 0.031$). Sildenafil also increased maximum workload and maximum cardiac output compared with placebo. At high-altitude, the drug had no effect on arterial oxygen saturation at rest nor during exercise compared with placebo, however, the sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$), during exercise ($P = 0.021$), increased maximum workload ($P = 0.002$), and cardiac output ($P= 0.015$). Two patients noted worsening headache at high-altitude with the drug. The authors conclude that sildenafil is the first drug to increase exercise capacity during severe hypoxia both at sea level and at high-altitude (*Ann Intern Med.* 2004;141:169-177). An accompanying editorial suggests that sildenafil is not a substitute for acclimatization to high-altitude and suggests that the findings of the study are compelling and that further research into a phosphodiesterase inhibitors in the treatment of pulmonary vascular disease is needed (*Ann Intern Med.* 2004;141:233-235).

### FDA Actions

Eli Lilly has received FDA approval to market duloxetine (Cymbalta) for the treatment of major depression. The drug is a serotonin and norepinephrine reuptake inhibitor (SNRI), similar to venlafaxine (Effexor-Wyeth). The drug is also being studied for the treatment of stress urinary incontinence and diabetic neuropathic pain. Lilly, and the drug approval process for duloxetine, came under scrutiny earlier this year when a 19-year-old female volunteer committed suicide after discontinuing the drug during clinical trials. The patient had no history of depression prior to the study.

Shire Pharmaceuticals has received expanded indication for its mixed amphetamine product Adderall XR for the treatment of adults with attention deficit hyperactivity disorder (ADHD). The drug is a one-a-day preparation that has been widely used in children since 2001.

The FDA and Genentech have issued a warning to physicians regarding the risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). The drug is an angiogenesis inhibitor, a novel antineoplastic used to treat metastatic colon cancer and other solid tumors. Reports of cerebral infarctions, myocardial infarctions, transient ischemic attacks, and angina have all been associated with use of the drug.

The FDA has approved an orally disintegrating form of carbidopa/levodopa for the treatment of Parkinson's disease. The preparation dissolves rapidly in the mouth without the need for water, allowing for dosing even when patients are rigid or suffering from "off periods," when producing can be problematic. It will be marketed under the trade name Parcopa and will be available in 10/100 tabs, 25/100 tabs, and 25/250 tabs, similar to brand name Sinemet levodopa/carbadopa.